Mediterranean Journal of Pharmacy & Pharmaceutical Sciences
www.medjpps.com

ISSN: 2789-1895 online
ISSN: 2958-3101 print

REVIEW article

A comprehensive analysis of disclosed synthetic strategies in prior arts from 2013-2024 (Part II) regarding the preparation of the renowned drug, Febuxostat, and its related scaffolds

Sanjay Sukumar Saralaya

Department of Chemistry, Shri Dharmasthala Manjunatheshwara Institute of Technology, SDM IT (affiliated to Visvesvaraya Technological University, VTU, Belagavi), Ujire-574 240, Karnataka, India

Article number: 184, **Received:** 10-11-2024, **Accepted:** 24-12-2024, **Published online:** 17-01-2025

HOW TO CITE THIS

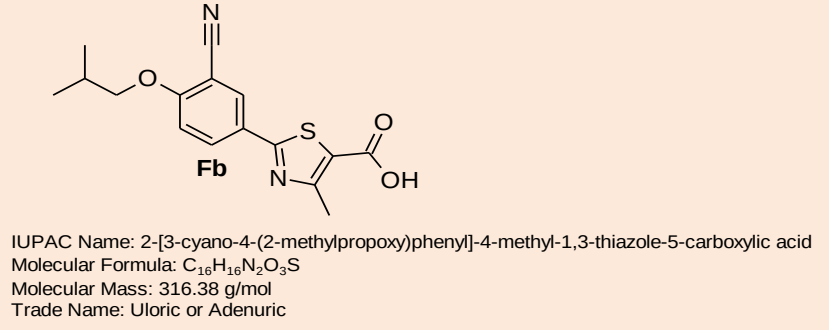
Sanjay SS (2025) A comprehensive analysis of disclosed synthetic strategies in prior arts from 2013-2024 (Part II) regarding the preparation of the renowned drug, Febuxostat, and its related scaffolds. Mediterr J Pharm Pharm Sci. 5 (1): 25-47. [Article number: 184]. https://doi.org/10.5281/zenodo.14645927

Keywords: Benzothioamide, Febuxostat prior arts raw materials, phenylthiazole, synthesis, reaction schemes

Abstract: This review segment (Part II) provides an essential collection of research disclosures about the synthesis of Febuxostat and its closely associated scaffolds from 2013-2024. During the process, 87 research communications (as patents and journal articles) were collected from various global online research repositories, and the essential components were systematically tabulated in the article for better readability. This review article would provide a useful platform for the researchers to understand the past ventures on the synthesis of Febuxostat and the knowledge of same can transform to develop some inventive or innovative ventures on the synthesis of Febuxostat and its related scaffolds in the near future.

Introduction

Febuxostat (**Fb**) is a popular drug to treat gout in adults and it is a xanthine oxidase (XO) inhibitor or antigout agent. It can reduce the formation of uric acid and hence assists in preventing gout flares. The gout flares are formed due to the presence of high uric acid levels in the body [1-6]. There are numerous drugs used to treat and prevent gout disease such as allopurinol, probenecid, benzbromarone, pegloticase, ibuprofen, naproxen, diclofenac, colchicine, prednisone, prednisolone, etc. [7, 8]. Additionally, some new and more effective drugs have emerged in recent years to treat and prevent gout [9]. In this review article, insights on the synthesis of **Fb** and its closely related moieties were comprehensively covered (**Figure 1**).



IUPAC Name: 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid
Molecular Formula: $C_{16}H_{16}N_2O_3S$
Molecular Mass: 316.38 g/mol
Trade Name: Uloric or Adenuric

Figure 1: IUPAC nomenclature Febuxostat

ISSN: 2789-1895 online
ISSN: 2958-3101 print

Sourcing the prior arts: Numerous research articles were disclosed by many researchers regarding the synthesis and isolation of **Fb**. The disclosures are mainly in the form of patents (applications/granted) and journal articles (original/review). The available prior arts are too high in number and hence the work was divided into two segments (**Part I** and **Part II**). The disclosed prior arts from 2013-2024 were sequentially tabulated within **Table 1** and it comprises brief information about the key aspects like details of author/s, year of disclosure, study coverage, reaction schemes, etc. More importantly, in detail reaction schemes were also furnished in this segment for an elaborate understanding of every research disclosure.

Table 1: Complete list of prior arts regarding the synthesis of **Fb** and its related scaffolds

Entry	Inventor/s or innovator/s	Disclosed data in brief	Synthetic route hint	Ref.
1	Sokhi et al.	Form R of **Fb** was synthesized and characterized.	NA	[10]
2	Shen et al.	A stable crystal form of **Fb** was reported	NA	[11]
3	Ge	**Fb** was prepared from **115** in a five-step process.	Scheme 1	[12]
4	Jetti et al.	Forms of **Fb** such as M_1 and K were prepared and characterized.	NA	[13]
5	Mizhiritskii et al.	**Fb** was prepared from **69** in a one/two-step process.	Scheme 2a & 2b	[14]
6	Shen et al.	Refining of **Fb** & then to formulation.	NA	[15]
7	Zhang et al.	**1** was synthesized from **38**.	Scheme 3	[16]
8	Kompella et al.	Form FC-1 of **Fb** was prepared and characterized.	NA	[17]
9	Zhou & Liu	**Fb** was prepared from **118** in a six-step process.	Scheme 4	[18]
10	Vellanki, et al.	**Fb** was prepared from **36** or **37** in a two-step process.	Scheme 5	[19]
11	Zhou	**Fb** was prepared from **36** in a three-step process.	Scheme 6	[20]
12	Lv et al.	**Fb** was synthesized from **36** in a three-step process.	Scheme 7	[21]
13	Kompalla et al.	**Fb** was prepared from **121** in a five-step process.	Scheme 8	[22]
14	Zhang	**Fb** was prepared from **38** in a seven-step process.	Scheme 9	[23]
15	Dwivedi et al.	**Fb** and its salts were synthesized from **14**.	Scheme 10	[24]
16	Luo et al.	Co-crystal of **Fb** with γ-picolinic acid was reported.	NA	[25]
17	Luo et al.	Co-crystal of **Fb** with methanol was disclosed.	NA	[26]
18	Salaet-Ferre & Marquillas-Olondriz	Form II of **Fb** was prepared and characterized.	NA	[27]
19	Marcom & Rubnov	Forms of **Fb** such as forms II, IV, VI, V, VII, VIII & IX were synthesized and characterized.	NA	[28]
20	Wang et al.	**1** was prepared from **38**.	Scheme 11	[29]
21	Wang et al.	**Fb** and some of its related compounds were reported.	Scheme 12	[30]
22	Komiyama	**14** was prepared from **72** & **114**.	Scheme 13	[31]
23	Zhang, et al.	**Fb** was synthesized from **38** in a five-step process.	Scheme 14	[32]
24	Sun et al.	Form A of **Fb** was prepared and characterized.	NA	[33]
25	Zhang	Forms of **Fb** like I, II & III were synthesized and characterized.	NA	[34]
26	Li	Synthesis of **1** & **17** was reported.	Scheme 15	[35]
27	Li et al.	**Fb** was prepared from **1** in a five-step process.	Scheme 16	[36]
28	Pranab et al.	**Fb** was prepared from **1** in a five-step process.	Scheme 17	[37]
29	Vallu et al.	Nine impurities of **Fb** were reported.	NA	[38]
30	Zhang et al.	Form S of **Fb** was prepared and characterized.	NA	[39]
31	Parthasaradhi et al.	**Fb** was prepared from **1** in a five-step process. Additionally, forms of **Fb** like H_1, H_3 & H_4 were reported.	Scheme 18	[40]
32	Huang & Huang	**Fb** was synthesized from **38** in a multi-step process.	Scheme 19	[41]
33	Xie et al.	Form A of **Fb** was reported.	NA	[42]
34	Chen & Su	Synthesis of **1** & **57**.	Scheme 20	[43]
35	Lou et al.	Synthesis of **14** from **38** in a two-step process.	Scheme 21	[44]
36	Praveen et al.	**Fb** was synthesized from **12** in a two-step process.	Scheme 22	[45]
37	Tamura et al.	**Fb** was prepared from **129** or **130** in a four-step process.	Scheme 23	[46]
38	Li & Li	**37** was prepared from **38** in a three-step process.	Scheme 24	[47]
39	Cui & Feng	**Fb** was synthesized from **38** in a six-step process.	Scheme 25	[48]
40	Wang, et al.	**Fb** was prepared from **36** in a single-step process.	Scheme 26	[49]
41	Wang et al.	**41** was synthesized from **38** in a three-step process.	Scheme 27	[50]
42	Koftis et al.	**Fb** was synthesized from **36** in a three-step process.	Scheme 28	[51]
43	Kang et al.	Co-crystals of **Fb** (**Fb**-isonicotinamide & **Fb**-arginine) were reported.	NA	[52]
44	Reddy et al.	Phosphonate derivatives of **Fb** were reported.	Scheme 29	[53]

