ITRACONAZOLE BRIEF MANUFACTURING PROCESS

BRIEF MANUFACTURING PROCESS:

Stage: IT-IA:

((2R,4S)-2-(bromomethyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methyl benzoate (Cis-Bromo benzoate) reacted with 1-H, - 1,2,4 Triazole in Dimethyl formamide to get Cis-2-(2-4-dichloro phenyl)-2-(1H-1,2,4 triazol-1-yl- methyl)1-3-dioxolane-4-yl- methyl alcohol. (IT-IA)

Stage: IT-IB:

Cis-2-(2-4 dichloro phenyl) 1,3-(phenyl)-2-(1,H- 1,2,4 Triazole-1-yl-methyl) 1-3-dioxolane –4-yl-methyl alcohol (IT-IA) reacted with Methane sulfphonyl chloride in the presence of methylene chloride with triethyl amine as alkali media. To get Cis-[2-(2,4-Dichloro phenyl) -2(1H-1,2,4 Triazole-1-yl methyl)-1,3-Dioxalane-4-yl]–methyl Methane sulphonate (IT-IB)

Stage: IT-VI

1-(4-methoxy phenyl) 4-(4-nitrophenyl) piperzine (IT – II) Hydrogenates in presence of Palladium carbon in Dimethyl formamide to get 4-(4-(4-methoxyphenyl)piperazin-1-yl)benzamine(IT – III).the reaction mass reacted with phenyl chloro formate in the presence of pyridine to get phenyl 4-(4-(4-methoxy phenyl)piperazin-1-yl) phenyl carbamate .The reaction mass Reacted with Hydrazine hydrate in the presence of Di methyl formamide to get N-(4-(4-(4-Methoxyphenyl)-1-piperazinyl) phenyl) hydrazine carboxamide. The reaction mass reacted with formamidine acetate to get 2, 4 di hydro 4 -(4-(-4-(4-Methoxy phenyl)-1 piperazinyl phenyl 3H-1,2,4 Triazole -3-one (IT – VI)

Stage: IT-VII

2,4 di hydro 4-(4-(4-(4-Methoxy phenyl)-1 piperazinyl phenyl 3H-1,2,4 Triazole -3-one (IT- VI) reacted with 2- Bromo butane in presence of DMSO with potassium Hydroxide to get 2,4 di hydro 4-(4-(4-(4-Methoxy phenyl)-1-piperazinyl phenyl-2-(1-methylpropyl)-3H-1,2,4 Triazole-3-one (IT-VII).

Stage: IT-VIII

2,4 Di hydro 4 – (4- (4 – (-4 Methyl phenyl)–1 piperazinyl phenyl –2-(1-Methyl propyl)3H-1,2,4 Triazole –3-one (IT- VII) reacted with hydro bromic acid to get 2,4 di hydro 4 – (4- (4 – (-4 Hydroxy phenyl) –1 piperazinyl phenyl –2-(1-Methyl propyl)-3H-1,2,4 tri azole–3-one (IT-VIII)

ITRACONAZOLE BRIEF MANUFACTURING PROCESS

Stage: IT-IX

2,4-Dihydro-4-[4–[4-[4–hydroxy phenyl]1-piperzinyl] Phenyl]-2-(1-methyl propyl)-3 H - 1,2,4 Triazol-3-one (IT-VIII) reacted with Cis – 2 – [(2,4 – di chloro phenyl) –2 - (1H- 1,2,4 Triazole – 1-yl Methyl) 1,3 Dioxalane – 4 yl] – methyl – methane sulphonate (IT – IB) in presence of DMSO to get (IT – IX) (Itraconazole crude).

Stage: Itraconazole API (IT-X)

The product Itraconazole crude (IT-IX) purified with methanol, acetone and toluene to get (Itraconazole pharma) 4-[4-[4-[4-[[Cis–2-(2,4-dichloro phenyl)–2-(1H-1,2,4-Triazole–1-yl methyl)-1,3-dioxolan–4-yl] methoxy] phenyl] piperazin-1-yl] phenyl]–2 -[(1RS)-1-methyl propyl]-2,4-dihydro–3H-1,2,4–Triazole-3-one. (Itraconazole)

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IT-IA Raw material List :

S.No	Raw Material
1.	*Cis*-Bromo Benzoate
2.	1,H - 1,2,4 Triazole
3.	Potassium carbonate
4.	Dimethyl formamide
5.	Water
6.	Toluene
7.	Hydrochloric Acid

IT-IB Raw material List :

S.No	Raw Material
1.	Cis-2-(2-4-dichloro phenyl)-2-(1H-1,2,4 triazol-1-yl- methyl)1-3-dioxolane-4-yl- methyl alcohol (IT-IA)
2.	Methylene chloride
3.	Methylene chloride
4.	Triethyl amine
5.	Methane sulphonyl chloride
6.	Methanol
7.	DM water

IT-III + VI Raw material List:

S.No	Raw Material
01.	1-(4-Methoxy phenyl) 4-(4-Nitro phenyl) Piperazine(IT-II)
02.	Palladium on Carbon
03.	Dimethyl formamide
04.	Nitrogen gas
05.	Hydrogen gas
06.	Pyridine
07	Phenyl Chloro Formate
08	Hydrazine hydrate
09	Formamidine acetate
10	Methanol
11	Water

IT-VII Raw material List:

S.No	Raw Material
01.	2,4 Di hydro4-(4-(4-(4methoxy phenyl)-1-piperazinyl phenyl 3H-1,2,4 triazole-3-one (IT-VI)
02.	DMSO
03.	Potassium Hydroxide
04.	2-Bromo butane
05.	Hydrochloric acid
06.	Chloroform
07	DM water

IT-VIII Raw material List:

S.No	Raw Material
01.	IT-VII
02.	Hydro bromic acid
03.	Acetic Acid
04.	Sodium carbonate
05.	DM water

IT-IX Raw material List:

S.No	Raw Material
01.	IT-VIII
02.	IT-IB
03.	Potassium hydroxide
04.	Dimethyl sulfoxide
05.	Methanol
06.	Acetone
07.	Dimethyl formamide
08.	DM water

IT-X(Itraconazole) Raw material List:

S.No	Raw Material
01.	Itraconazole tech [IT-IX](Wet)
02.	Methanol
03.	Toluene
04.	Activated carbon

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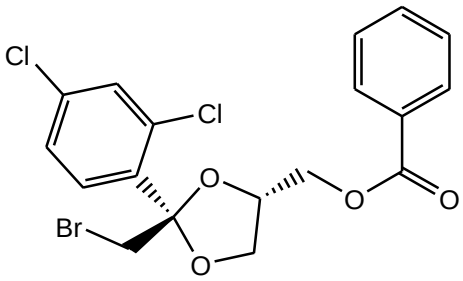
UNIT-IV

REACTION SCHEME

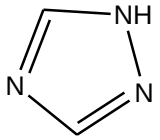
Reaction scheme of IT-IA [Itraconazole Intermediate-IT-IA]:



((2*R*,4*S*)-2-(bromomethyl)-2-(2,4-dichlorophenyl) -1,3-dioxolan-4-yl)methyl benzoate

