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Review IJCSCR

Comprehensive Manufacturing Processes, Chemical Syntheses, and Mass Balance Analyses for Ten Essential Fungicides in Agrochemical Production

Ashok K. Rathoure[1,*], Anika Rathoure[2]

Abstract

This research paper presents a detailed examination of the manufacturing processes for ten key fungicides used in agrochemical applications: Amisulbrom, Azoxystrobin, Benzovindiflupyr, Bixafen, Boscalid, Carboxin, Carpropamid, Cyazofamid, Cyclobutrifluram, and Cyflufenamid. For each fungicide, the synthesis pathways are outlined, including step-by-step chemical reactions, basic chemistry, reactant stoichiometries, and mass calculations based on a standardized production scale of 1000 kg of the final product. Mass balances are provided to account for inputs (reactants, solvents, and auxiliaries) and outputs (products, by-products, recoveries, losses, and effluents), ensuring compliance with environmental and efficiency considerations. The processes highlight key reactions such as sulfonylation for Amisulbrom, multi-step condensations and substitutions for Azoxystrobin, and amide couplings for others like Cyclobutrifluram and Cyflufenamid. Furthermore, this study provides a comparative evaluation of synthetic methodologies, emphasizing yield optimization, reaction selectivity, and purification techniques. Advanced catalytic systems, green solvents, and continuous-flow synthesis approaches are discussed for their potential to enhance sustainability and reduce waste generation. The assessment also includes an energy balance analysis, addressing reaction temperature profiles, solvent recovery, and energy consumption per production cycle. By integrating green chemistry principles, the work proposes feasible modifications to conventional routes to minimize toxic reagent use and effluent load. The economic and environmental implications of each process are also evaluated, providing insight into industrial feasibility and regulatory compliance. Overall, this study contributes to advancing eco-efficient fungicide manufacturing, promoting innovation in chemical process engineering, and supporting the global shift toward cleaner agrochemical production technologies.

Keywords: Agrochemicals, fungicides, manufacturing processes, mass balance, route of synthesis, yield optimization

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INTRODUCTION

Fungicides play a critical role in modern agriculture by protecting crops from fungal pathogens, thereby ensuring food security and enhancing agricultural productivity [1, 2]. The global demand for effective and environmentally sustainable agrochemicals has driven significant advancements in the synthesis and production of fungicides [3–6]. This research paper focuses on the manufacturing processes of ten essential fungicides (Table 1) – Amisulbrom, Azoxystrobin, Benzovindiflupyr, Bixafen, Boscalid, Carboxin, Carpropamid, Cyazofamid, Cyclobutrifluram, and Cyflufenamid – widely used for their efficacy in

controlling a broad spectrum of plant diseases [5–10]. These fungicides belong to diverse chemical classes, including triazole sulfonamides, strobilurins, carboxamides, and others, each requiring unique synthetic pathways and process optimization to achieve high yields and purity at an industrial scale. The production of these agrochemicals involves complex organic reactions, such as sulfonylation, amide coupling, and catalytic cross-couplings, alongside careful management of reactants, solvents, and by-products to ensure economic viability and environmental compliance [8–13]. This study provides a detailed examination of the chemical synthesis routes, stoichiometric calculations, and mass balance analyses for producing 1000 kg of each fungicide, emphasizing resource efficiency, waste minimization, and scalability. By integrating insights from existing literature [1–13], this paper aims to contribute to the optimization of industrial fungicide production, supporting sustainable agricultural practices and addressing the challenges of large-scale agrochemical manufacturing.

Table 1. List of 10 fungicides with CAS.

S. N.	Name of Fungicides	CAS
1	Amisulbrom	348635-87-0
2	Azoxystrobin	131860-33-8
3	Benzovindiflupyr	1072957-71-1
4	Bixafen	581809-46-3
5	Boscalid	188425-85-6
6	Carboxin	5234-68-4
7	Carpropamid	104030-54-8
8	Cyazofamid	120116-88-3
9	Cyclobutrifluram	1460292-16-3
10	Cyflufenamid	180409-60-3

PROCESS DESCRIPTION

Amisulbrom Cas# 348635-87-0

Manufacturing Process

3-bromo-6-fluoro-2-methyl-1H-indole reacts with 1-(dimethylsulfamoyl)-1,2,4-triazole-3-sulfonyl chloride to form Amisulbrom (Figure 1).

Basic Chemistry

3-bromo-6-fluoro-2-methyl-1H-indole (MF: C_9H_7BrFN MW: 228.06 g/mol) reacts with 1-(dimethylsulfamoyl)-1,2,4-triazole-3-sulfonyl chloride (MF: $C_4H_7ClN_4O_4S_2$ MW: 274.7 g/mol) to form Amisulbrom (MF: $C_{13}H_{13}BrFN_5O_4S_2$ MW: 466.3 g/mol).

$$C_9H_7BrFN + C_4H_7ClN_4O_4S_2 + KOH \rightarrow C_{13}H_{13}BrFN_5O_4S_2 + KCl + H_2O$$

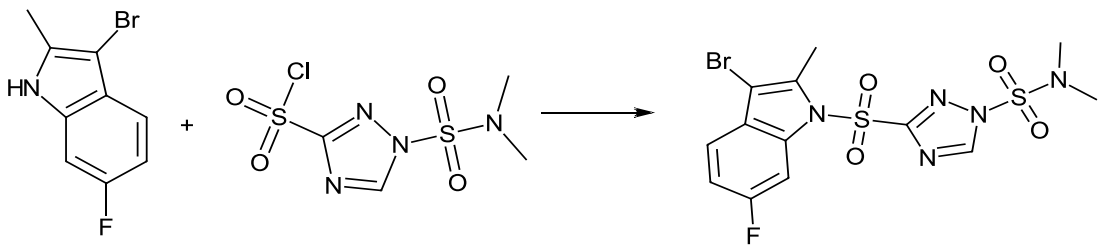


Figure 1. Route of synthesis of Amisulbrom.

- *Reactant 1:* 3-bromo-6-fluoro-2-methyl-1H-indole.
- *Molecular Formula (MF):* C_9H_7BrFN.

- *Molecular Weight (MW):* 228.06 g/mol.
- *Reactant 2:* 1-(dimethylsulfamoyl)-1,2,4-triazole-3-sulfonyl chloride.
- *Molecular Formula (MF):* $C_4H_7ClN_4O_4S_2$.
- *Molecular Weight (MW):* 274.7 g/mol.
- *Product*: Amisulbrom.
- *Molecular Formula (MF):* $C1_3H_{13}BrFN_5O_4S_2$.
- *Molecular Weight (MW):* 466.3 g/mol.

Moles of Amisulbrom required:

- *Mass of Amisulbrom:* 1000 kg = 1,000,000 g.

$$\text{Moles of Amisulbrom: } \frac{1{,}000{,}000\,\text{g}}{466.3\,\text{g/mol}} \approx 2145.23\,\text{mol}$$

Reactant Quantities

3-bromo-6-fluoro-2-methyl-1H-indole

- *Stoichiometry:* 1:1 ratio with Amisulbrom.
- *Moles Required:* 2145.23 mol.
- *Mass Required:* 2145.23 mol × 228.06 g/mol ≈ 489,125.74 g = 489.13 kg.

1-(dimethylsulfamoyl)-1,2,4-triazole-3-sulfonyl chloride

- *Stoichiometry:* 1:1 ratio with Amisulbrom.
- *Moles Required:* 2145.23 mol.
- *Mass Required*: 2145.23 mol × 274.7 g/mol ≈ 589,118.18 g = 589.12 kg.
- *Mass of KOH* = 2145.23 mol × 56.1 g/mol ≈ 120,369.39 g = 120.37 kg.
- *Mass of KCl Produced* = 2145.23 mol × 74.55 g/mol ≈ 159,910.79 g = 159.91 kg.

The mass balance of Amisulbrom is detailed in Table 2 below.

Table 2. Mass balance of Amisulbrom.