ISSN: 2789-1895 online
ISSN: 2958-3101 print

45	Wei	Impurity-free **36** was prepared from **7** in a single-step process.	Scheme 30	[54]
46	Zhao et al.	**36** was prepared from **7** in a single-step process.	Scheme 31	[55]
47	Liu et al.	**Fb** was synthesized from **135** in a seven-step process.	Scheme 32	[56]
48	Shi et al.	Form A and a new form of **Fb** was reported.	NA	[57]
49	Zhai & Fan	Reports the conversion of aromatic nitriles to thioamides using NaHS or KHS or $(NH_4)_2S$.	NA	[58]
50	An et al.	Co-crystal study of **Fb** (**Fb**-pyroglutamic acid)	NA	[59]
51	Kang et al.	Studies of two novel co-crystals of **Fb**.	NA	[60]
52	Gong et al.	**34** was prepared **36** in a single-step process.	Scheme 33	[61]
53	Komiyama et al.	**Fb** was synthesized from **114** in a three-step process.	Scheme 34	[62]
54	Shi et al.	**Fb** was prepared from **34** in a single-step process.	Scheme 35	[63]
55	Zeng et al.	Form W of **Fb** was prepared and characterized.	NA	[64]
56	Zhou et al.	**Fb** was synthesized from **38** in a six-step process.	Scheme 36	[65]
57	Zhang et al.	**139** was prepared from **36** in a three-step process.	Scheme 37	[66]
58	Huang et al.	**Fb** was synthesized from **138** in a four-step process.	Scheme 38	[67]
59	Huang et al.	**34** was prepared from **80** in a four-step process.	Scheme 39	[68]
60	Zhang et al.	**Fb** was prepared from **36** in a three-step process.	Scheme 40	[69]
61	Wang et al.	**Fb** was synthesized from **36** in a three-step process with additional refining methods.	Scheme 41	[70]
62	Yan et al.	**14** was prepared from **7** in a single-step process.	Scheme 42	[71]
63	Zhang et al.	**Fb** was prepared from **36** in a single-step process.	Scheme 43	[72]
64	Zhou et al.	**14** was synthesized from **34** in a single-step process.	Scheme 44	[73]
65	Gao et al.	Imidazolium salt hydrate of **Fb** was reported.	NA	[74]
66	Zhang et al.	**7** was prepared from **87** in a single-step process.	Scheme 45	[75]
67	Bao et al.	Form A of **Fb** having high purity was reported.	NA	[76]
68	Xu et al.	Large crystals of Form A of **Fb** were disclosed.	NA	[77]
69	Lyu & Guo	**Fb** was prepared from **87** or **38** in a multi-step process.	Scheme 46a. 46b	[78]
70	Tang et al.	**Fb** was synthesized from **7** in a four-step process.	Scheme 47	[79]
71	Tang et al.	**Fb** was synthesized from **7** in a four-step process.	NA	[80]
72	Lu	**Fb** was prepared from **7** in a four-step process.	Scheme 48	[81]
73	Liu & Su	**Fb** was synthesized from **36** in a single-step process.	Scheme 49	[82]
74	Sun et al.	**14** was prepared from **34** in a single-step process.	Scheme 50	[83]
75	Xu et al.	Impurities of **Fb** were reported.	Scheme 51	[84]
76	Xu et al.	Impurities like 134, 146 & 147 were synthesized and characterized.	NA	[85]
77	Liu et al.	Impurities of **Fb** were disclosed.	Scheme 52	[86]
78	Song & Li	**10** was synthesized from **152**.	Scheme 53	[87]
79	Lai et al.	**Fb** was prepared from **36** in a single-step micro reactor-driven process.	Scheme 54	[88]
80	Peng et al.	Form A of **Fb** was reported.	NA	[89]
81	Sun & Yang	Impurities of **Fb** were reported.	Scheme 55	[90]
82	Chai et al.	**154** was prepared from **Fb**.	Scheme 56	[91]
83	Ji et al.	**Fb** was prepared from **117** in a five-step process.	Scheme 57	[92]
84	Leng et al.	**Fb** was synthesized from **7** in a four-step process.	Scheme 58	[93]
85	Ungur et al.	Crystal study of **Fb** (**Fb**-p-toluene sulfonic acid).	NA	[94]
86	Manda et al.	**Fb** was prepared from **12** in a two-step process.	Scheme 59	[95]
87	Ungur et al.	Crystal structure study of form A of **Fb**.	NA	[96]

Statistical data of prior arts: The prior arts were collected from the online research repositories by the use of various search terms and sorted according to the year of disclosure. The sorting outcome had hinted that, 2013 had recorded 23 research work disclosures as patents or journal publications. Meanwhile, 2014, 2019, and 2020 had witnessed the disclosure of 10 scientific communications about the synthesis of **Fb** and its related scaffolds (**Table 2**).

Nomenclature: In this review segment around **154** compounds were featured in the reaction schemes in various stages. The compounds (as reagents/intermediates) from **1** to **154** were listed in **Table 3** along with the IUPAC name. Meanwhile, in the tabulated reaction schemes only compound number was mentioned to reduce the area occupancy on paper by the reaction schemes.

ISSN: 2789-1895 online
ISSN: 2958-3101 print

Table 2: Year-wise statistics of disclosed prior arts

Year of disclosure	Number of disclosures
2013	23
2014	10
2015	6
2016	5
2017	7
2018	6
2019	10
2020	10
2021	4
2022	1
2023	3
2024	2
2013-2024	**87**

Table 3: IUPAC name of compounds appearing in the reaction schemes as raw materials/intermediates

C. No.	IUPAC nomenclature
1	4-Hydroxybenzenecarbothioamide
2	Chloroacetaldehyde
3	1-Chloropropan-2-one
4	Ethyl 2-bromo-3-oxobutanoate
5	4-(1,3-Thiazol-2-yl)phenol
6	4-(4-Methyl-1,3-thiazol-2-yl)phenol
7	Ethyl 2-(4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
8	4-Nitrobenzonitrile
9	1-Bromo-2-methylpropane
10	4-(2-Methylpropoxy)benzene-1,3-dicarbonitrile
11	Ethanethioamide
12	3-Cyano-4-(2-methylpropoxy)benzenecarbothioamide
13	Ethyl 2-chloro-3-oxobutanoate
14	Ethyl 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylate
15	4-Hydroxy-3-nitrobenzaldehyde
16	4-Hydroxy-3-nitrobenzonitrile
17	4-Hydroxy-3-nitrobenzenecarbothioamide
18	Ethyl 2-(4-hydroxy-3-nitrophenyl)-4-methyl-1,3-thiazole-5-carboxylate
19	Ethyl 4-methyl-2-[4-(2-methylpropoxy)-3-nitrophenyl]-1,3-thiazole-5-carboxylate
20	4-Methyl-2-[4-(2-methylpropoxy)-3-nitrophenyl]-1,3-thiazole-5-carboxylic acid
21	4-Chloro-3-nitrobenzaldehyde
22	4-Chloro-3-nitrobenzonitrile
23	4-Chloro-3-nitrobenzenecarbothioamide
24	Ethyl 2-(4-chloro-3-nitrophenyl)-4-methyl-1,3-thiazole-5-carboxylate
25	2-Methylpropan-1-ol
26	Ethyl 4-methyl-2-[4-(2-methylpropoxy)-3-nitrophenyl]-1,3-thiazole-5-carboxylate
27	Ethyl 2-(3-chloro-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
28	Ethyl 2-(3-bromo-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
29	Ethyl 2-[3-chloro-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylate
30	Ethyl 2-[3-bromo-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylate
31	2-[3-Chloro-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid
32	2-[3-Bromo-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid
33	Ethyl 4-methyl-2-[4-(2-methylpropoxy)phenyl]-1,3-thiazole-5-carboxylate
34	Ethyl 2-[3-formyl-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylate
35	2-[3-Formyl-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid
36	Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
37	Ethyl 2-(3-cyano-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
38	4-Hydroxybenzonitrile
39	4-(2-Methylpropoxy)benzonitrile
40	3-Bromo-4-(2-methylpropoxy)benzonitrile
41	3-Bromo-4-(2-methylpropoxy)benzenecarbothioamide
42	2-Chlorophenol
43	1-Chloro-2-(3-methylbutyl)benzene
44	Ethyl {[3-chloro-4-(2-methylpropoxy)phenyl]carbonothioyl}carbamate
45	3-Chloro-4-(2-methylpropoxy)benzenecarbothioamide
46	Ethyl 2-[3-iodo-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylate

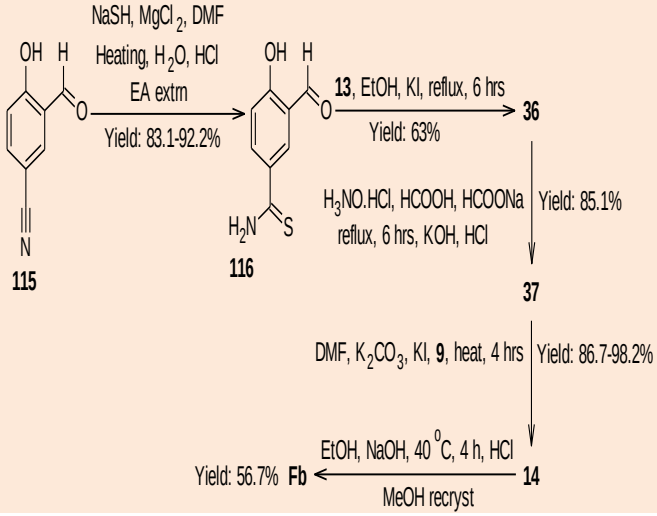
ISSN: 2789-1895 online
ISSN: 2958-3101 print