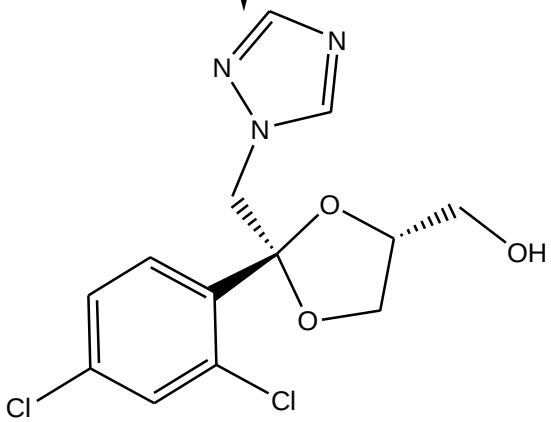
(Cis Bromo benzoate)

+



1 H -1,2,4 triazole

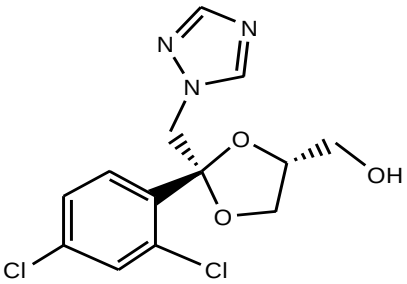
Potassium carbonate
Dimethylformamide
Toluene
Hydrochloric acid
DM Water



Cis-2-(2-4-dichloro phenyl)-2-(1H-1,2,4 triazol-1-yl-methyl)1-3-dioxolane-4-yl- methyl alcohol

REACTION SCHEME

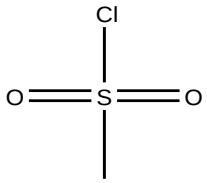
Reaction Scheme IT-IB [Itraconazole Intermediate-IT-IB]



Cis-2-(2-4-dichloro phenyl)-2-(1H-1,2,4 triazol-1-yl- methyl)1-3-dioxolane-4-yl- methyl alcohol

$C_{13}H_{13}Cl_2N_3O_3$
Mol. Wt.: 330.167

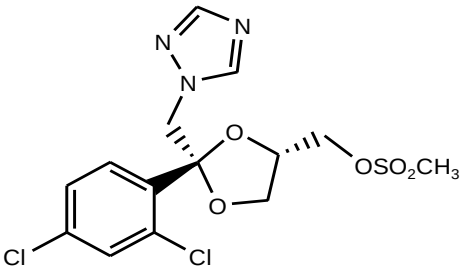
+



Methane sulfonyl chloride

CH_3ClO_2S
Mol. Wt.: 114.551

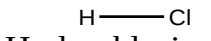
Triethyl amine
Methylene chloride
Methanol
Water



Cis - 2-[(2,4 - dichloro phenyl) - 2-(1H- 1,2,4,triazol - 1- yl methyl)1,3 dioxolane -4yl]-methyl- methane sulphonate

$C_{14}H_{15}Cl_2N_3O_5S$
Mol. Wt.: 408.257

+



Hydrochloric acid

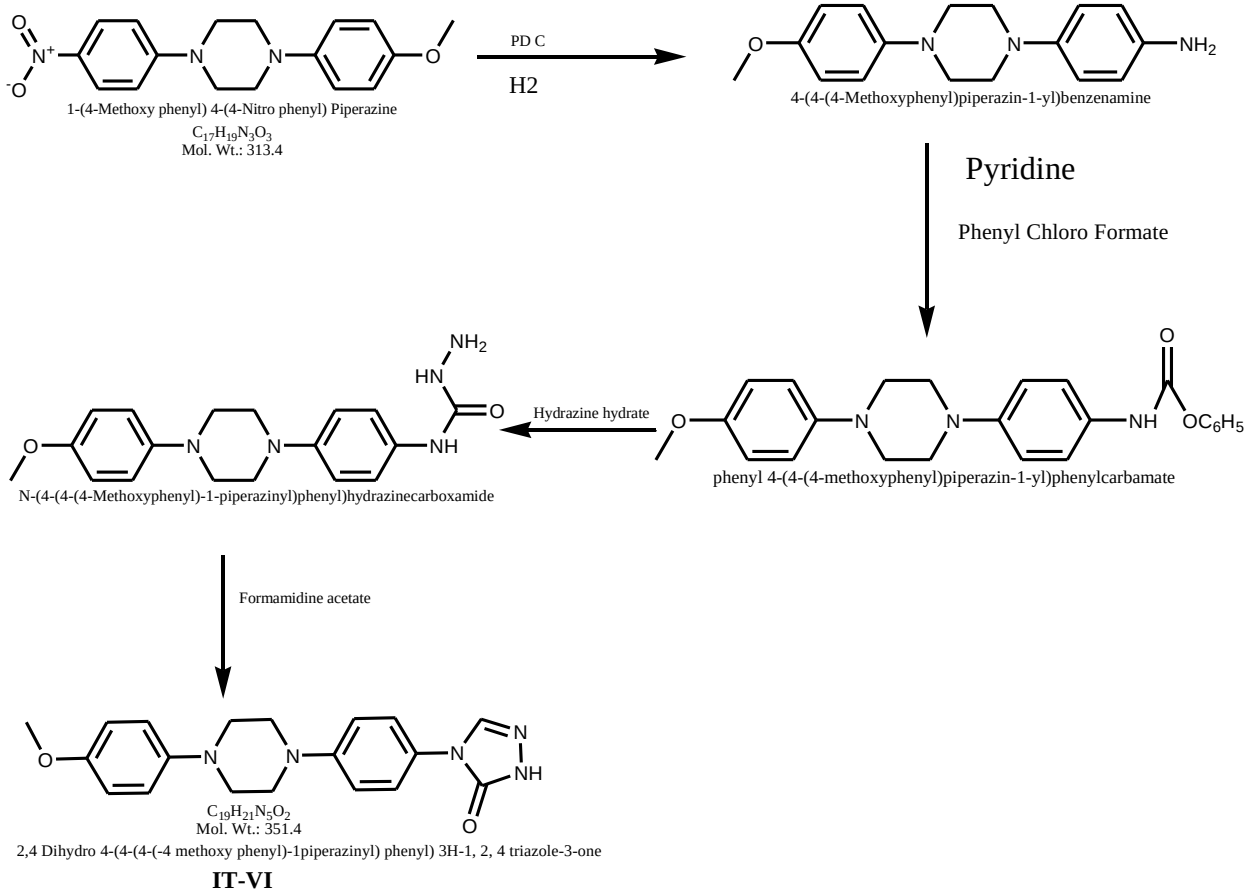
ClH
Mol. Wt.: 36.461

UNIT-IV

REACTION SCHEME

Stage wise ROS details

Stage: IT-VI



1-(4-Methoxy phenyl) 4-(4-Nitro phenyl) Piperazine

$C_{17}H_{19}N_3O_3$

Mol. Wt.: 313.4

4-(4-(4-Methoxyphenyl)piperazin-1-yl)benzenamine

phenyl 4-(4-(4-methoxyphenyl)piperazin-1-yl)phenylcarbamate

N-(4-(4-(4-Methoxyphenyl)-1-piperazinyl)phenyl)hydrazinecarboxamide

$C_{19}H_{21}N_5O_2$

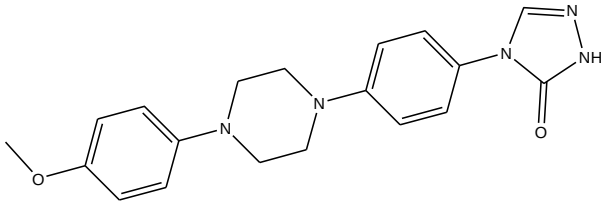
Mol. Wt.: 351.4

2,4 Dihydro 4-(4-(4-(-4 methoxy phenyl)-1piperazinyl) phenyl) 3H-1, 2, 4 triazole-3-one