Input (kg)		**Output (kg)**		**Remarks**
3-bromo-6-fluoro-2-methyl-1H-indole	489.13	Amisulbrom	1000	Product
1-(dimethylsulfamoyl)-1,2,4-triazole-3-sulfonyl chloride	589.12	KCl 30%	533	Rule 9
Dimethylformamide	5500	DMF	5362	Recovered
Water for KCl	373	DMF	138	Loss
Water	8250	Effluent	8288.62	To ETP
KOH	120.37	Residue	–	Rule 9
Total	15321.62	*Total*	15321.62	–

Azoxystrobin Cas# 131860-33-8

Manufacturing Process

- *Step 1:* 2-hydroxybenzamide form under high-temperature conditions to 2-hydroxy benzonitrile.
- *Step 2:* 4-hydroxy-1H-pyrimidin-6-one reacts with phosphoryl trichloride to form 4,6-dichloropyrimidine.
- *Step 3:* 3H-1-benzofuran-2-one reacts with trimethoxymethane to form (3E)-3-(methoxymethylidene)-1-benzofuran-2-one.
- *Step 4:* (3E)-3-(methoxymethylidene)-1-benzofuran-2-one reacts with 4,6-dichloropyrimidine to form methyl (E)-2-[2-(6-chloropyrimidin-4-yl) oxyphenyl]-3-methoxyprop-2-enoate.
- *Step 5:* methyl (E)-2-[2-(6-chloropyrimidin-4-yl) oxyphenyl]-3-methoxyprop-2-enoate reacts with 2-hydroxybenzonitrile to produce Azoxystrobin.

Basic Chemistry (Figure 2)

- *Step 1:* 2-hydroxybenzamide (MF: $C_7H_7NO_2$ MW: 137.14 g/mol) formed under high-temperature conditions to 2-hydroxybenzonitrile (MF: C_7H_5NO MW: 119.12 g/mol).

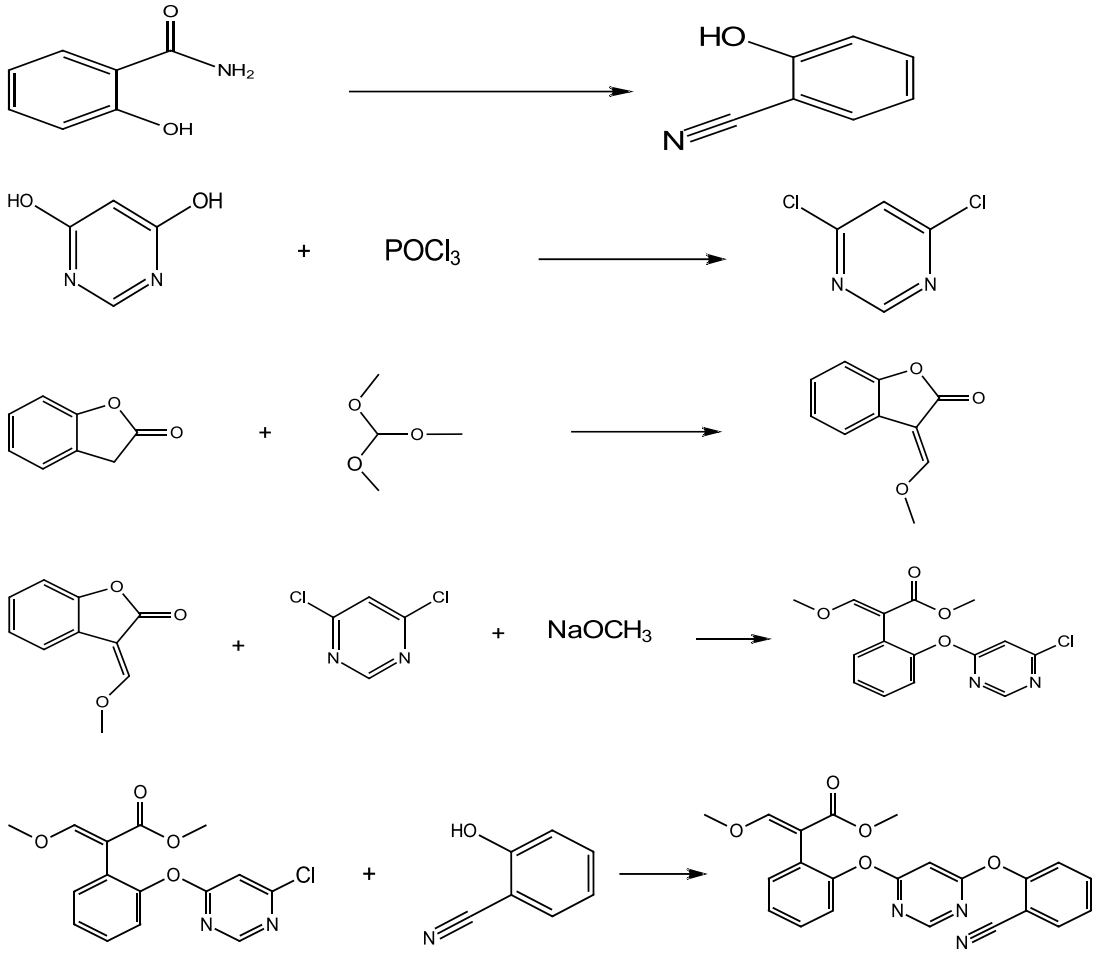


Figure 2. Route of synthesis of azoxystrobin.

$C_7H_7NO_2 \rightarrow C_7H_5NO + H_2O$

- *Step 2:* 4-hydroxy-1H-pyrimidin-6-one (MF: $C_4H_4N_2O_2$ MW: 112.09 g/mol) reacts with phosphoryl trichloride (MF: Cl_3OP MW: 153.33 g/mol) to form 4,6-dichloropyrimidine (MF: $C_4H_2Cl_2N_2$ MW: 148.98 g/mol).

$C_4H_4N_2O_2 + Cl_3OP \rightarrow C_4H_2Cl_2N_2 + HCl + H_2O$

- *Step 3:* 3H-1-benzofuran-2-one (MF: $C_8H_6O_2$ MW: 134.13 g/mol) reacts with trimethoxymethane (MF: $C_4H_{10}O_3$ MW: 106.12 g/mol) to form (3E)-3-(methoxymethylidene)-1-benzofuran-2-one (MF: $C_{10}H_8O_3$ MW: 176.17 g/mol).

$C_8H_6O_2 + C_4H_{10}O_3 \rightarrow C_{10}H_8O_3 + CH_3OH$

- *Step 4:* (3E)-3-(methoxymethylidene)-1-benzofuran-2-one (MF: $C_{10}H_8O_3$ MW: 176.17 g/mol) reacts with 4,6-dichloropyrimidine (MF: $C_4H_2Cl_2N_2$ MW: 148.98 g/mol) and sodium methanolate (MF: CH_3NaO MW: 54.024 g/mol) to form methyl (E)-2-[2-(6-chloropyrimidin-4-yl) oxyphenyl]-3-methoxyprop-2-enoate (MF: $C_{15}H_{13}ClN_2O_4$ MW: 320.73 g/mol).

$C_{10}H_8O_3 + C_4H_2Cl_2N_2 + CH_3NaO \rightarrow C_{15}H_{13}ClN_2O_4 + NaCl$

- *Step 5:* methyl (E)-2-[2-(6-chloropyrimidin-4-yl) oxyphenyl]-3-methoxyprop-2-enoate (MF: $C_{15}H_{13}ClN_2O_4$ MW: 320.73 g/mol) reacts with 2-hydroxybenzonitrile (MF: C_7H_5NO MW: 119.12 g/mol) to produce Azoxystrobin (MF: $C_{22}H_{17}N_3O_5$ MW: 403.4 g/mol).

$C_{15}H_{13}ClN_2O_4 + C_7H_5NO \rightarrow C_{22}H_{17}N_3O_5 + HCl$

Step 1: Formation of 2-Hydroxybenzamide to 2-Hydroxybenzonitrile

- Molecular weight (MW) of 2-Hydroxybenzamide ($C_7H_7NO_2$) = 137.14 g/mol.
- MW of 2-Hydroxybenzonitrile (C_7H_5NO) = 119.12 g/mol.
- MW of Water (H_2O) = 18.02 g/mol.

Mole Ratio

1 mole of $C_7H_7NO_2$ produces 1 mole of C_7H_5NO and 1 mole of H_2O.

Mass Calculation

To produce 1 ton (1000 kg) of Azoxystrobin in the final step, it is required to determine the amount of 2-Hydroxybenzonitrile needed through the reactions.

In Step 5, 1 mole of 2-Hydroxybenzonitrile (119.12 g) is used to produce 1 mole of Azoxystrobin (403.4 g). Therefore, to produce 1000 kg of Azoxystrobin:

$$\text{Moles of Azoxystrobin required} = \frac{1000,000\,\text{g}}{403.4\,\text{g/mol}} = 2478.71\,\text{moles}$$

Thus, there is a need for 2478.71 moles of 2-Hydroxybenzonitrile.

The corresponding mass of 2-Hydroxybenzonitrile:

- Mass of 2-Hydroxybenzonitrile = 2478.71 moles × 119.12 g/mol = 295,243g = 295.24 kg.

This amount of 2-Hydroxybenzonitrile comes from the conversion of 2-Hydroxybenzamide.