47	5-Bromo-2-hydroxybenzaldehyde
48	5-Bromo-2-(2-methylpropoxy)benzaldehyde
49	3-Formyl-4-(2-methylpropoxy)benzonitrile
50	3-Formyl-4-(2-methylpropoxy)benzenecarbothioamide
51	4-Methylbenzonitrile
52	4-Methylbenzenecarbothioamide
53	Benzonitrile
54	Benzenecarbothioamide
55	4-Bromobenzonitrile
56	4-Bromobenzenecarbothioamide
57	4-(2-Methylpropoxy)benzenecarbothioamide
58	4-Hydroxy-3-iodobenzonitrile
59	3-Iodo-4-(2-methylpropoxy)benzonitrile
60	*tert*-Butyl 4-methyl-1,3-thiazole-5-carboxylate
61	5-Iodo-2-(2-methylpropoxy)benzonitrile
62	3-Bromo-4-hydroxybenzonitrile
63	4-Nitrobenzenecarbothioamide
64	Ethyl 4-methyl-2-(4-nitrophenyl)-1,3-thiazole-5-carboxylate
65	1-Chloro-2-methylpropane
66	Thiourea
67	Ethyl 2-amino-4-methyl-1,3-thiazole-5-carboxylate
68	Ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate
69	5-Bromo-2-(2-methylpropoxy)benzonitrile
70	3-Cyano-4-isobutoxy phenyl boronic acid
71	*tert*-Butyl 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylate
72	2-Methylpropan-1-ol
73	4-Methylphenol
74	Propanethioamide
75	Ethyl bromoacetate
76	2,4-Dibromophenol
77	Ethyl 2-{3-[(*E*)-(hydroxyimino)methyl]-4-(2-methylpropoxy)phenyl}-4-methyl-1,3-thiazole-5-carboxylate
78	2-{3-[(*E*)-(Hydroxyimino)methyl]-4-(2-methylpropoxy)phenyl}-4-methyl-1,3-thiazole-5-carboxylic acid
79	4-Hydroxy-3-methylbenzaldehyde
80	4-Hydroxy-3-methylbenzonitrile
81	3-Methyl-4-(2-methylpropoxy)benzonitrile
82	3-Formyl-4-(2-methylpropoxy)benzonitrile
83	3-Formyl-4-(2-methylpropoxy)benzenecarbothioamide
84	2-Fluoro-5-iodobenzonitrile
85	2-(2-methylpropoxy) 5-(tetramethyl dioxaborane) benzonitrile
86	Ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate
87	4-Hydroxybenzaldehyde
88	4-(2-Methylpropoxy)benzaldehyde
89	3-Bromo-4-(2-methylpropoxy)benzaldehyde
90	(*E*)-1-[3-Bromo-4-(2-methylpropoxy)phenyl]-N-hydroxymethanimine
91	Benzonitrile
92	Benzenecarbothioamide
93	4-Methoxybenzonitrile
94	4-Methoxybenzenecarbothioamide
95	4-Chlorobenzonitrile
96	4-Chlorobenzenecarbothioamide
97	4-Bromo-2-methylbenzonitrile
98	4-Bromo-2-methylbenzenecarbothioamide
99	4-Bromo-2-hydroxy-6-methylbenzonitrile
100	4-Bromo-2-hydroxy-6-methylbenzenecarbothioamide
101	2,4-Dibromo-1-(2-methylpropoxy)benzene
102	4-(2-Methylpropoxy)benzamide
103	3-Bromo-4-(2-methylpropoxy)benzamide
104	3-Cyano-4-(2-methylpropoxy)benzamide
105	2-Chloro-N,N-dimethylacetamide
106	2-(4-Hydroxyphenyl)-N,N,4-trimethyl-1,3-thiazole-5-carboxamide
107	2-(3-Formyl-4-hydroxyphenyl)-N,N,4-trimethyl-1,3-thiazole-5-carboxamide
108	2-[3-Formyl-4-(2-methylpropoxy)phenyl]-N,N,4-trimethyl-1,3-thiazole-5-carboxamide
109	2-(3-Cyano-4-hydroxyphenyl)-N,N,4-trimethyl-1,3-thiazole-5-carboxamide
110	2-[3-Cyano-4-(2-methylpropoxy)phenyl]-N,N,4-trimethyl-1,3-thiazole-5-carboxamide
111	2-[3-Formyl-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid
112	4-Methyl-1,3-thiazole-5-carboxylic acid
113	2-Methylpropan-2-ol

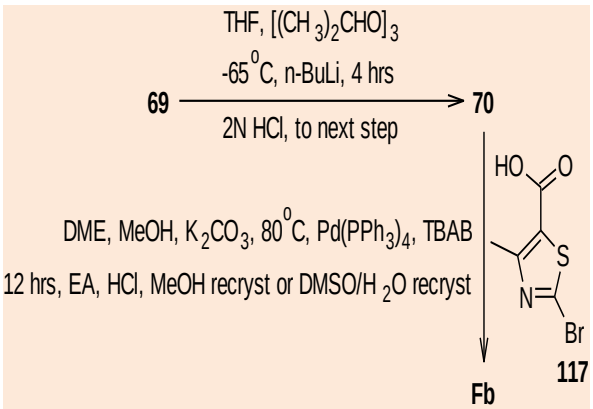
ISSN: 2789-1895 online
ISSN: 2958-3101 print

114	5-Bromo-2-fluorobenzonitrile
115	3-Formyl-4-hydroxybenzonitrile
116	3-Formyl-4-hydroxybenzenecarbothioamide
117	2-Bromo-4-methyl-1,3-thiazole-5-carboxylic acid
118	2-Hydroxybenzaldehyde
119	4-Hydroxybenzene-1,3-dicarbaldehyde
120	4-Hydroxybenzene-1,3-dicarbonitrile
121	3-Bromo-4-hydroxybenzaldehyde
122	3-Bromo-4-hydroxybenzenecarbothioamide
123	Sodium 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylate
124	Potassium 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylate
125	Ethyl 4-methyl-1,3-thiazole-5-carboxylate
126	Methoxyacetyl chloride
127	3-(Chloromethyl)-4-(2-methylpropoxy)benzonitrile
128	3-Hydroxymethyl)-4-(2-methylpropoxy)benzonitrile
129	4-Bromophenol
130	4-Iodophenol
131	1-Iodo-2-methylpropane
132	1-Bromo-4-(2-methylpropoxy)benzene
133	1-Iodo-4-(2-methylpropoxy)benzene
134	Ethyl 2-(3,5-diformyl-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
135	Ethyl 4-hydroxybenzoate
136	Ethyl 3-formyl-4-hydroxybenzoate
137	Ethyl 3-formyl-4-(2-methylpropoxy)benzoate
138	Ethyl 3-cyano-4-(2-methylpropoxy)benzoate
139	2-Bromobenzonitrile
140	2-(2-Methylpropoxy)benzonitrile
141	Ethyl (4-methyl-5-boronoic acid)-1,3-thiazole-5-carboxylate
142	4-[(*Z*)-(Hydroxyimino)methyl]phenol
143	2-Methylpropyl methanesulfonate
144	2-Methylpropyl benzenesulfonate
145	2-Methylpropyl 4-methylbenzenesulfonate
146	Ethyl 2-(3,5-dicyano-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
147	2-(3,5-Dicyano-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylic acid
148	Ethyl 2-[3,5-diformyl-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylate
149	Ethyl 2-[3,5-dicyano-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylate
150	2-[3,5-Dicyano-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid
151	Dimethyl 4-(2-methylpropoxy)benzene-1,3-dicarboxylate
152	4-(2-Methylpropoxy)benzene-1,3-dicarboxamide
153	2-[3-Carbamoyl-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid
154	Ethyl 2-(1λ^5-diazyn-1-ylidene)-3-oxobutanoate

REACTION SCHEMES



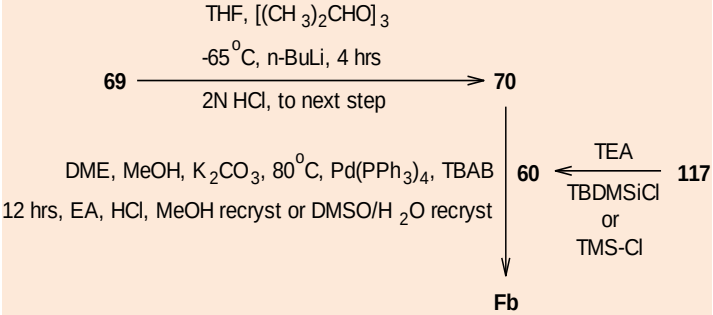
Scheme 1: Synthesis of **Fb** from **115** as per the disclosure by Ge [12]



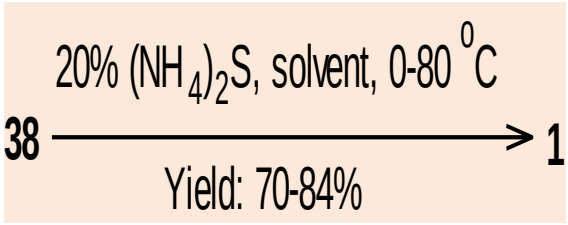
Scheme 2a: Synthesis of **Fb** from **69** as per the disclosure by Mizhiritskii et al. [14]