IT-VI

REACTION SCHEME

IT-VII ROS



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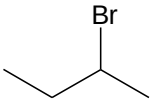


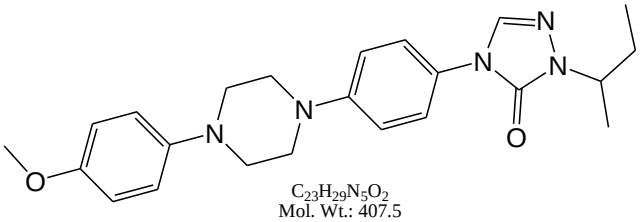
2-Bromobutane

+ K^+ OH^-

2,4-dihydro-4-(4-[4-(4-methoxyphenyl)-1-piperazinyl] phenyl)-3H-1,2,4-triazole-3-one

$C_{19}H_{21}N_5O_2$
Mol. Wt.: 351.4

Dimethyl solfoxide



$C_{23}H_{29}N_5O_2$
Mol. Wt.: 407.5

2,4-dihydro-4-(4-[4-(4-methoxyphenyl)-1-piperazinyl] phenyl)-2-(1-methyl propyl)-3H-1,2,4-triazole-3-one

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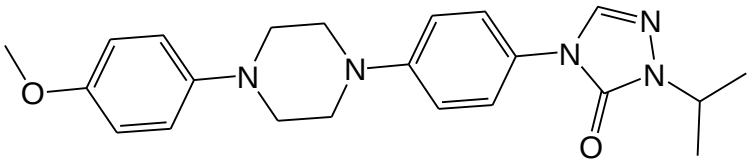
UNIT-IV

REACTION SCHEME

IT-VIII ROS

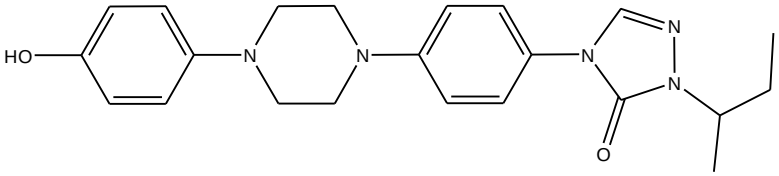


2,4-dihydro-4-(4-[4-(4-methoxyphenyl)-1-piperazinyl]
phenyl)-2-(1-methyl propyl)-3H-1,2,4-triazole-3-one

$C_{23}H_{29}N_5O_2$
Mol. Wt.: 407.5

HBr

Acetic Acid



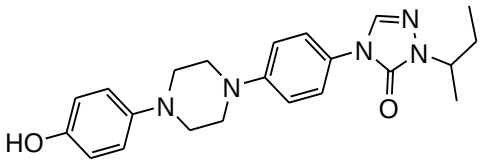
$C_{22}H_{27}N_5O_2$
Mol. Wt.: 393.5

2,4-dihydro-4-(4-[4-(4-hydroxy phenyl)-1-piperazinyl]
phenyl)-2-(1-methyl propyl)-3h-1,2,4-triazole-3-one

IT-VIII

ITRACONAZOLE
Reaction scheme

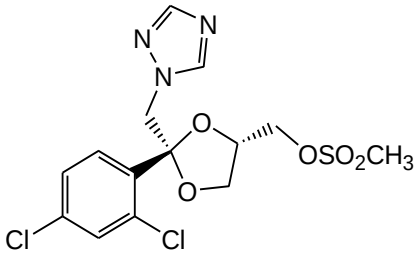
Stage: IT-IX :



2,4-dihydro-4-{4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl} -2-(1-methyl propyl)-3H-1,2,4-triaz ol-3-one

$C_{22}H_{27}N_5O_2$
Mol. Wt.: 393.48

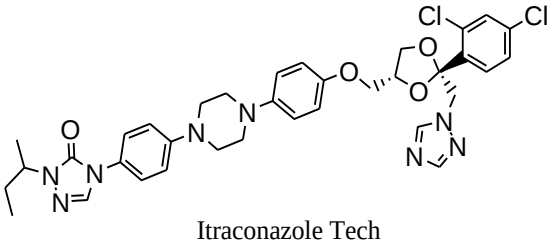
+



Cis - 2-[(2,4 - dichloro phenyl) - 2-(1H- 1,2,4,triazol - 1- yl methyl)1,3 dioxolane -4yl]-methyl- methane sulphonate