The mass of 2-Hydroxybenzamide required:

- Mass of 2-Hydroxybenzamide = 2478.71 moles × 137.14 g/mol = 339,887g = 339.89 kg.

By-Product

Water (H_2O) is produced in this step.

- Mass of water = 2478.71 moles × 18.02 g/mol = 44,636 g = 44.64 kg

Step 2: Reaction of 4-Hydroxy-1H-pyrimidin-6-one with Phosphoryl Trichloride

- MW of 4-Hydroxy-1H-pyrimidin-6-one ($C_4H_4N_2O_2$) = 112.09 g/mol.
- MW of Phosphoryl Trichloride (Cl_3OP) = 153.33 g/mol.
- MW of 4,6-Dichloropyrimidine ($C_4H_2Cl_2N_2$) = 148.98 g/mol.
- MW of HCl = 36.46 g/mol.
- MW of Phosphoryl Oxychloride ($POCl_3$) = 153.33 g/mol.

Mole Ratio

1 mole of $C_4H_4N_2O_2$ reacts with 1 mole of Cl_3OP to produce 1 mole of $C_4H_2Cl_2N_2$, 1 mole of HCl.

The amount of 4,6-Dichloropyrimidine required for Step 4 is calculated similarly.

Mass of 4,6-Dichloropyrimidine = 2478.71 moles × 148.98 g/mol = 369,051 g = 369.05 kg.

Reactant Masses

To produce this much $C_4H_2Cl_2N_2$,

- Mass of $C_4H_4N_2O_2$ = 2478.71 moles × 112.09 g/mol = 277,751 g = 277.75 kg.
- Mass of Cl_3OP = 2478.71 moles × 153.33 g/mol = 380,045 g = 380.05 kg.

By-Products

HCl by-products are produced in this step.

- Mass of HCl = 2478.71 moles × 36.46 g/mol = 90,398 g = 90.4 kg.

Step 3: Reaction of 3H-1-Benzofuran-2-one with Trimethoxymethane

- MW of 3H-1-Benzofuran-2-one ($C_8H_6O_2$) = 134.13 g/mol.
- MW of Trimethoxymethane ($C_4H_{10}O_3$) = 106.12 g/mol.
- MW of (3E)-3-(Methoxymethylidene)-1-benzofuran-2-one ($C_{10}H_8O_3$) = 176.17 g/mol.
- MW of Methanol (CH_3OH) = 32.04 g/mol.

Mole Ratio

1 mole of $C_8H_6O_2$ reacts with 1 mole of $C_4H_{10}O_3$ to produce 1 mole of $C_{10}H_8O_3$ and 1 mole of CH_3OH.

The mass of (3E)-3-(Methoxymethylidene)-1-benzofuran-2-one needed for Step 4 is calculated based on 1 ton of Azoxystrobin production.

Mass of (3E)-3-(Methoxymethylidene)-1-benzofuran-2-one = 2478.71moles × 176.17 g/mol

= 436,245 g = 436.25 kg.

Reactant Masses

Mass of 3H-1-Benzofuran-2-one = 2478.71 moles × 134.13 g/mol = 332,438 g = 332.44 kg.

- Mass of Trimethoxymethane = 2478.71 moles × 106.12 g/mol = 263,002 g = 263.00 kg.

By-Products

Methanol (CH_3OH) is produced as a by-product.

- Mass of Methanol = 2478.71 moles × 32.04 g/mol = 79,421 g = 79.42 kg

Step 4: Reaction of (3E)-3-(Methoxymethylidene)-1-benzofuran-2-one with 4,6-Dichloropyrimidine

- MW of (3E)-3-(Methoxymethylidene)-1-benzofuran-2-one ($C_{10}H_8O_3$) = 176.17 g/mol.
- MW of 4,6-Dichloropyrimidine ($C_4H_2Cl_2N_2$) = 148.98 g/mol.
- MW of Methyl (E)-2-[2-(6-chloropyrimidin-4-yl) oxyphenyl]-3-methoxyprop-2-enoate ($C_{15}H_{13}ClN_2O_4$) = 320.73 g/mol.
- MW of NaCl = 58.44 g/mol.
- MW of $NaOCH_3$ = 54.024 g/mol.

Mole Ratio

1 mole of $C_{10}H_8O_3$ reacts with 1 mole of $C_4H_2Cl_2N_2$ and 1 mole $NaOCH_3$ to produce 1 mole of $C_{15}H_{13}ClN_2O_4$ and 1 mole of NaCl.

Mass of Reactants

For 1 ton of Azoxystrobin production, there is a need of 2478.71 moles of the product ($C_{15}H_{13}ClN_2O_4$).

Thus, the reactants needed are:

Mass of (3E)-3-(Methoxymethylidene)-1-benzofuran-2-one = 2478.71 moles × 176.17 g/mol = 436,245 g = 436.25 kg.

Mass of 4,6-Dichloropyrimidine = 2478.71 moles × 148.98 g/mol = 369,051 g = 369.05 kg.

Mass of Sodium methanolate = 2478.71 moles × 54.024 g/mol = 133,909 g = 133.90 kg.

By-Product

NaCl is produced as a by-product.

Mass of NaCl = 2478.71 moles × 58.44 g/mol = 144,855 g = 144.85 kg.

Step 5: Final Reaction to Form Azoxystrobin

- MW of Methyl (E)-2-[2-(6-chloropyrimidin-4-yl) oxyphenyl]-3-methoxyprop-2-enoate ($C_{15}H_{13}ClN_2O_4$) = 320.73 g/mol.
- MW of 2-Hydroxybenzonitrile (C_7H_5NO) = 119.12 g/mol.
- MW of Azoxystrobin ($C_{22}H_{17}N_3O_5$) = 403.4 g/mol.
- MW of HCl = 36.46 g/mol.

Mole Ratio

1 mole of $C_{15}H_{13}ClN_2O_4$ reacts with 1 mole of C_7H_5NO to produce 1 mole of $C_{22}H_{17}N_3O_5$ and 1 mole of HCl.

Mass of Reactants

For 1 ton of Azoxystrobin production (1000 kg or 1000,000 g), we need 2478.71 moles.

Mass of Methyl (E)-2-[2-(6-chloropyrimidin-4-yl) oxyphenyl]-3-methoxyprop-2-enoate = 2478.71 moles × 320.73 g/mol = 795,233 g = 795.23 kg.

Mass of 2-Hydroxybenzonitrile = 2478.71 moles × 119.12 g/mol = 295,243 g = 295.24 kg.

By-Product

HCl is produced as a by-product.

Mass of HCl = 2478.71 moles × 36.46 g/mol = 90,398 g = 90.4 kg.

The mass balance of Azoxystrobin is detailed in Table 3 below.

Table 3. Mass balance of azoxystrobin.

Input (kg)		Output (kg)		Remarks
2-Hydroxybenzamide	339.89	Azoxystrobin	1000	Product.
4-Hydroxy-1H-pyrimidin-6-one	277.75	Spent acetic acid	325	Rule 9.
Phosphoryl Trichloride	380.05	HCl 30%	613	Rule 9.
3H-1-Benzofuran-2-one	332.44	$NaHSO_3$ 25%	1049	Rule 9.
Trimethoxymethane	263	Methanol	79.42	By-Product.
4,6-Dichloropyrimidine	369.05	Toluene	7313	Recovered.
2-Hydroxybenzonitrile	295.24	Toluene	187	Loss.
Sodium methanolate	133.90	Effluent	11250	To ETP.

Toluene	7500	NaCl	494	To TSDF.
Water	11250	Residue	441.9	Rule 9.
Water for HCl	421		–	
Acetic anhydride	300		–	
Thionyl chloride	300		–	
K_2CO_3	380		–	
NaOH 48%	210		–	
Total	*22752.32*	*Total*	*22752.32*	

Benzovindiflupyr Cas# 1072957-71-1

Manufacturing Process

Benzovindiflupyr is prepared in 3 steps.

Step 1: Preparation of 5-chloro-9- dichloromethylene-1, 2, 3, 4-Tetrahydro-1, 4-methano-naphthalene

5-chloro-1,2,3,4-tetrahydro-1,4-methano-naphthalen-9-one (Keto derivative) reacts with Triphenyl phosphine in presence of CCl_4 gives pure white solid.