Mediterranean Journal of
Pharmacy & Pharmaceutical Sciences
www.medjpps.com

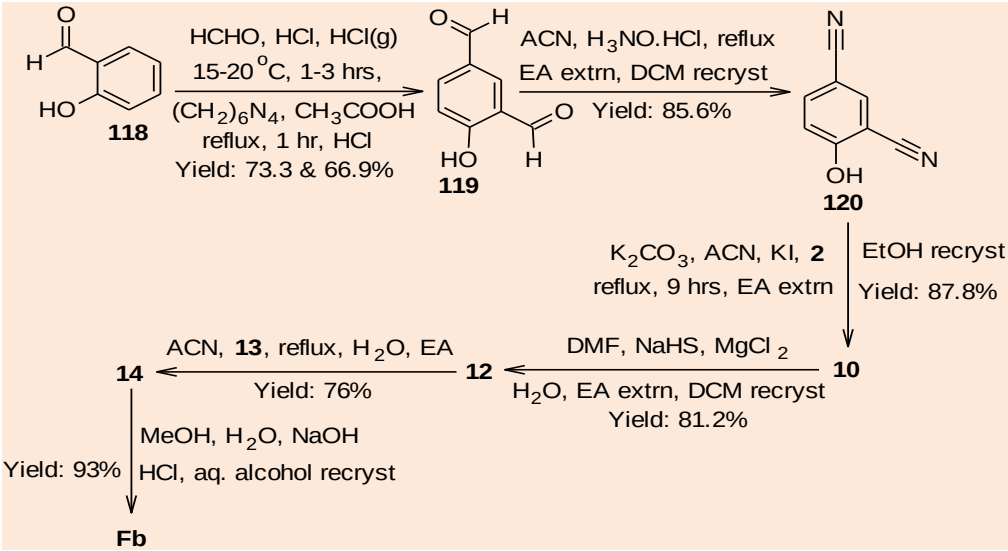
ISSN: 2789-1895 online
ISSN: 2958-3101 print



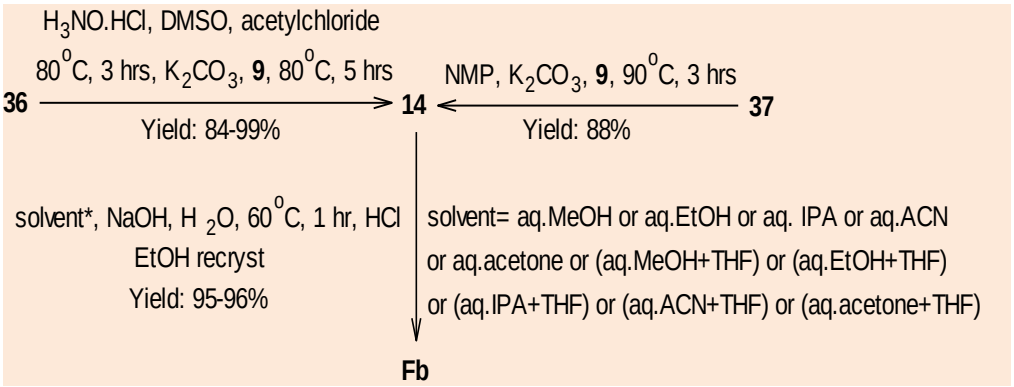
Scheme 2b: Synthesis of **Fb** from **69** as per the disclosure by Mizhiritskii et al. [14]



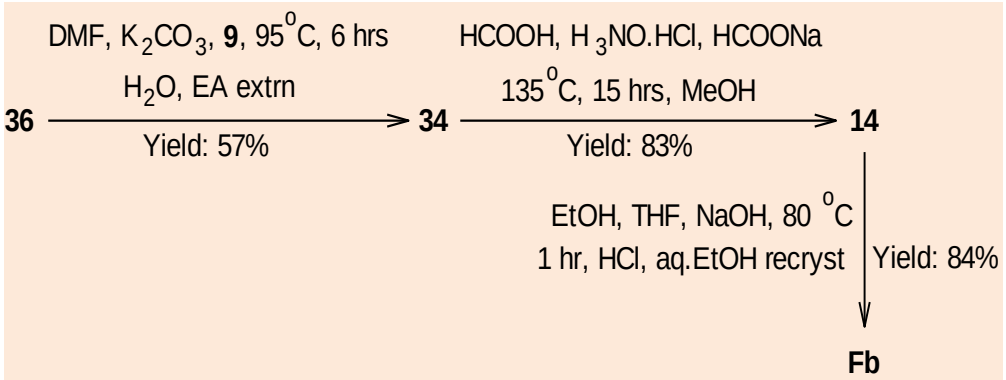
Scheme 3: Synthesis of **1** from **38** as per the disclosure by Zhang et al. [16]



Scheme 4: Synthesis of **Fb** from **118** as per the disclosure by Zhou & Liu [18]

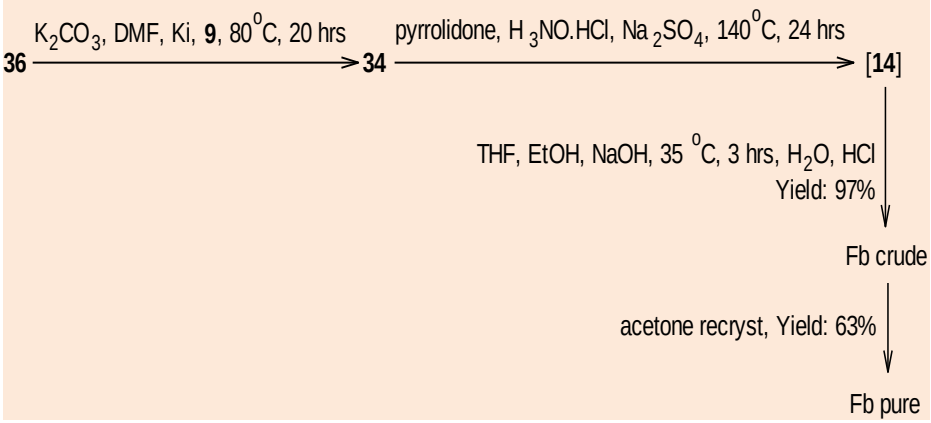


Scheme 5: Synthesis of **Fb** from **36** or **37** as per the disclosure by Vellanki et al. [19]

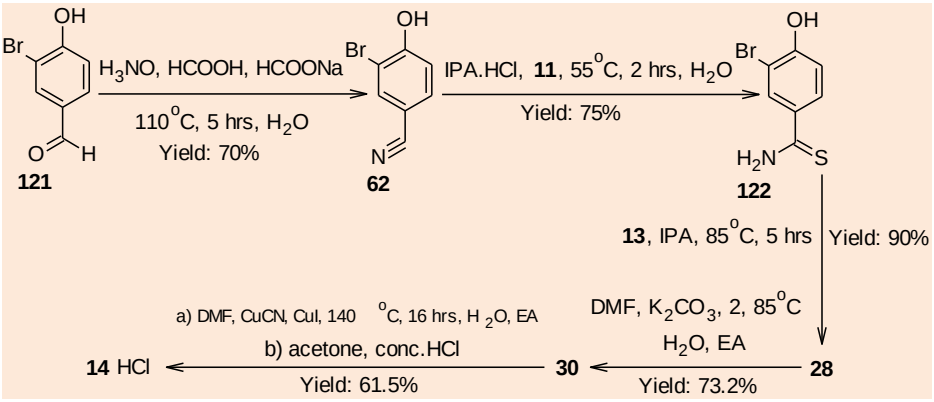


Scheme 6: Synthesis of **Fb** from **36** as per the disclosure by Zhou [20]

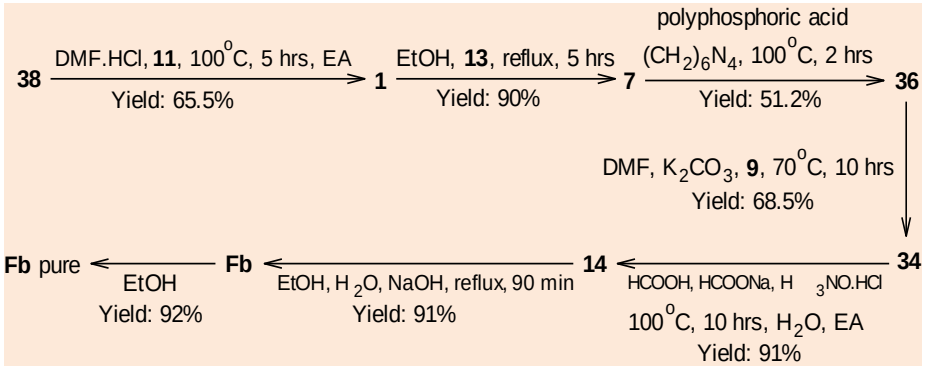
ISSN: 2789-1895 online
ISSN: 2958-3101 print



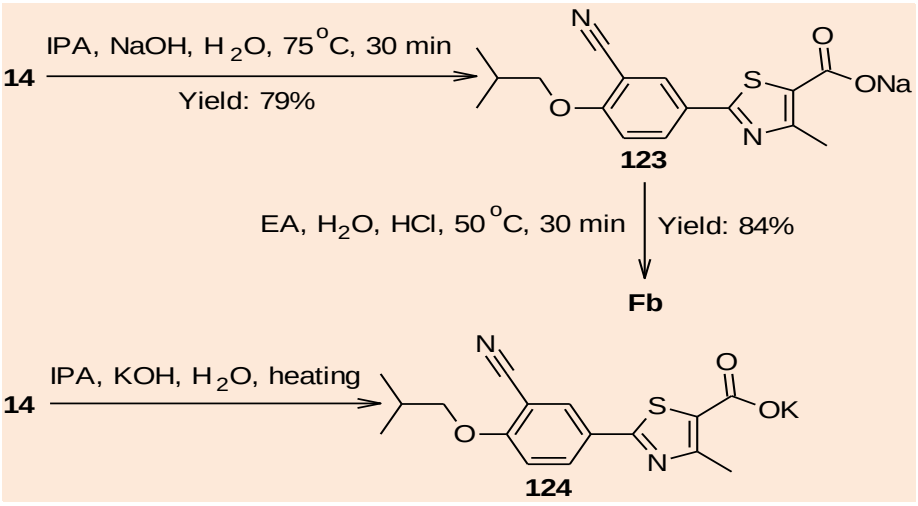
Scheme 7: Synthesis of **Fb** from **36** as per the disclosure by Lv et al. [21]