$C_{14}H_{15}Cl_2N_3O_5S$
Mol. Wt.: 408.257

DMSO KOH



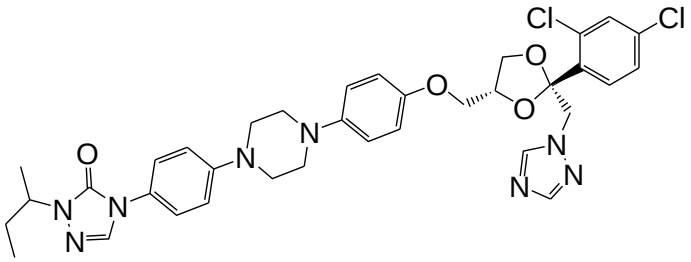
+ CH_3SO_3H
Mol. Wt.: 96.106

Itraconazole Tech

$C_{35}H_{38}Cl_2N_8O_4$
Mol. Wt.: 705.633

ITRACONAZOLE
Reaction scheme

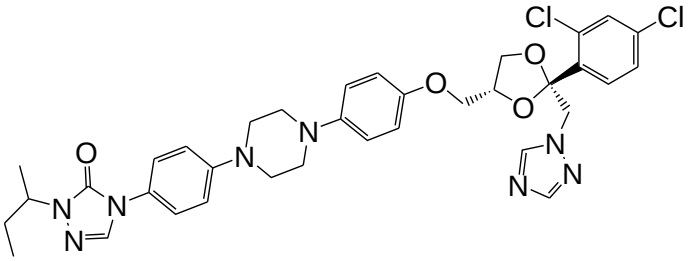
STAGE: IT-IX



Itraconazole Tech

$C_{35}H_{38}Cl_2N_8O_4$
Mol. Wt.: 705.633

Methanol , Toluene
Activated carbon



Itraconazole pharma

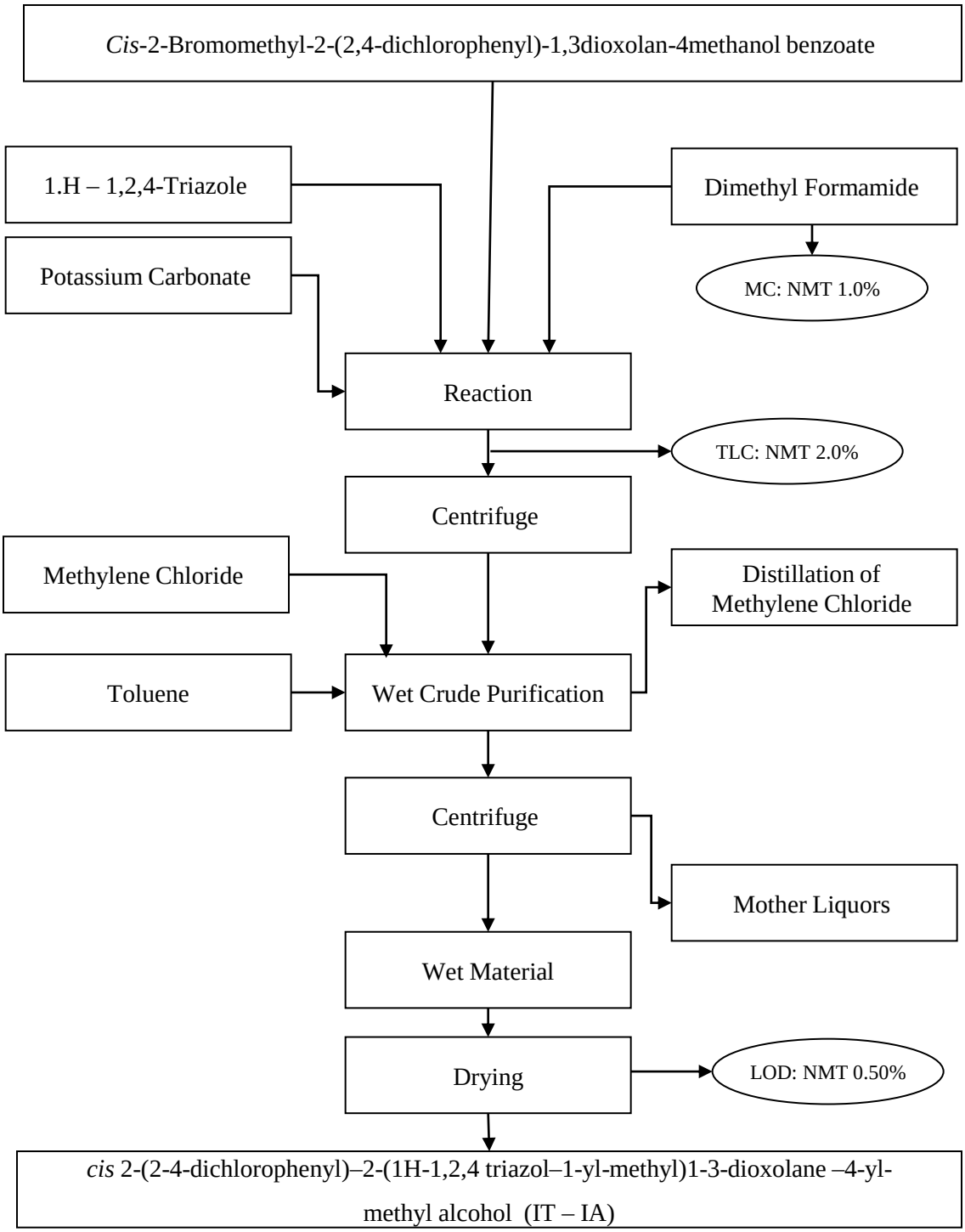
$C_{35}H_{38}Cl_2N_8O_4$
Mol. Wt.: 705.633