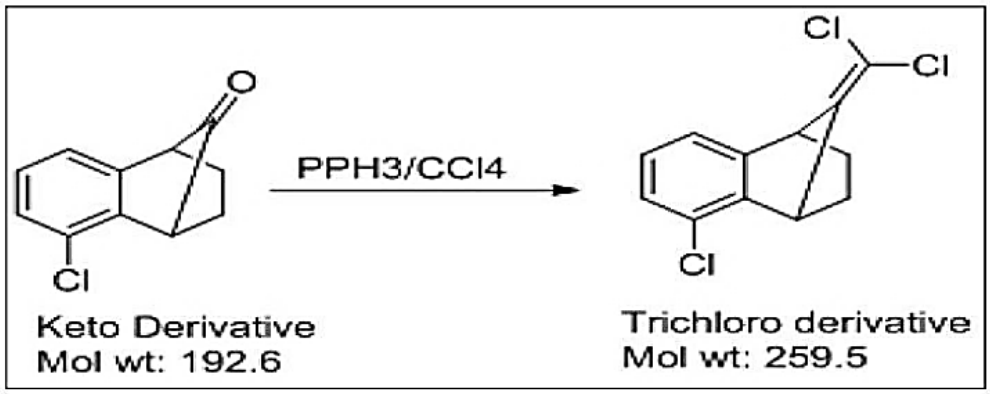
Step 2: Preparation of 9-dichloromethylene-1, 2, 3, 4-tetrahvdro-1, 4-methano-naphthalene 5-ylamine

5-chloro-9-dichloromethylene-1,2,3,4-tetrahydro-1, 4-methano-naphthalene converted into 9-dichloromethylene-1,2,3,4-tetrahvdro-1, 4-methanonaphthalen5-ylamine in presence of sodium tert butoxide in Dimethyl ether and palladium acetate catalyst.

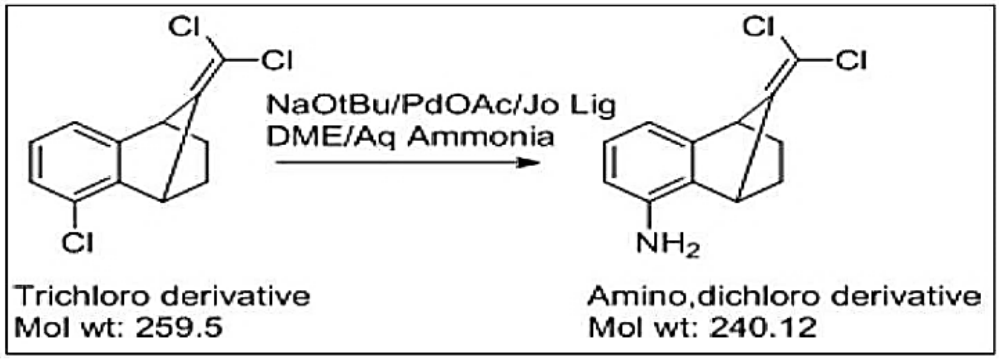
Step 3: Preparation of Benzovindiflupyr

The pure product, Benzovindiflupyr, is formed by the coupling of 3′(RS)-(9-dichloromethylene-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl) amine with 3-(difluoromethyl)-1H-pyrazole-4-carbonyl chloride in the presence of triethylamine Figure 3.

Step: 1



Step: 2



Step: 3

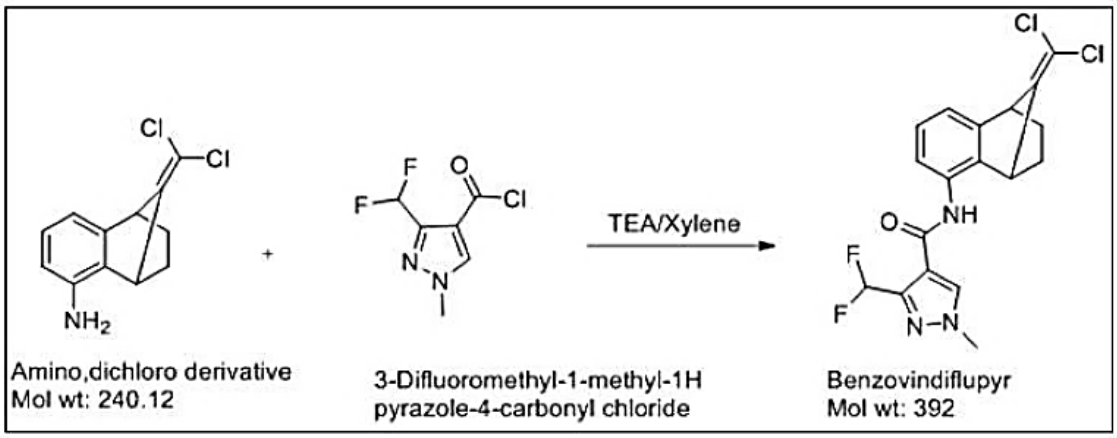


Figure 3. Route of synthesis of Benzovindiflupyr.

The mass balance of Benzovindiflupyr is given in Table 4.

Table 4. Mass balance of Benzovindiflupyr.

Raw Materials	**Kg**		**Product/By-Product**	**Kg**
5-Chloro-1,2,3,4-tetrahydro-1,4-methano-naphthalen-9-one	850		Benzovindiflupyr	1,000
Triphenylphosphine	2,678		R. Acetonitrile	6,442
CCl_4	1,630		R. MDC	10,725
Sodium tertiary butoxide	730		R. Acetone	5,155
Palladium acetate	34		R. Cyclohexane	5,059
3-Difluoromethyl-1H-pyrazole-4-carbonyl chloride	320		R. Dimethyl ether	10,137
Tetraethyl amine	312	→	R. Xylene	5,184
Methylcyclohexane	2,700		R. Methylcyclohexane	2,192
Xylene	5,400		Aq. Effluent	21,854
Ammonia gas	1,760		Residue	2,294
Josiphos ligand	30			
Acetonitrile	6,990			
MDC	11,290			
Acetone	11,290			
Cyclohexane	5,270			
Dimethyl ether	10,560			
Water	14,294			
Total Input	*70,442*		*Total Output*	*70,442*

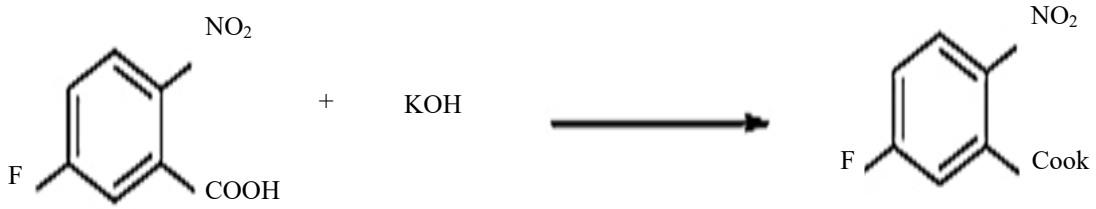
Bixafen Cas# 581809-46-3

Manufacturing Process

Bixafen is prepared in three steps as follows:

Step1: Preparation of potassium salt of 5-fluoro-2-nitro-benzoic acid (Figure 4)

5-Fluoro-2-nitrobenzoic acid was reacted with potassium hydroxide to prepare the potassium salt of 5-fluoro-2-nitrobenzoic acid.



5-Fluoro-2-nitobenzoic Acid

M.F: $C_7H_4FNO_4$

M.W: 185.11

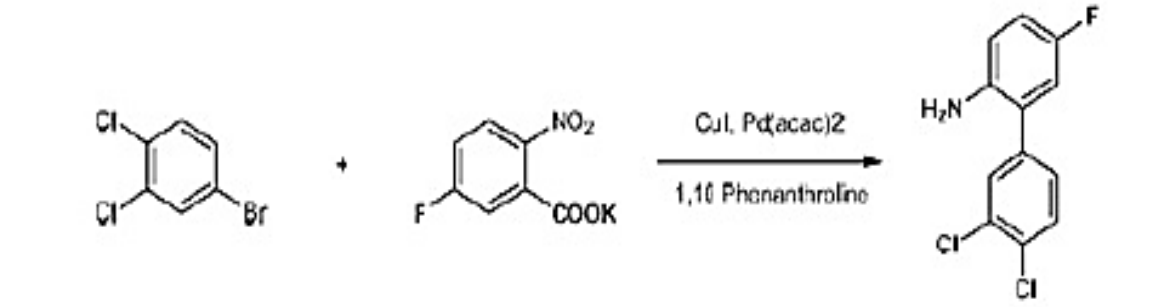
Potassium Salt

5-Fluoro-2-nitobenzoic Acid

M.F: $C_7H_3FKNO_4$,

M.W: 223.20

Figure 4. Preparation of potassium salt of 5-fluoro-2-nitro-benzoic acid (Figure 5).



3,4-dichlorobromobenzene

M.F : $C_6H_3BrCl_2$

M.W : 225.89

Potassium salt
5-Fluoro-2-nitobenzoic acid
M.F : $C_7H_3FKNO_4$
M.W : 223.20

2-(3,4-dichlorophenyl)-4-fluoro-aniline
M.F : $C_{12}H_8Cl_2FN$
M.W : 256.10

Figure 5. Preparation of 2-(3,4-dichlorophenyl)-4-fluoro-aniline.