Scheme 8: Synthesis of **Fb** from **121** as per the disclosure by Kompalla et al. [22]



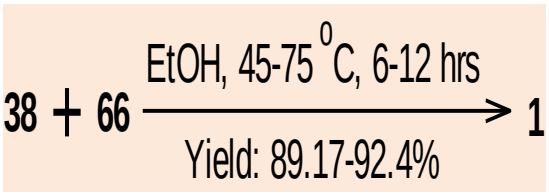
Scheme 9: Synthesis of **Fb** from **38** as per the disclosure by Zhang [23]



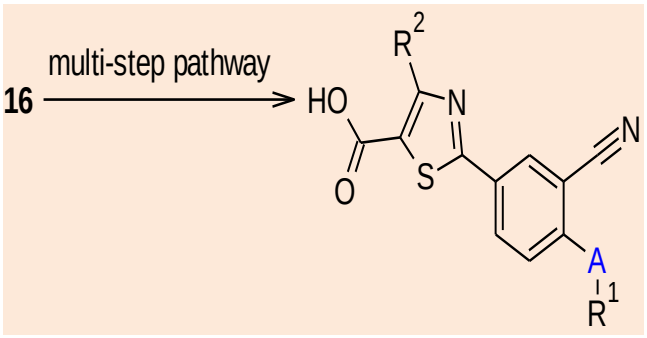
Scheme 10: Synthesis of **Fb** and its salts from **14** as per the disclosure by Dwivedi et al. [24]

Mediterranean Journal of
Pharmacy & Pharmaceutical Sciences
www.medjpps.com

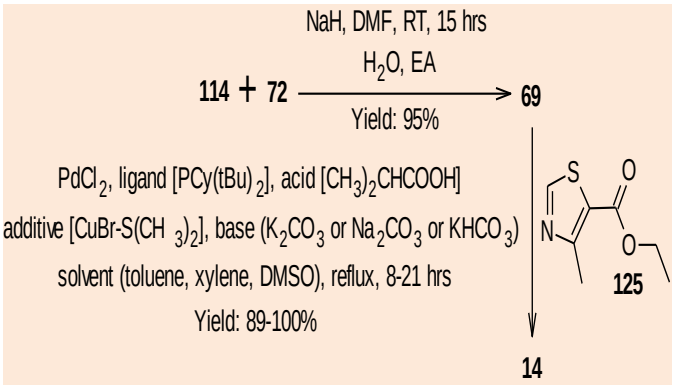
ISSN: 2789-1895 online
ISSN: 2958-3101 print



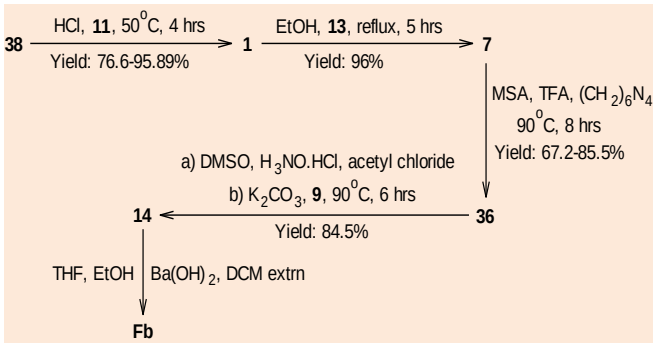
Scheme 11: Synthesis of **1** from **38** as per the disclosure by Wang et al. [29]



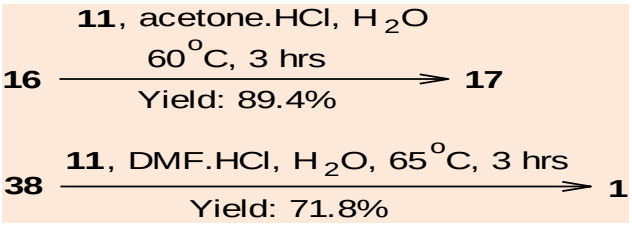
Scheme 12: Synthesis of **Fb** and some of its related compounds as per the disclosure by Wang et al. [30]



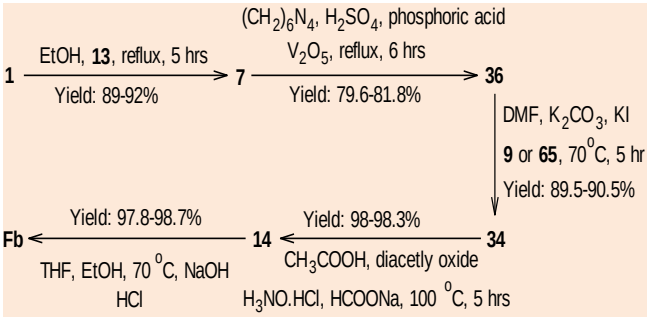
Scheme 13: Synthesis of **14** from **72** & **114** as per the disclosure by Komiyama [31]



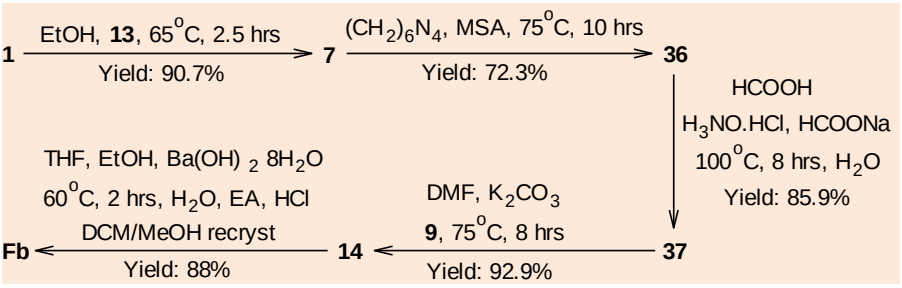
Scheme 14: Synthesis of **Fb** from **38** as per the disclosure by Zhang et al. [32]



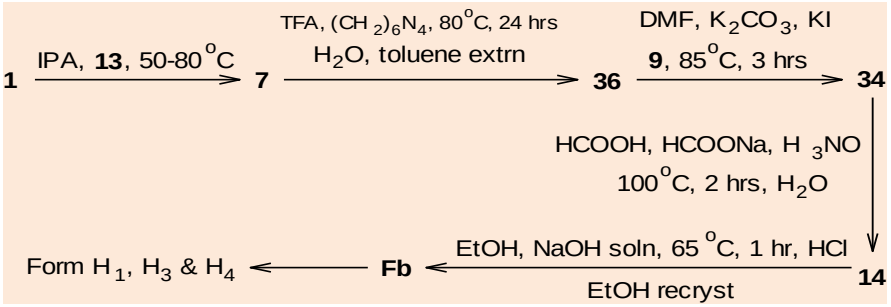
Scheme 15: Synthesis of **1** & **17** as per the disclosure by Li [35]



Scheme 16: Synthesis of **Fb** from **1** as per the disclosure by Li et al. [36]

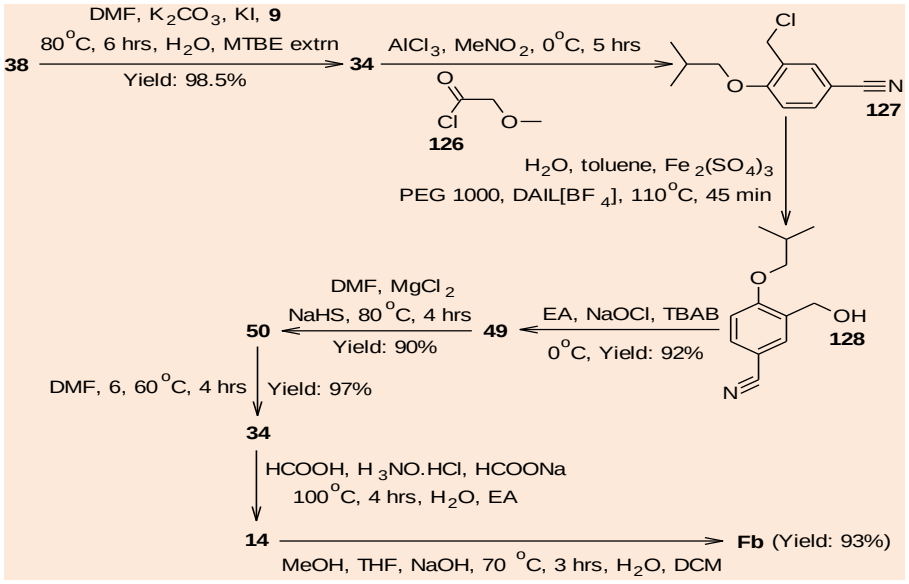


Scheme 17: Synthesis of **Fb** from **1** as per the disclosure by Pranab et al. [37]