ITRACONZOLE

Stage: IT-IA

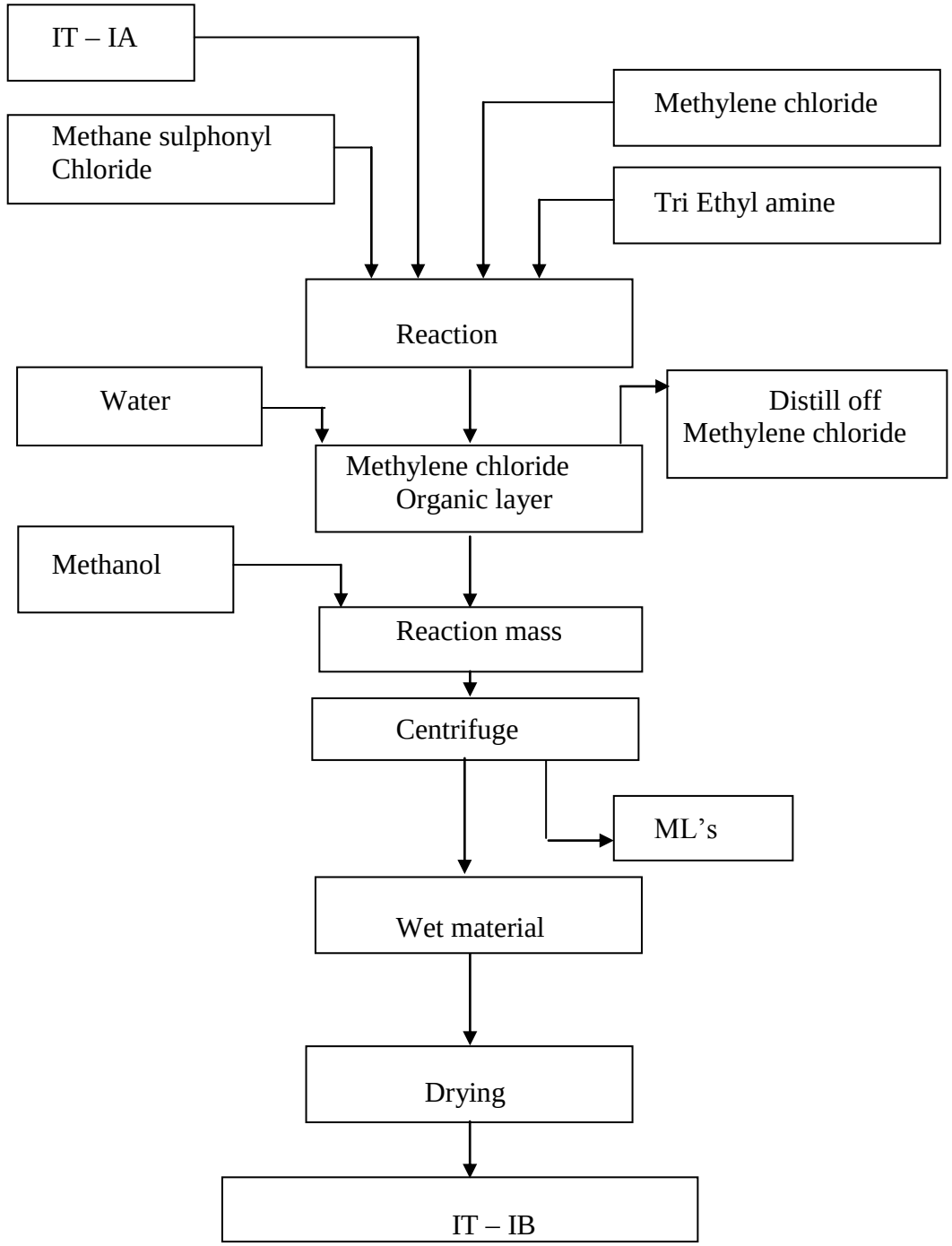
Process Flow Chart for

***cis* 2-(2-4-dichlorophenyl)–2-(1H-1,2,4 triazol–1-yl-methyl)1-3-dioxolane –4-yl-methyl alcohol (IT – IA)**



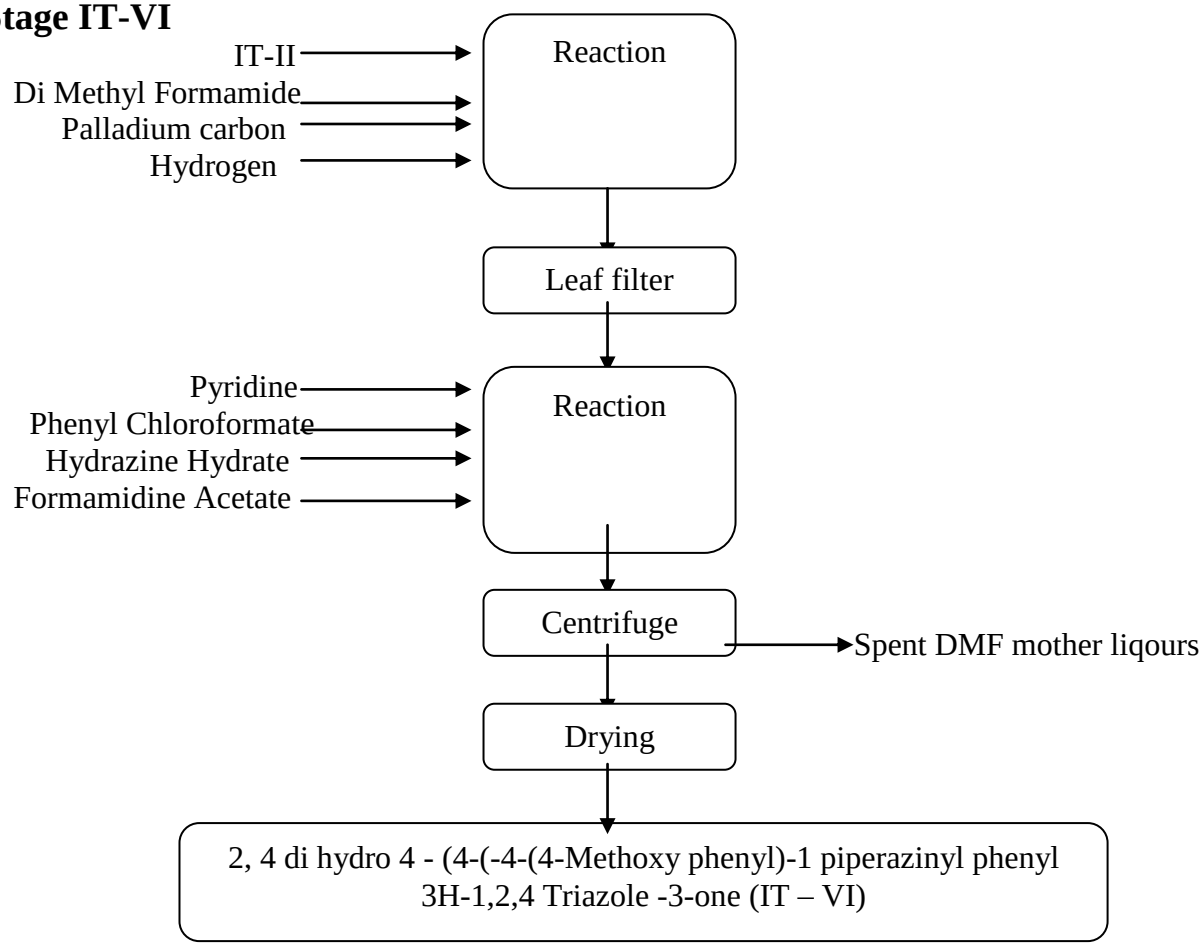
ITRACONAZOLE

FLOW CHAT FOR STAGE : IT – IB



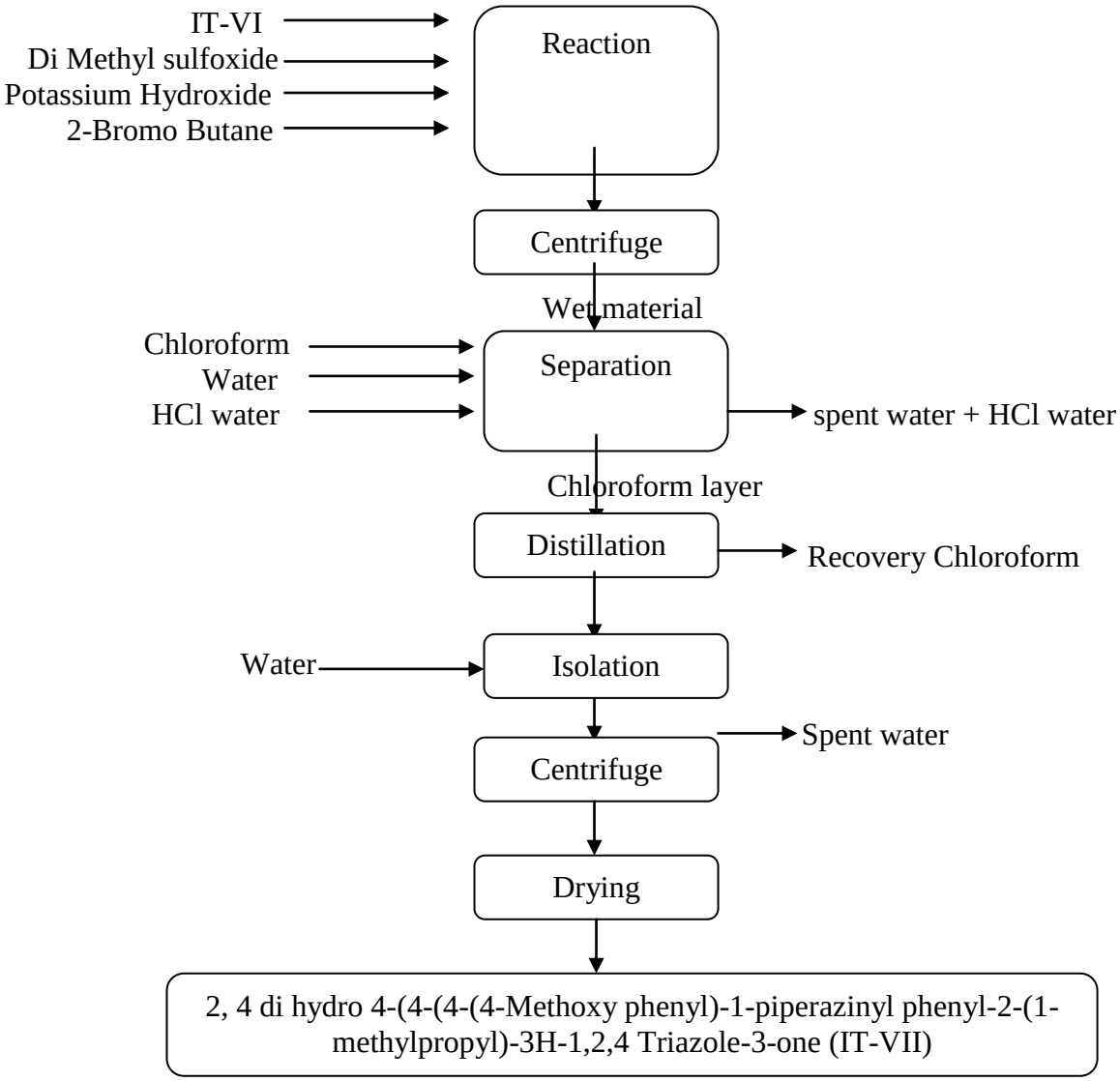
Stage wise flow charts

Stage IT-VI



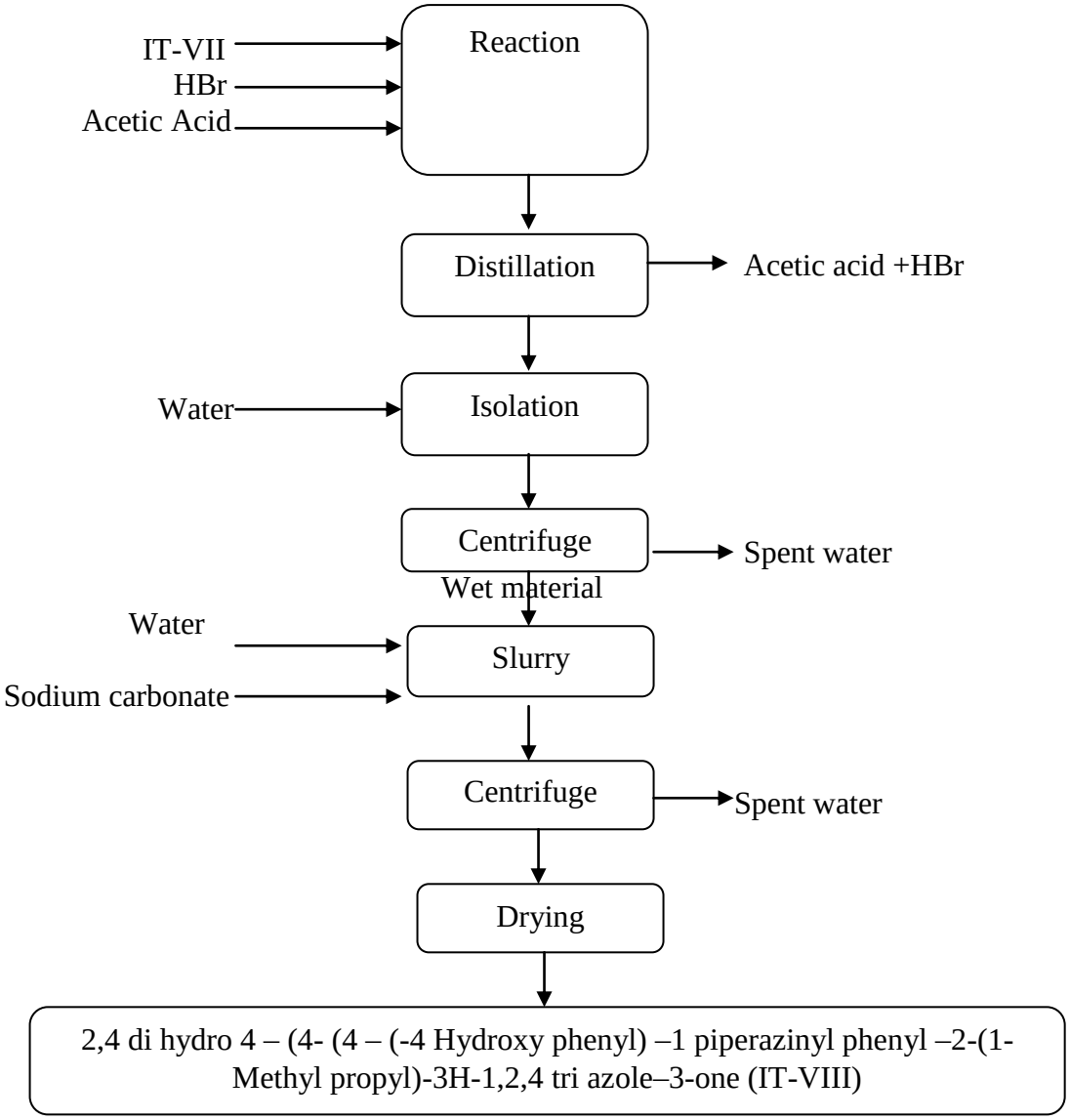
ITRACONAZOLE

Stage IT-VII



ITRACONAZOLE