Table X. xxxxx xxxxxxxxxxxxxx.

Raw Materials	**Kg**		**Product / By-Product**	**Kg**
2-nitro-5-fluorobenzoic acid	1101		Step-1 product	895
Potassium hydroxide	780	→	Ethanol	11529
Ethanol	12010		Residue	481
			Aqueous MLR	986
Input	*13891*		*Output*	*13891*

Step 2: Preparation of 2-(3,4-dichlorophenyl)-4-fluoro-aniline

The Step-1 product was reacted with 3,4-dichlorobromobenzene under catalysis by copper iodide, palladium acetate, and phenanthroline to obtain the Step-2 product.

Basic Reaction & Mass Balance

Step 3: Preparation of Bixafen (Figure 6)

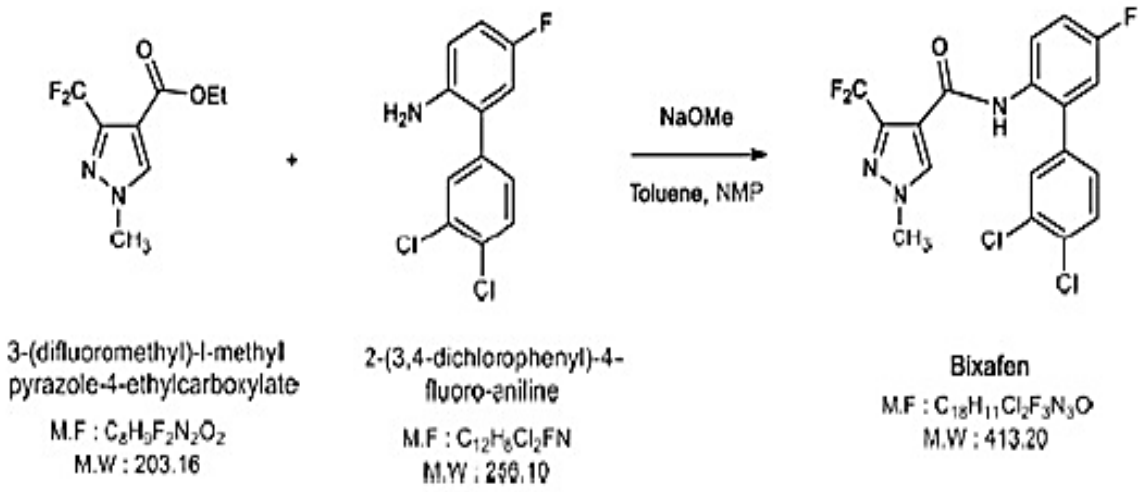


Figure 6. Preparation for Bixafen.

Bixafen was synthesized by condensing the Step-2 product with ethyl 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylate using sodium methoxide as a base (Tables 5 and 6).

Table 5. Mass balance of Bixafen Step 2.

Raw Materials	**Kg**	**Product / By-Product**	**Kg**
Step-1 product	895	Step-2 product	652
3,4-Dichlorobromobenzene	771	Toluene rec.	11,242
Copper Iodide	14	Residue	933
Palladium acetylacetonate	79	Loss as CO_2	150
Triphenylphosphine	24	Aqueous MLR	17,023
Phenanthroline	24		
PEG-400	3,260		
Toluene	11,590		
Water	13,343		
Total Input	*30,000*	*Total Output*	*30,000*

Table 6. Mass balance of Bixafen Step 3.

Raw Materials	**Kg**	**Product / By-Product**	**Kg**
Step-2 product	652	Bixafen	1,000
3-(Difluoromethyl)-1-methyl pyrazole-4-ethylcarboxylate	520	Toluene recovered	5,376
Sodium methoxide	463	Aqueous MLR	10,528
N-methylpyrrolidone	376	Residue	194
Toluene	5,600		
Water	9,487		
Total Input	17,098	Total Output	17,098

Boscalid Cas# 188425-85-6

Manufacturing Process (Figure 7)

Step 1: Synthesis of N-(2-methylphenyl)-2-(4-chlorophenyl)ethan-1-imine (or Similar Intermediate)

1. Charge 1,2-dichloroethane and 4-chlorophenylboronic acid (4-CPBA) into the reactor.
2. Cool the mixture to 0°C.
3. Slowly add o-toluidine over a period of 3 hours, maintaining the temperature at 0°C.
4. Add sodium carbonate portion-wise for over 2 hours, maintaining the temperature at 0°C.
5. Warm the reaction mixture to 30°C and maintain for 4 hours.
6. Add water and separate the aqueous phase. Retain the organic phase.

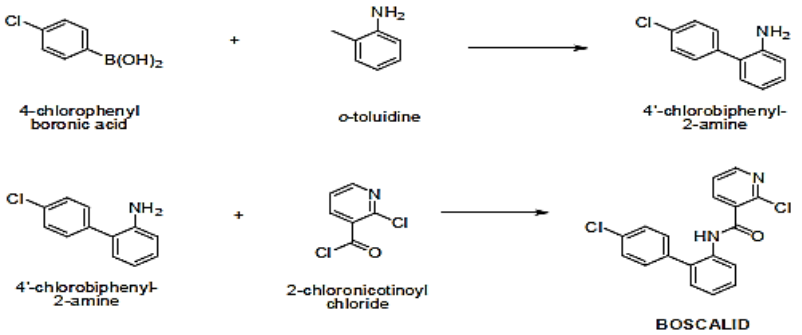


Figure 7. Route of synthesis of Boscalid.

Step 2: Synthesis of Boscalid

1. To the organic phase, add 2-chloronicotinoyl chloride over a period of 2 hours.
2. After the addition is complete, maintain the mixture for an additional 2 hours.
3. Heat the reaction mixture to reflux and reflux for 4 hours.
4. Cool the slurry to 5°C and age for 1 hour.
5. Filter the solid product.
6. Dry the wet cake to obtain Boscalid.

The mass balance of Boscalid is given in Table 7.

Table 7. Mass balance of Boscalid.

Input	Qty (kg)	Process Step	Output	Qty (kg)
Dichloroethane	2500	Reaction		
4-CPBA	490	Separation		
o-Toluidine	340	Reaction		
Sodium Carbonate	175	Crystallization, Filtration &		
Water	1000	Distillation	Aqueous Effluent	1310
2-Chloronicotinoyl Chloride	545	Drying & Packaging	ML	110
			Dichloroethane Residue	2450
			Organic Residue	50
			Drying Loss	130
			Boscalid (Final Product)	1000
Total	5050		Total	5050

Carboxin Cas# 5234-68-4

Manufacturing Process (Figure 8):

Carboxin is manufactured via a three-step sequence.

- *Step 1:* Acetoacetanilide is treated with sulfuryl chloride (SO_2Cl_2) to yield the intermediate, 2-chloro-3-oxo-N-phenylbutanamide.
- *Step 2:* This intermediate undergoes nucleophilic displacement with 2-mercaptoethanol in the presence of sodium hydrogen carbonate (sodium bicarbonate) to form 2-[(2-hydroxyethyl)thio]-3-oxo-N-phenylbutanamide.

- *Step 3:* The final step involves acid-catalyzed cyclization using p-toluenesulfonic acid (PTSA) to afford crude carboxin. The product is then purified by crystallization from methanol to yield technical grade carboxin.