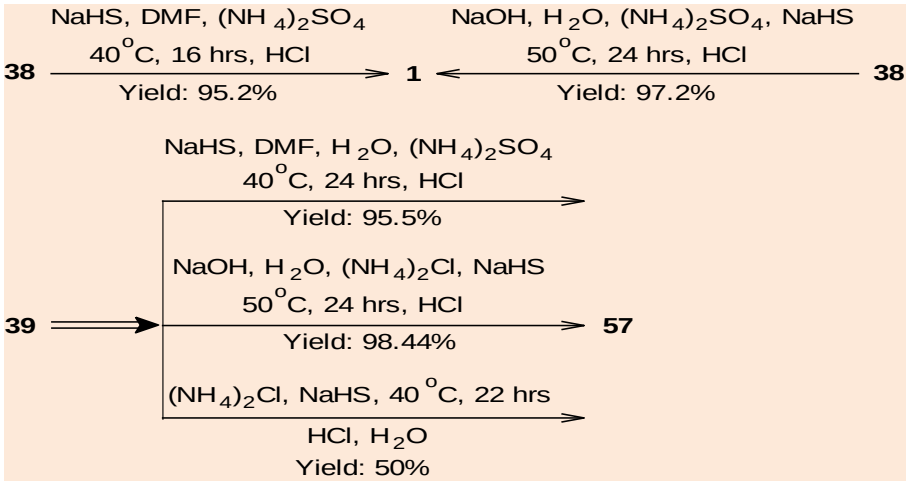


Scheme 18: Synthesis of **Fb** from **1** as per the disclosure by Parthasaradhi et al. [40]

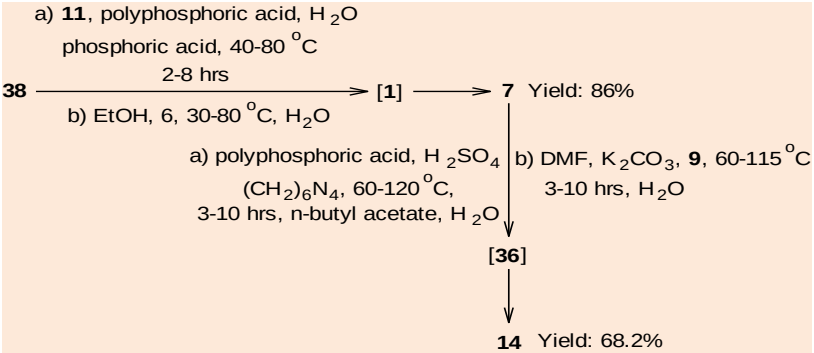
ISSN: 2789-1895 online
ISSN: 2958-3101 print



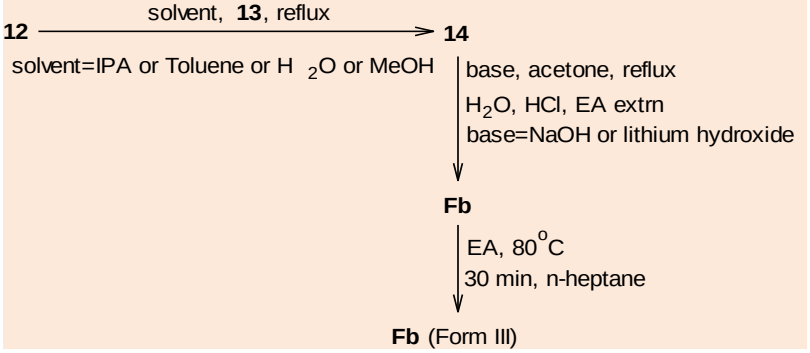
Scheme 19: Synthesis of **Fb** from **38** as per the disclosure by Huang & Huang [41]



Scheme 20: Synthesis of **1** & **57** as per the disclosure by Chen & Su [43]

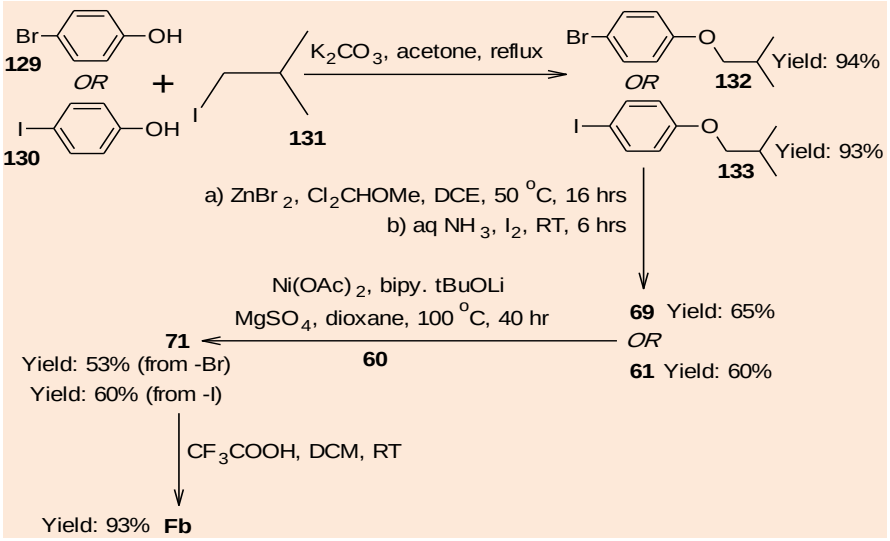


Scheme 21: Synthesis of **14** from **38** as per the disclosure by Lou et al. [44]

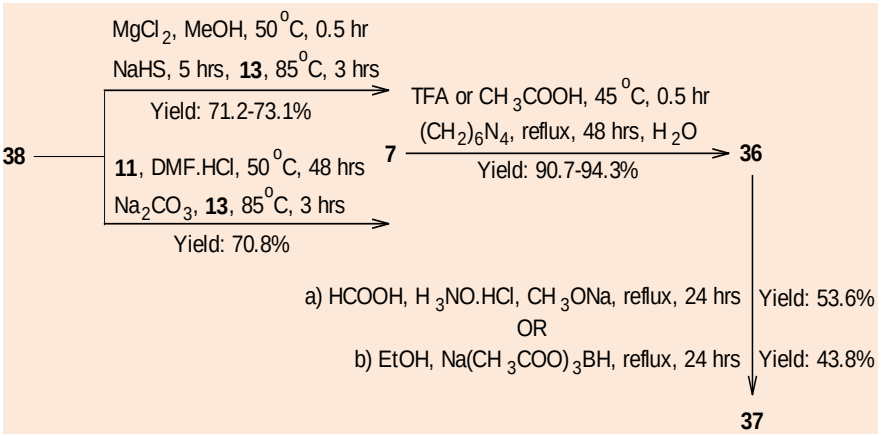


ISSN: 2789-1895 online
ISSN: 2958-3101 print

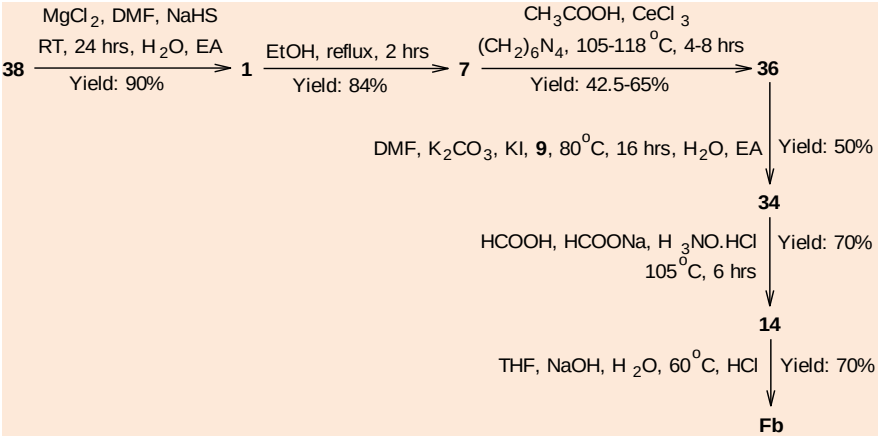
Scheme 22: Synthesis of **Fb** from **12** as per the disclosure by Praveen et al. [45]



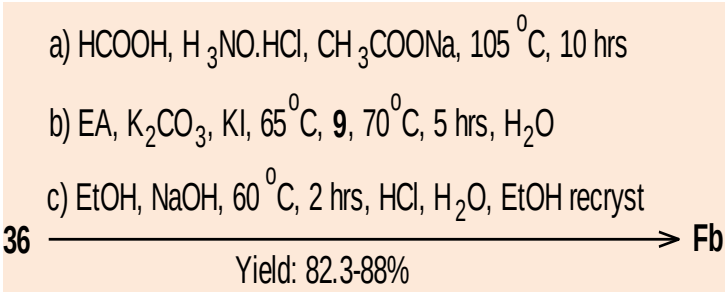
Scheme 23: Synthesis of **Fb** from **129** or **130** as per the disclosure by Tamura et al. [46]



Scheme 24: Synthesis of **37** from **38** as per the disclosure by Li & Li [47]

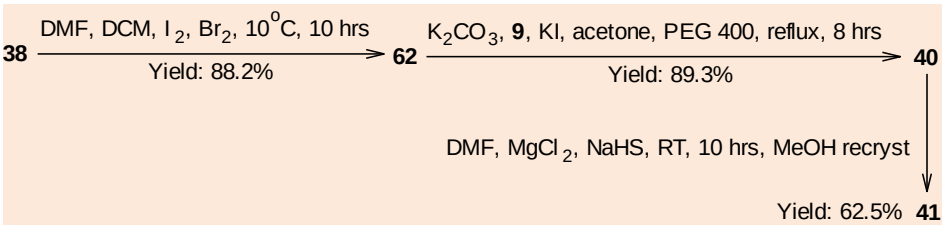


Scheme 25: Synthesis of **Fb** from **38** as per the disclosure by Cui & Feng [48]