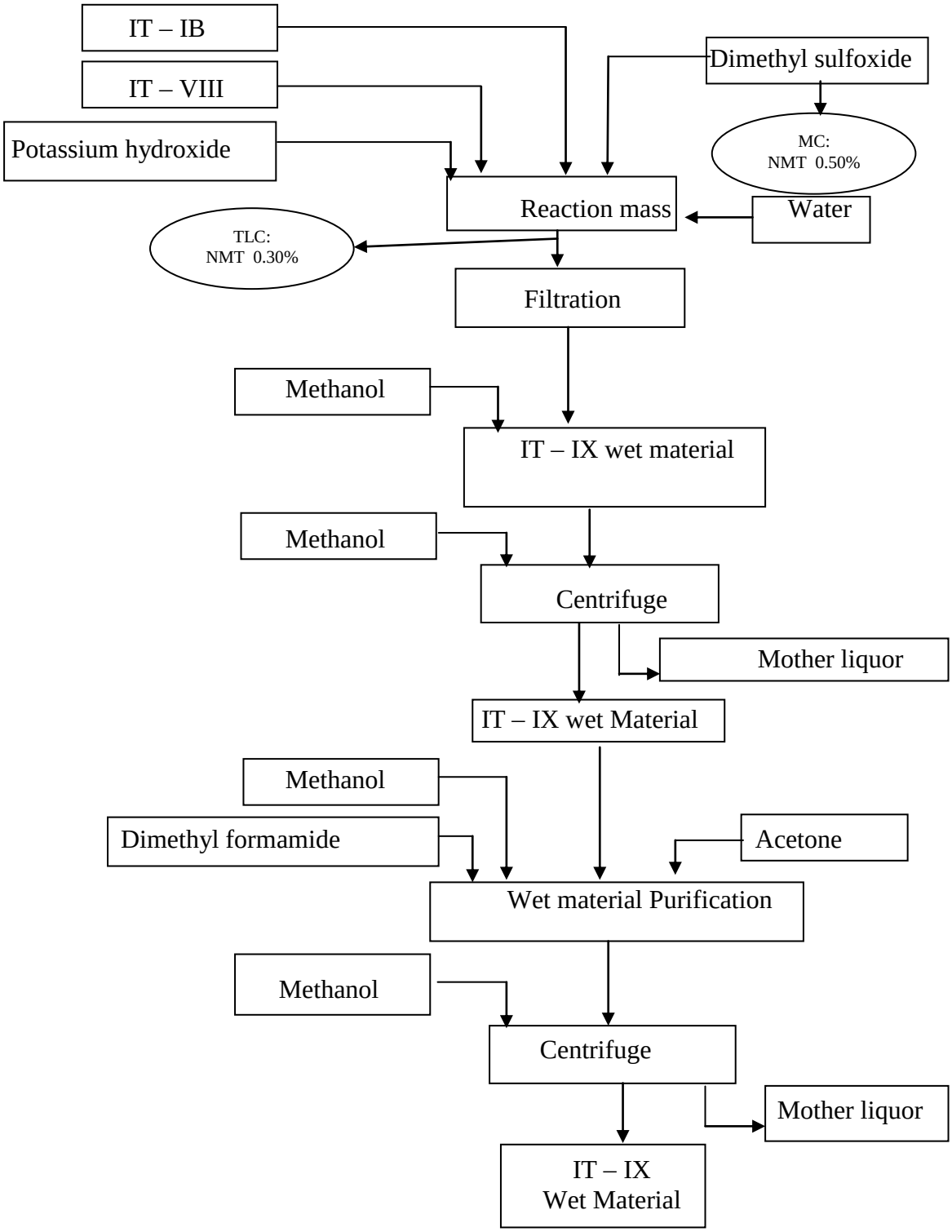
Stage IT-VIII



UNIT-IV

ITRACONAZOLE FLOW CHART

FLOW CHART FOR STAGE – IX



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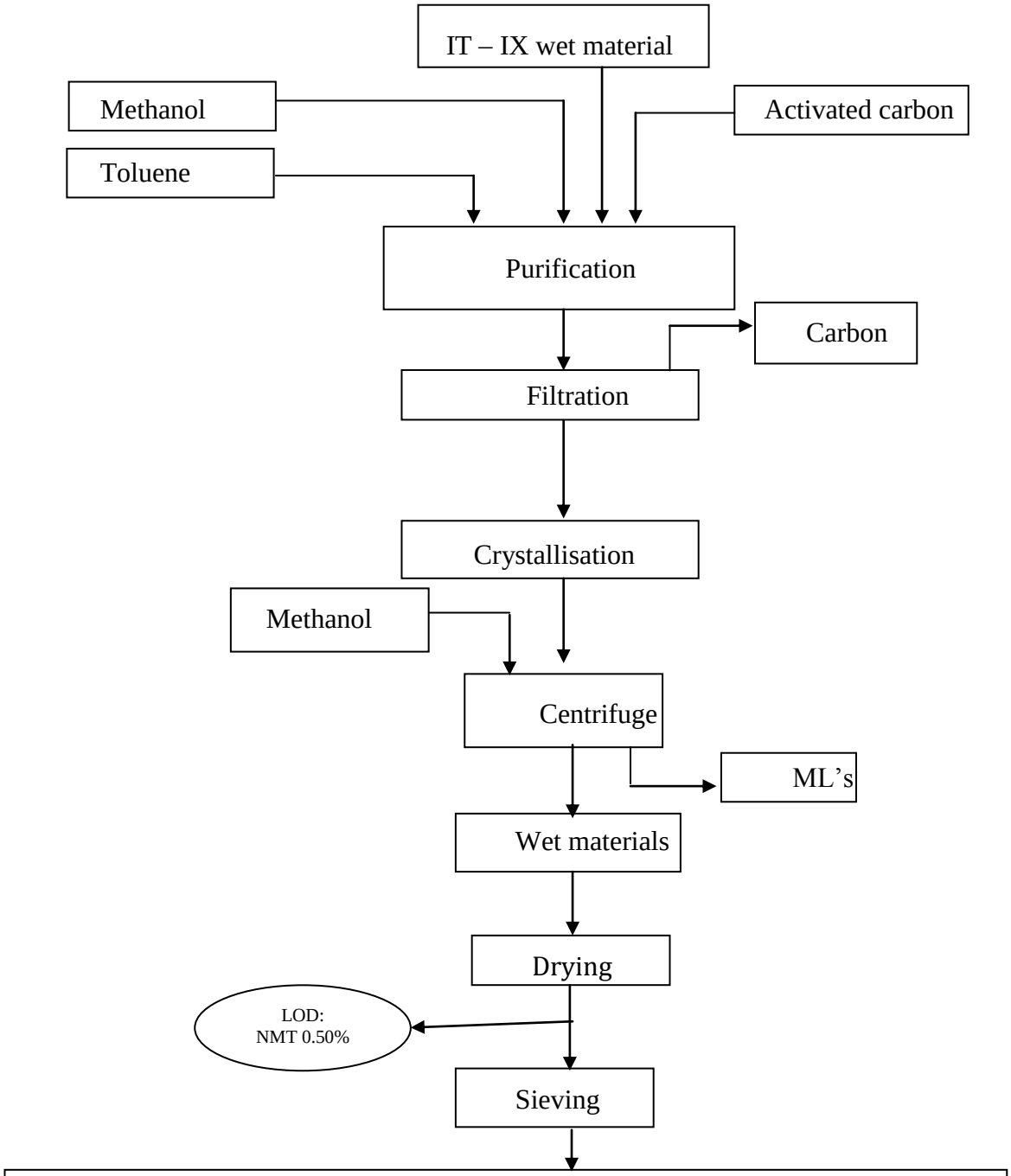
UNIT-IV

ITRACONAZOLE FLOW CHART

FLOW CHAT FOR STAGE: IT – X



4 -[4 -[4 - [4 - [[Cis –2 - (2,4 - dichloro phenyl) –2 - (1H - 1,2,4 - Triazole – 1-yl methyl) -1,3 - dioxolan – 4 -yl] methoxy] phenyl] piperazin -1-yl] phenyl] – 2 - [(1RS) -1- methyl propyl] - 2,4 - dihydro –3H-1,2,4 – Triazole -3-one.
(**Itraconazole**)

IT-IA(3 TONS PER MONTH)

STAGE	NO BATCH FOR MONTH	EFFLUENT FOR BATCH (QTY LTS)	RESIDUE FOR BATCH (QTY KG)	SOLIDE WASTE (QTY KG)	SPENT CORBON (QTY KG)
IT-IA (600 KG CBB)	12	4000	---	---	---

IT-IB (1 TONS PER MONTH)

STAGE	NO BATCH FOR MONTH	EFFLUENT FOR BATCH (QTY LTS)	RESIDUE FOR BATCH (QTY KG)	SOLIDE WASTE (QTY KG)	SPENT CORBON (QTY KG)
IT-IB (250 KG IT-IA)	4	1000	---	---	---

IT-III + VI (3 TONS PER MONTH)