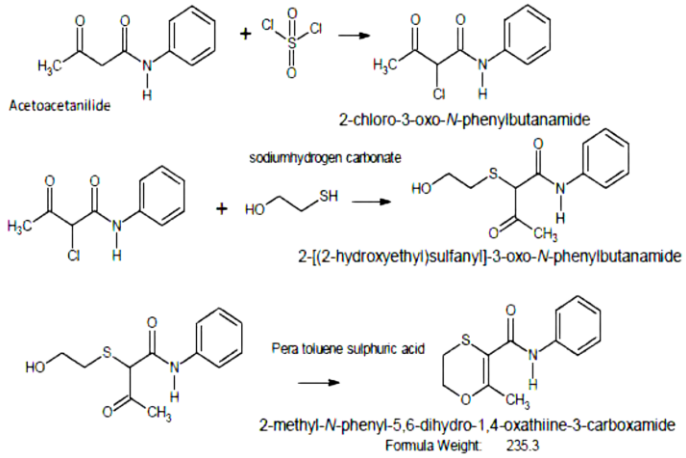
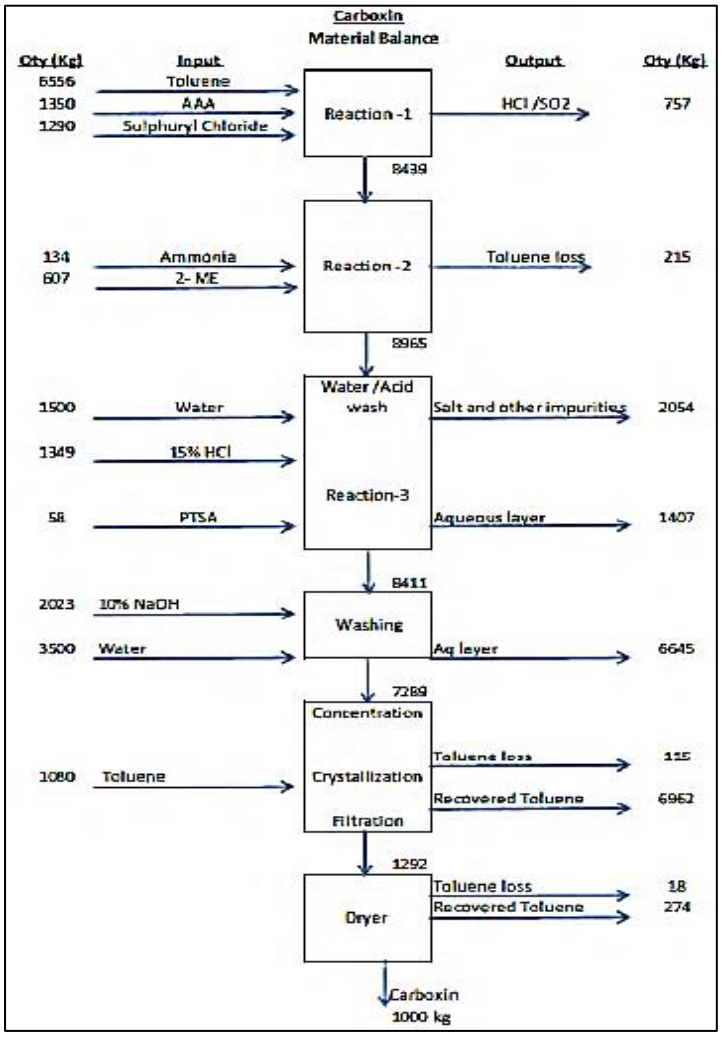


Figure 8. Basic reaction for synthesis of carboxin.

The mass balance of Carboxin is given in Table 8.

Table 8. Mass balance of carboxin.



Carpropamid Cas# 104030-54-8

Manufacturing Process

- *Step 1:* 2,2-dichloro-1-ethyl-3-methylcyclopropane-1-carboxylic acid react with Thionyl chloride to form 2,2-dichloro-1-ethyl-3-methylcyclopropane-1-carbonyl chloride.
- *Step 2:* 2,2-dichloro-1-ethyl-3-methylcyclopropane-1-carbonyl chloride reacts with 1-(4-chlorophenyl) ethanamine to form Carpropamid.

Basic Chemistry (Figure 9)

- *Step 1:* 2,2-dichloro-1-ethyl-3-methylcyclopropane-1-carboxylic acid (MF: $C_7H_{10}Cl_2O_2$ MW: 197.06 g/mol) react with Thionyl chloride (M.F.: $SOCl_2$ M.Wt.:118.97) to form 2,2-dichloro-1-ethyl-3-methylcyclopropane-1-carbonyl chloride (MF: $C_7H_9Cl_3O$ MW: 215.5 g/mol).
- *Step 2:* 2,2-dichloro-1-ethyl-3-methylcyclopropane-1-carbonyl chloride (MF: $C_7H_9Cl_3O$ MW: 215.5 g/mol) react with 1-(4-chlorophenyl) ethanamine (MF: $C_8H_{10}ClN$ MW: 155.62 g/mol) to form Carpropamid (MF: $C_{15}H_{18}Cl_3NO$ MW: 334.7 g/mol).

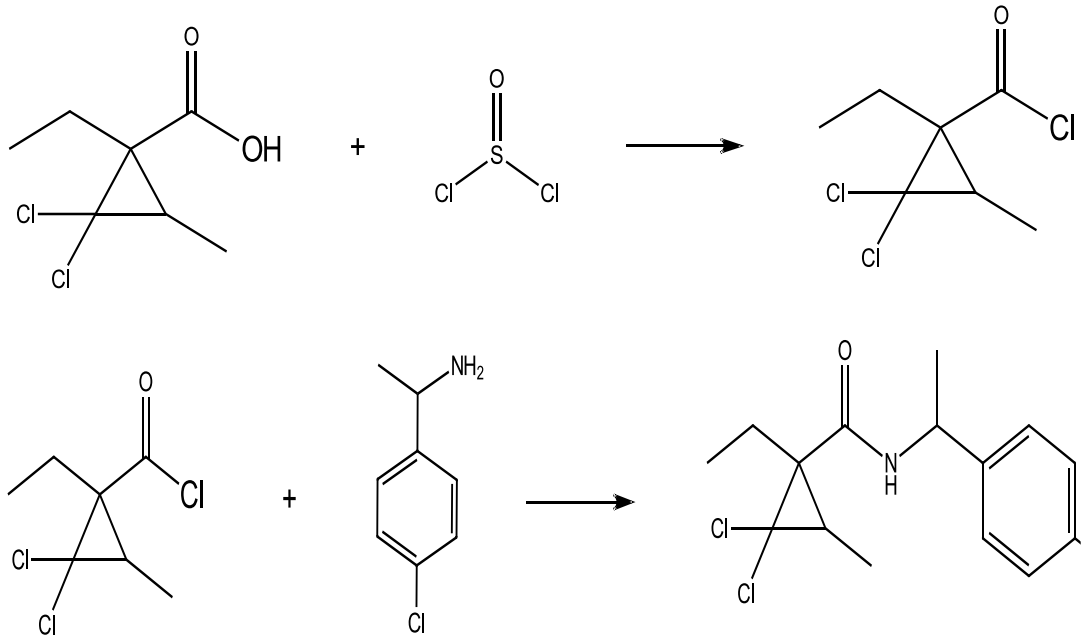


Figure 9. Route of synthesis of Carpropamid.

Step 1: Formation of 2,2-Dichloro-1-ethyl-3-methylcyclopropane-1-carbonyl chloride

Reactants

1. *2,2-Dichloro-1-ethyl-3-methylcyclopropane-1-carboxylic acid ($C_7H_{10}Cl_2O_2$, MW:* 197.06 g/mol).
2. *Thionyl chloride ($SOCl_2$, MW:* 118.97 g/mol).

Product

1. *2,2-Dichloro-1-ethyl-3-methylcyclopropane-1-carbonyl chloride ($C_7H_9Cl_3O$, MW:* 215.5 g/mol).

By-Products

1. *Hydrogen chloride (HCl, MW:* 36.46 g/mol).
2. *Sulfur dioxide (SO_2, MW:* 64.07 g/mol).

Reaction Equation

$$C_7H_{10}Cl_2O_2 + SOCl_2 \rightarrow C_7H_9Cl_3O + SO_2 + HCl$$

Step 2: Formation of Carpropamid

Reactants

1. 2,2-Dichloro-1-ethyl-3-methylcyclopropane-1-carbonyl chloride ($C_7H_9Cl_3O$, MW: 215.5 g/mol).
2. *1-(4-Chlorophenyl) ethanamine ($C_8H_{10}ClN$, MW:* 155.62 g/mol).

Product

1. *Carpropamid ($C_{15}H_{18}Cl_3NO$, MW:* 334.7 g/mol).

By-Product

1. *Hydrogen chloride (HCl, MW:* 36.46 g/mol).

Reaction Equation

$$C_7H_9Cl_3O + C_8H_{10}ClN \rightarrow C_{15}H_{18}Cl_3NO + HCl$$

Mass Balance

1. Moles of Carpropamid ($C_{15}H_{18}Cl_3NO$) to be produced:
   - *Desired Amount:* 1 ton = 1000 kg = 1,000,000 g.

Moles of Carpropamid Required

$$\text{Moles of Carpropamid} = \frac{1,000,000\ \text{g}}{334.7\ \text{g/mol}} \approx 2,987.04\ \text{moles}$$

To produce the required product:

Step 1: Required Reactants and By-Products

1. 2,2-Dichloro-1-ethyl-3-methylcyclopropane-1-carboxylic acid:
   - 2,987.04 moles × 197.06 g/mol ≈ 588,678.18 g = 588.68 kg.
   - Thionyl chloride ($SOCl_2$): 2,987.04 moles × 118.97 g/mol ≈ 355,797.08 g = 355.80 kg.