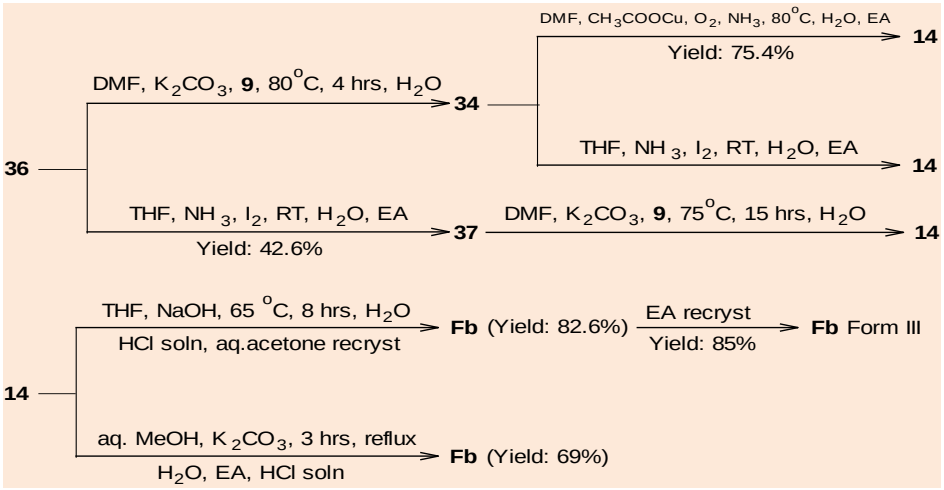


Scheme 26: Synthesis of **Fb** from **36** as per the disclosure by Wang et al. [49]

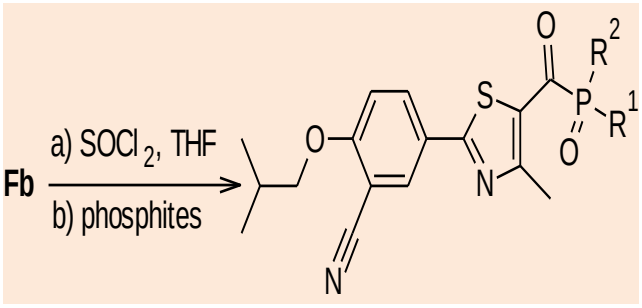
ISSN: 2789-1895 online
ISSN: 2958-3101 print



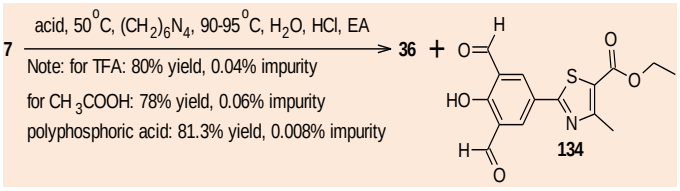
Scheme 27: Synthesis of **41** from **38** as per the disclosure by Wang et al. [50]



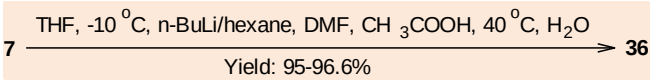
Scheme 28: Synthesis of **Fb** from **36** as per the disclosure by Koftis et al. [51]



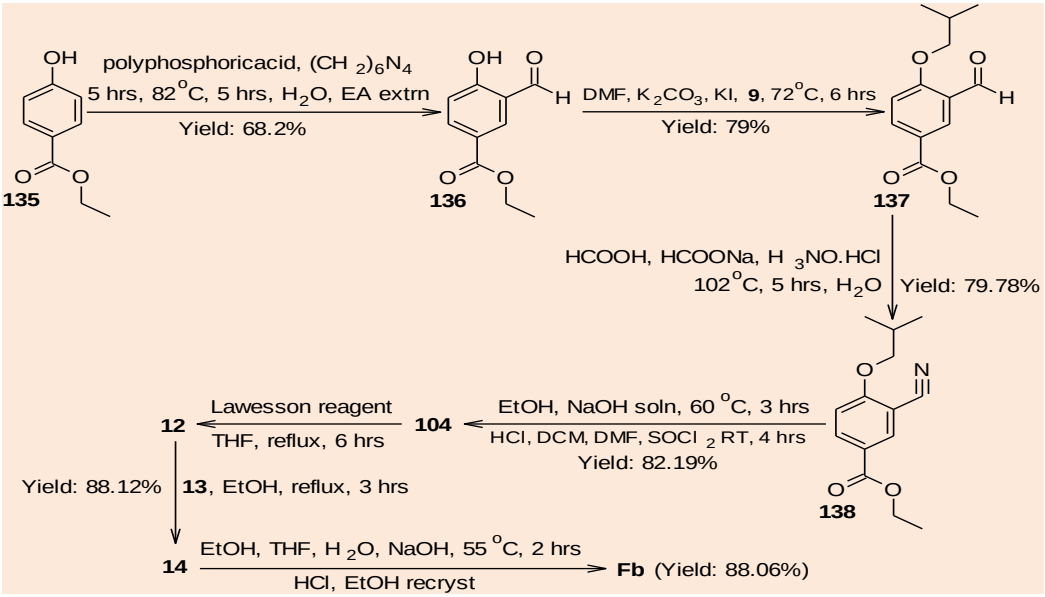
Scheme 29: Synthesis of phosphonate derivatives of **Fb** as per the disclosure by Reddy et al. [53]



Scheme 30: Synthesis of impurity-free **36** from **7** as per the disclosure by Wei [54]



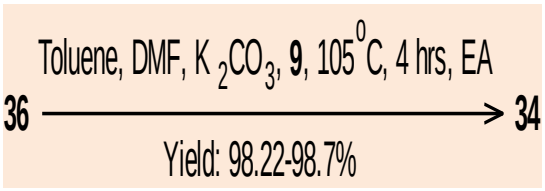
Scheme 31: Synthesis of **36** from **7** as per Zhao et al. [55]



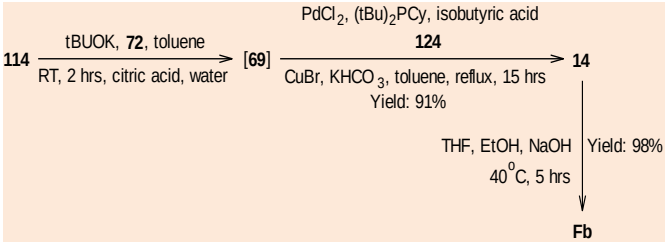
Scheme 32: Synthesis of **Fb** from **135** as per the disclosure by Liu, et al. [56]

Mediterranean Journal of
Pharmacy & Pharmaceutical Sciences
www.medjpps.com

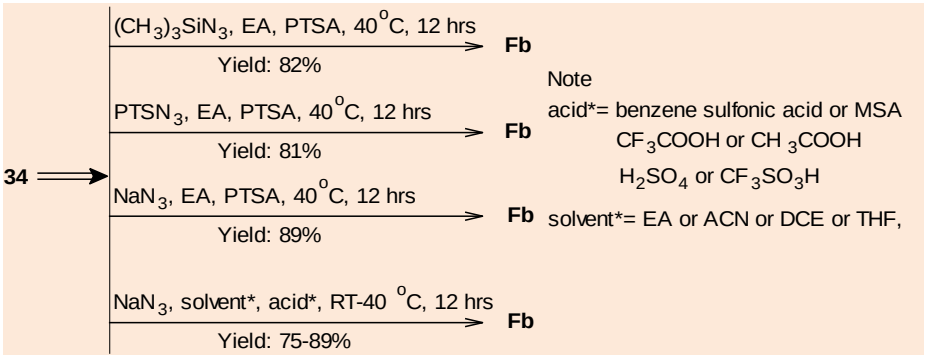
ISSN: 2789-1895 online
ISSN: 2958-3101 print



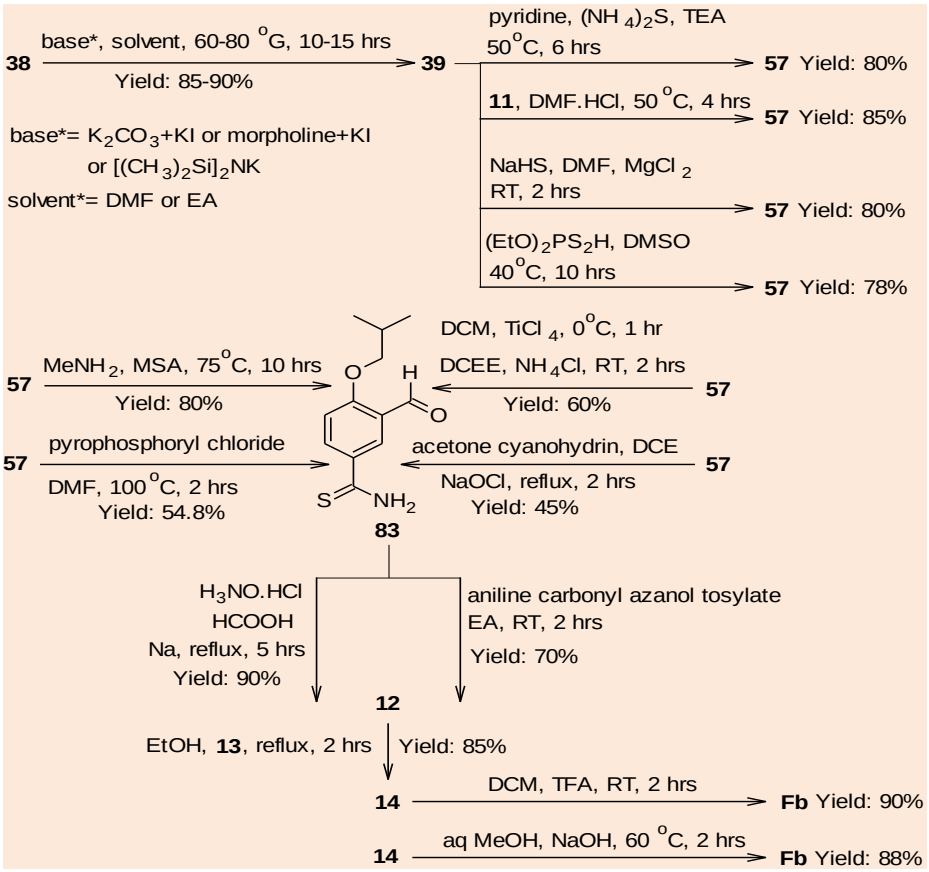
Scheme 33: Synthesis of **34** from **36** as per the disclosure by Gong, et al. [61]