STAGE	NO BATCH FOR MONTH	EFFLUENT FOR BATCH (QTY LTS)	RESIDUE FOR BATCH (QTY KG)	SOLIDE WASTE (QTY KG)	SPENT CORBON (QTY KG)
IT-III +VI (200 KG IT-II)	18	1000	---	---	---

IT-VII

STAGE	NO BATCH FOR MONTH	EFFLUENT FOR BATCH (QTY LTS)	RESIDUE FOR BATCH (QTY KG)	SOLIDE WASTE (QTY KG)	SPENT CORBON (QTY KG)
IT-VII (200 KG IT-VI)	7	1000	---	---	---

IT-VIII(1 TONS PER MONTH)

STAGE	NO BATCH FOR MONTH	EFFLUENT FOR BATCH (QTY LTS)	RESIDUE FOR BATCH (QTY KG)	SOLIDE WASTE (QTY KG)	SPENT CORBON (QTY KG)
IT-VIII (150 KG IT-VII)	9	1000	---	---	---

IT-IX

STAGE	NO BATCH FOR MONTH	EFFLUENT FOR BATCH (QTY LTS)	RESIDUE FOR BATCH (QTY KG)	SOLIDE WASTE (QTY KG)	SPENT CORBON (QTY KG)
IT-IX (100 KG IT-VIII)	15	1000			

IT-X (2 TONS PER MONTH)

STAGE	NO BATCH FOR MONTH	EFFLUENT FOR BATCH (QTY LTS)	RESIDUE FOR BATCH (QTY KG)	SOLIDE WASTE (QTY KG)	SPENT CORBON (QTY KG)
IT-X (200 KG IT-IX)	15	1000			

sms LifeSciences UNIT-IV	**ACYCLOVIR** **ROS & FLOW CHRT**

BRIEF DESCRIPTION OF THE MANUFACTURING PROCESS OF ACYCLOVIR:

Stage I Guanine is acylated with acetic anhydride to get Diacetyl Guanine

Stage II Diosalane is reacted with acetic anhydride to get Dioxalane diacetate.

Stage III Diacetyl Guanine is condensed with dioxalane diacetate to get N – acetyl compound which on treatment with ammonia gives Acyclovir and is dried.

LIST OF RAW MATERIAL:

STAGE : I Raw material List :

S.No	Raw Material
01.	Guanine
02.	Acetic Anhydride
03.	Acetone
04.	Water

STAGE : II Raw material List :

S.No	Raw Material
01.	Stage – I Product
02.	Diacetyl Acetate
03.	Toulene
04.	Acetone

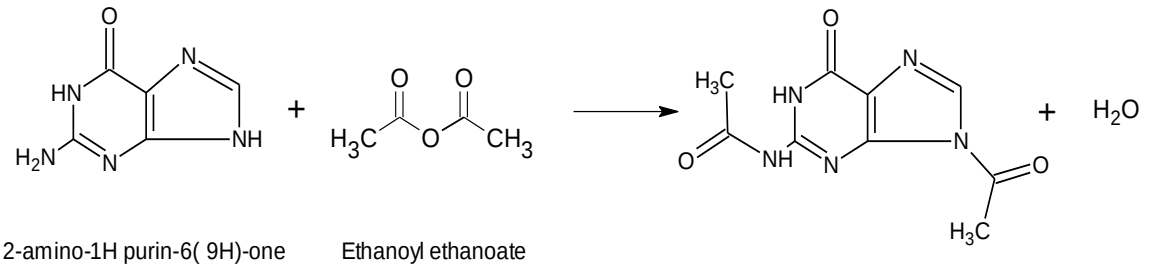
STAGE : III Raw material List :

S.No	Raw Material
01.	Stage –II Product
02.	Acetone
03.	Carbon

UNIT-IV

ACYCLOVIR
ROS & FLOW CHRT

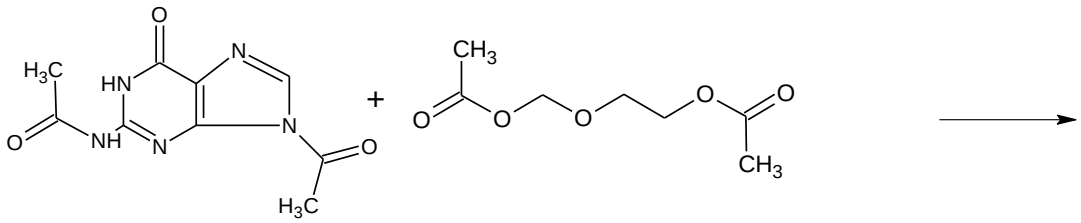
Stage - I



2-amino-1H purin-6(9H)-one — Ethanoyl ethanoate

Guanine — **Acetic Anhydride** — **Diacetyl guanine** — **Water**

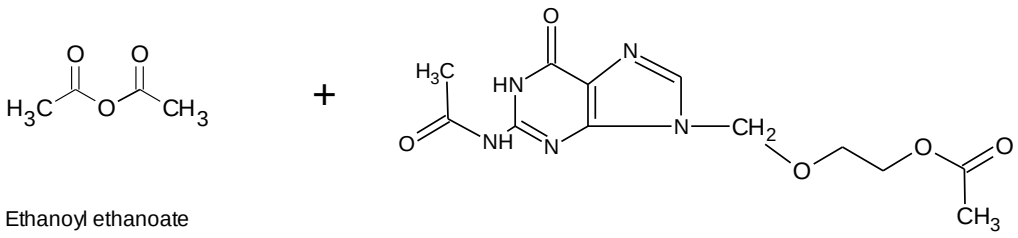
Stage – II



Diacetyl guanine

2-oxo-1, 4--butanediol diacetate

Dioxalane diacetate



Ethanoyl ethanoate

Acetic Anhydride

Stage -II product

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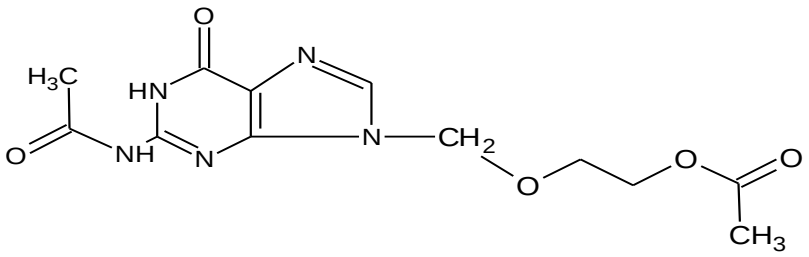
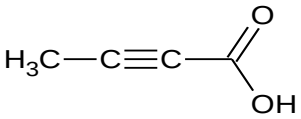
Stage – III

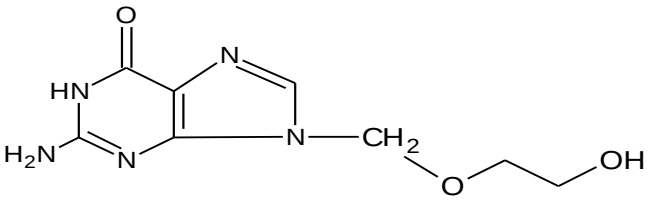


Stage -II product



2- Butynoic acid

+



9-(2-hydroxyethoxymethyl)guanine

Acyclovir

UNIT-IV

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