By-Products

1. *Hydrogen chloride (HCl):* 2,987.04 moles × 36.46 g/mol ≈ 108,921.02 g = 108.92 kg.
2. *Sulfur dioxide (SO_2):* 2,987.04 moles × 64.07 g/mol ≈ 191,383.82 g = 191.38 kg.

Step 2: Required Reactants and By-product

1. 2,2-Dichloro-1-ethyl-3-methylcyclopropane-1-carbonyl chloride:
   - 2,987.04 moles × 215.5 g/mol ≈ 643,238.92 g = 643.24 kg
   - *1-(4-Chlorophenyl) ethanamine:* 2,987.04 moles × 155.62 g/mol ≈ 464,832.96 g = 464.83 kg

By-Product HCl

- 2,987.04 moles × 36.46 g/mol ≈ 108,921.02 g = 108.92 kg.

The mass balance of carpropamid is given in Table 9.

Table 9. Mass balance of Carpropamid.

Input (kg)		Output (kg)		Remarks
2,2-Dichloro-1-ethyl-3-methylcyclopropane-1-carboxylic acid	588.68	Carpropamid	1000	Product
1-(4-Chlorophenyl) ethanamine	464.83	HCl 30%	725	Rule 9
Thionyl chloride ($SOCl_2$)	355.80	$NaHSO_3$ 25%	1240	Rule 9

Toluene	6000	Toluene	5850	Recovered
Water for HCl	508	Toluene	150	Loss
Water	9000	Salt	185.33	To TSDF
Water for $NaHSO_3$	800	Effluent	9000	To ETP
TEBAcl	100	Residue	555.98	Rule 9
Sodium Carbonate	200	–	–	–
NaOCl	400	–	–	–
Acetic Acid	40	–	–	–
NaOH	249	–	–	–
Total	*18706.31*	*Total*	*18706.31*	–

Cyazofamid Cas# 120116-88-3

Manufacturing Process (Figure 10)

Step 1: Formation of the Imidazole Nucleus

1. Charge methanol, 2,2-dichloro-1-(p-tolyl) ethan-1-one (2,2-DCPTE), glyoxal, and hydroxylamine hydrochloride (HAHC) to the reactor.
2. Heat the mixture to reflux and maintain for 2 hours.
3. Distill off the methanol under reduced pressure.
4. Cool the resulting mass to 30°C.

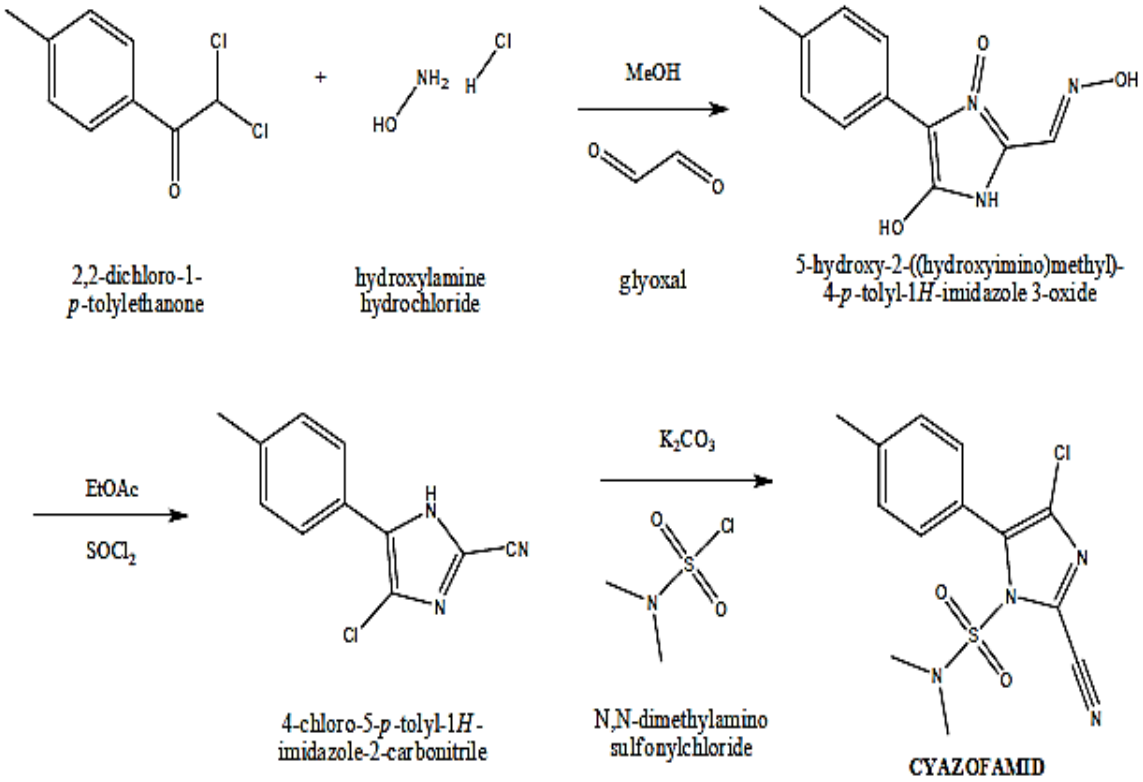


Figure 10. Route of synthesis of Cyazofamid.

Step 2: Chlorination and Cyclization to 4-Chloroimidazole

1. Charge ethyl acetate to the reactor.
2. Add thionyl chloride (likely facilitating chlorination and dehydration).
3. Heat the mixture to reflux and maintain for 3 hours to complete the cyclization.
4. Cool the reaction mass to 30°C. The product, 4-chloro-5-(p-tolyl)-1H-imidazole-2-carbonitrile, precipitates or is obtained in solution.

Step 3: Sulfonylation to Yield Cyazofamid

1. Charge potassium carbonate (to act as a base).
2. Add N, N-dimethylsulfamoyl chloride (NNDMASC).
3. Heat the mixture to 70°C and maintain for 3 hours to facilitate the N-sulfonylation reaction.
4. Cool the reaction mixture to 30°C.
5. Add water and separate the organic phase.
6. Cool the organic phase to 0°C to crystallize the product.
7. Filter the resulting slurry.
8. Dry the solid to obtain Cyazofamid Technical.

The mass balance of Cyazofamid is given in Table 10.

Table 10. Mass balance of Cyazofamid.

Mass Balance of Cyazofamid							
Input	**kg**					**Output**	**kg**
Methanol	4000	→	Reaction & Filteration		→	Methanol	3900
2,2-DCPTE	660	→			→	Residue	100
Glyoxal 45& soln	420	→					
Hydroxylamine HCl	700	→					
ethyl acetate	2500	→	Reaction		→	HCl	119
Thionyl chloride	390	→			→	SO2	210
Potassium carbonate	225	→	Reaction & Separation		→	Aqueous effluent	2900
NNDMASC	470	→					
water	1500	→					
			Crystallization, Filteration & Distillation		→	ethyl acetate	2450
					→	organic residue	50
			Drying & Packaging		→	Drying loss	136
					→	**Cyazofamid**	**1000**
Total	**10865**						**10865**

Cyclobutrifluram Cas# 1460292-16-3

Manufacturing Process

(1R,2R)-2-(2,4-dichlorophenyl) cyclobutan-1-amine react with 2-(trifluoromethyl) pyridine-3-carbonyl chloride to form Cyclobutrifluram

Basic Chemistry (Figure 11)

(1R,2R)-2-(2,4-dichlorophenyl) cyclobutan-1-amine (MF: $C_{10}H_{11}Cl_2N$ MW: 216.1 g/mol) react with 2-(trifluoromethyl) pyridine-3-carbonyl chloride (MF: $C_7H_3ClF_3NO$ MW: 209.55 g/mol) to form Cyclobutrifluram (MF: $C_{17}H_{13}Cl_2F_3N_2O$ MW: 389.2 g/mol).

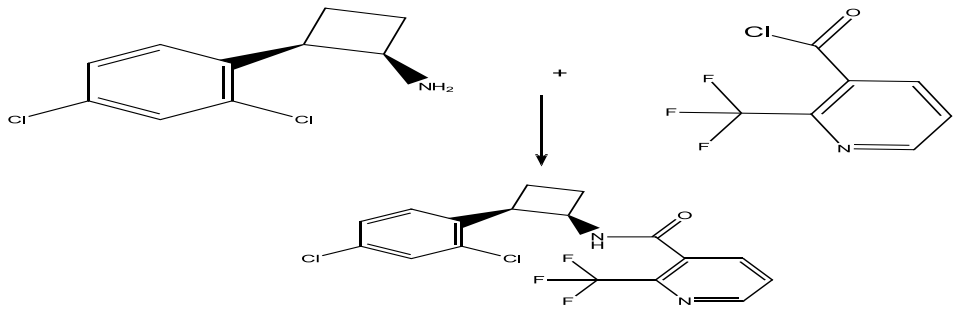


Figure 11. Route of synthesis of Cyclobutrifluram.

Reactants
1. *(1R,2R)-2-(2,4-dichlorophenyl) cyclobutan-1-amine ($C_{10}H_{11}Cl_2N$, MW:* 216.1 g/mol).
2. *2-(trifluoromethyl) pyridine-3-carbonyl chloride ($C_7H_3ClF_3NO$, MW:* 209.55 g/mol).

Product
1. *Cyclobutrifluram ($C_{17}H_{13}Cl_2F_3N_2O$, MW:* 389.2 g/mol).

By-Product
1. Hydrogen chloride (HCl, MW: 36.46 g/mol).

Reaction Equation

$$C_{10}H_{11}Cl_2N + C_7H_3ClF_3NO \rightarrow C_{17}H_{13}Cl_2F_3N_2O + HCl$$

Mass Balance
1. Moles of Cyclobutrifluram ($C_{17}H_{13}Cl_2F_3N_2O$) to be produced:
   - *Desired amount:* 1 ton = 1000 kg = 1,000,000 g.
2. Moles of Cyclobutrifluram required:

$$\text{Moles of Cyclobutrifluram} = \frac{1,000,000\ \text{g}}{389.2\ \text{g/mol}} \approx 2,568.32\ \text{moles}$$

Required Reactants
1. *(1R,2R)-2-(2,4-dichlorophenyl) cyclobutan-1-amine:* 2,568.32 moles × 216.1 g/mol ≈ 554,991.31 g = 555.0 kg.
2. (*Trifluoromethyl) pyridine-3-carbonyl chloride:* 2,568.32 moles × 209.55 g/mol ≈ 538,510.45 g = 538.51 kg.
3. *By-Product (HCl):* 2,568.32 moles × 36.46 g/mol ≈ 93,630.16 g = 93.63 kg.

The mass balance of Cyclobutrifluram is given in Table 11.

Table 11. Mass balance of Cyclobutrifluram.

Input (kg)		**Output (kg)**		**Remarks**
(1R,2R)-2-(2,4-dichlorophenyl) cyclobutan-1-amine	555.0	Cyclobutrifluram	1000	Product
2-(trifluoromethyl) pyridine-3-carbonyl chloride	538.51	$HCl_{30\%}$	312	Rule 9
Toluene	5000	Toluene	4925	Recovered
Water	7500	Toluene	75	Loss
Water for HCl	218	Pyridine HCl	305.51	
Pyridine	230	Effluent	7424	To ETP
Total	*14041.51*	*Total*	*14041.51*	–

Cyflufenamid Cas# 180409-60-3

Manufacturing Process

N-[[2,3-difluoro-6-(trifluoromethyl) phenyl]-methylsulfonylmethylidene]-2-phenylacetamide react with O-(cyclopropylmethyl) hydroxylamine to form Cyflufenamid.

Basic Chemistry (Figure 12)

N-[[2,3-difluoro-6-(trifluoromethyl) phenyl]-methylsulfonylmethylidene]-2-phenylacetamide (MF: $C_{17}H_{12}F_5NO_3S$ MW: 405.3 g/mol) react with O-(cyclopropylmethyl) hydroxylamine (MF: C_4H_9NO MW: 87.12 g/mol) to form Cyflufenamid (MF: $C_{20}H_{17}F_5N_2O_2$ MW: 412.4 g/mol).

$$C_{17}H_{12}F_5NO_3S + C_4H_9NO \rightarrow C_{20}H_{17}F_5N_2O_2 + H_2O$$

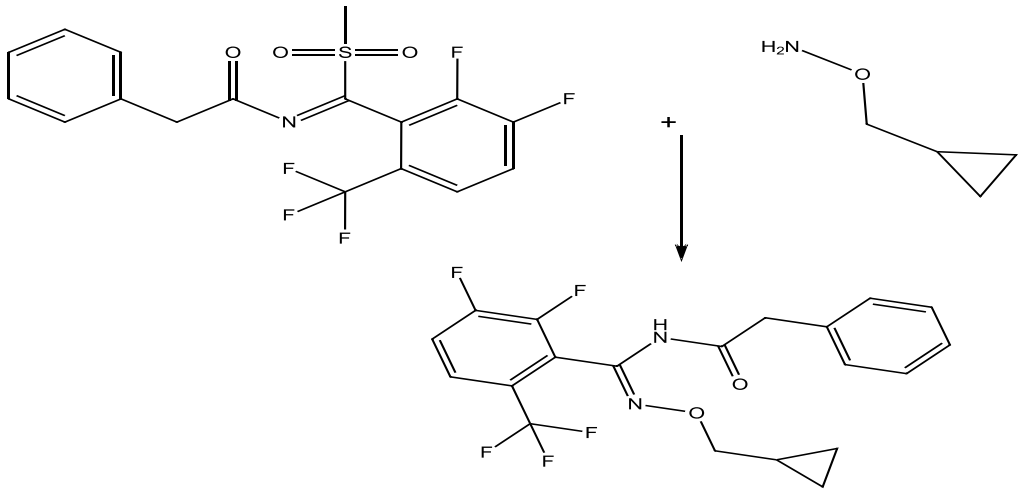


Figure 12. Route of synthesis of Cyflufenamid.

Reactants

1. -N-[[2,3-difluoro-6-(trifluoromethyl)phenyl]-methylsulfonylmethylidene]-2-phenylacetamide ($C_{17}H_{12}F_5NO_3S$, MW: 405.3 g/mol).
2. - *O-(cyclopropylmethyl) hydroxylamine (C_4H_9NO, MW:* 87.12 g/mol).

Product

- *Cyflufenamid ($C_{20}H_{17}F_5N_2O_2$, MW:* 412.4 g/mol).

Mass Balance

Calculate Moles of Cyflufenamid ($C_{20}H_{17}F_5N_2O_2$) to be produced:

1. *Desired amount:* 1 ton = 1000 kg = 1,000,000 g

$$\text{Moles of Cyflufenamid} = \frac{1,000,000 \text{ g}}{412.4 \text{ g/mol}} \approx 2,424.62 \text{ moles}$$

Calculate Required Reactants

1. N-[[2,3-difluoro-6-(trifluoromethyl) phenyl]-methylsulfonylmethylidene]-2-phenylacetamide:
   - 2,424.62 moles × 405.3 g/mol ≈ 982,964.89 g = 982.96 kg.
   - *O-(cyclopropylmethyl) hydroxylamine:* 2,424.62 moles × 87.12 g/mol ≈ 211,263.93 g = 211.26 kg.

The detailed mass balance of Cyflufenamid is provided in Table 12.

Table 12. Mass balance of Cyflufenamid.

Input (kg)		Output (kg)		Remarks
N-[2,3-difluoro-6-(trifluoromethyl) phenyl]-methylsulfonylmethylidene]-2-phenylacetamide	982.96	Cyflufenamid	1000	Product
O-(cyclopropylmethyl) hydroxylamine	211.26	Toluene	4850	Recovered
Toluene	5000	Toluene	150	Loss
Water	7500	Salt	37.63	To TSDF
–	–	Effluent	7543.7	To ETP
–	–	Residue	112.89	Rule 9
Total	*13694.22*	*Total*	*13694.22*	–

CONCLUSIONS

The comprehensive analysis of the manufacturing processes for ten essential fungicides – Amisulbrom, Azoxystrobin, Benzovindiflupyr, Bixafen, Boscalid, Carboxin, Carpropamid, Cyazofamid, Cyclobutrifluram, and Cyflufenamid – demonstrates the complexity and diversity of chemical synthesis pathways employed in agrochemical production. Each fungicide's synthesis involves multi-step reactions, precise stoichiometric calculations, and careful management of by-products, solvents, and effluents to achieve efficient production at a 1000 kg scale. The detailed mass balance analyses highlight the importance of resource optimization, waste minimization, and environmental compliance, with significant portions of solvents like toluene and dimethylformamide being recovered, while effluents and residues are directed to appropriate treatment or disposal systems. These processes underscore the integration of advanced organic chemistry techniques, such as sulfonylation, amide coupling, and catalytic reactions, to achieve high yields and product purity. The findings provide valuable insights for industrial scalability, offering pathways to enhance process efficiency, reduce environmental impact, and support sustainable agrochemical manufacturing. Future research could focus on greener catalysts, alternative solvents, and energy-efficient methods to further improve the sustainability of these production processes, ensuring their viability in addressing global agricultural demands while minimizing ecological footprints.

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