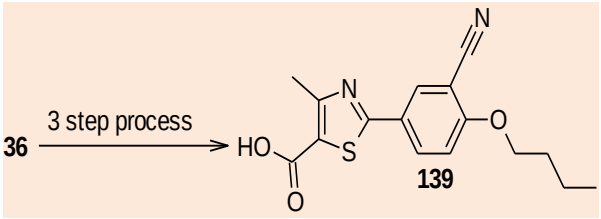
Scheme 34: Synthesis of **Fb** from **114** as per the disclosure by Komiyama, et al. [62]



Scheme 35: Synthesis of **Fb** from **34** as per the disclosure by Shi et al. [63]

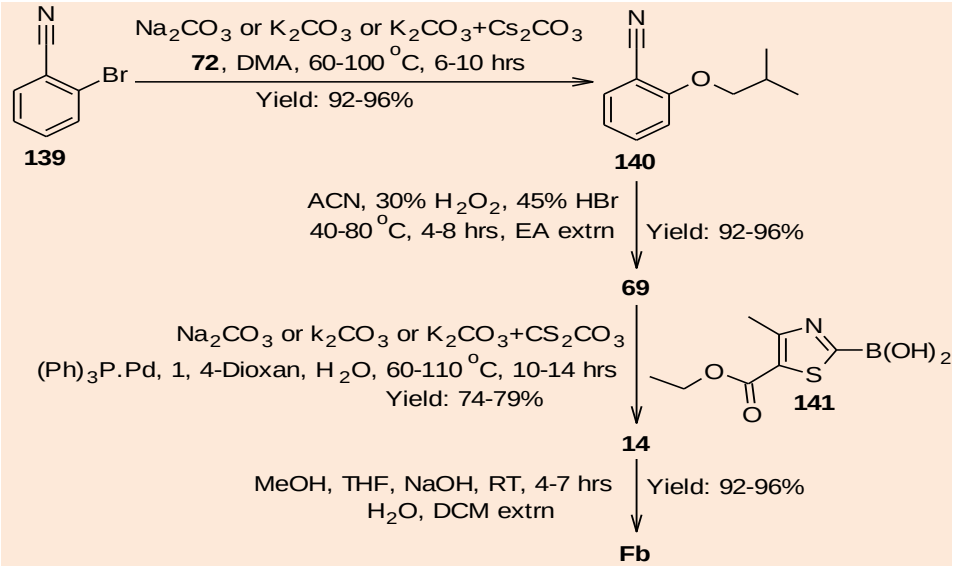


Scheme 36: Synthesis of **Fb** from **38** as per the disclosure by Zhou et al. [65]

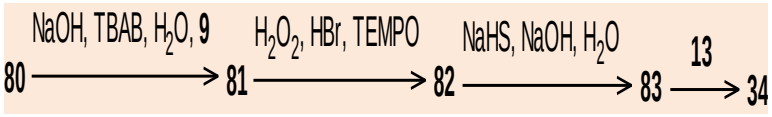


Scheme 37: Synthesis of **139** from **36** as per the disclosure by Zhang et al. [66]

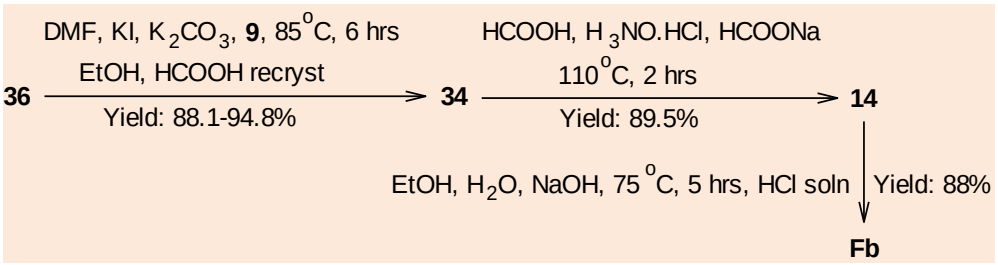
ISSN: 2789-1895 online
ISSN: 2958-3101 print



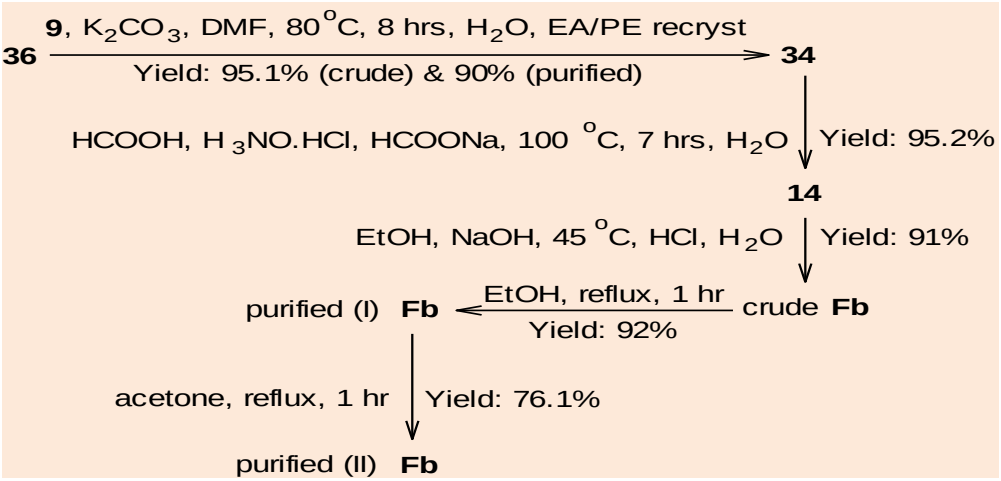
Scheme 38: Synthesis of **Fb** from **138** as per the disclosure by Huang et al. [67]



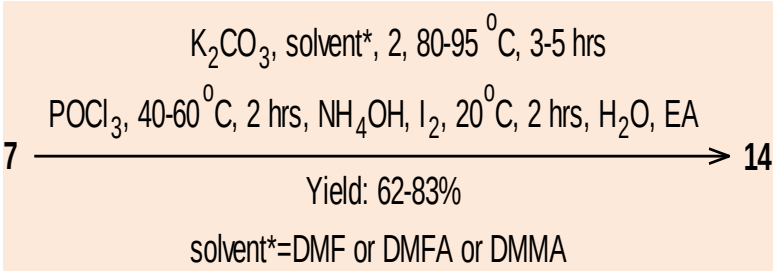
Scheme 39: Synthesis of **34** from **80** as per the disclosure by Huang, et al. [68].



Scheme 40: Synthesis of **Fb** from **36** as per the disclosure by Zhang et al. [69]

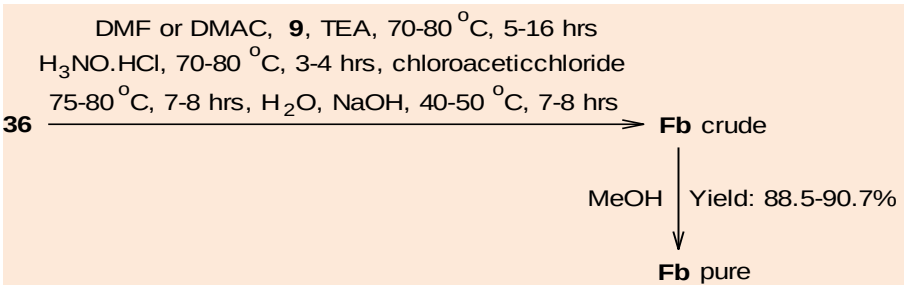


Scheme 41: Synthesis of **Fb** from **36** as per the disclosure by Wang et al. 2019 [70]

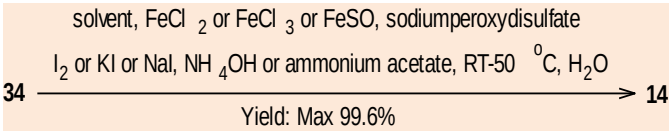


Scheme 42: Synthesis of **14** from **7** as per the disclosure by Yan et al. [71]

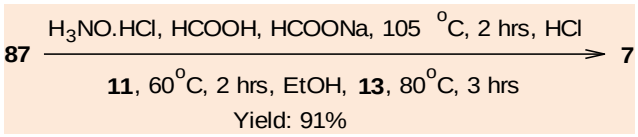
ISSN: 2789-1895 online
ISSN: 2958-3101 print



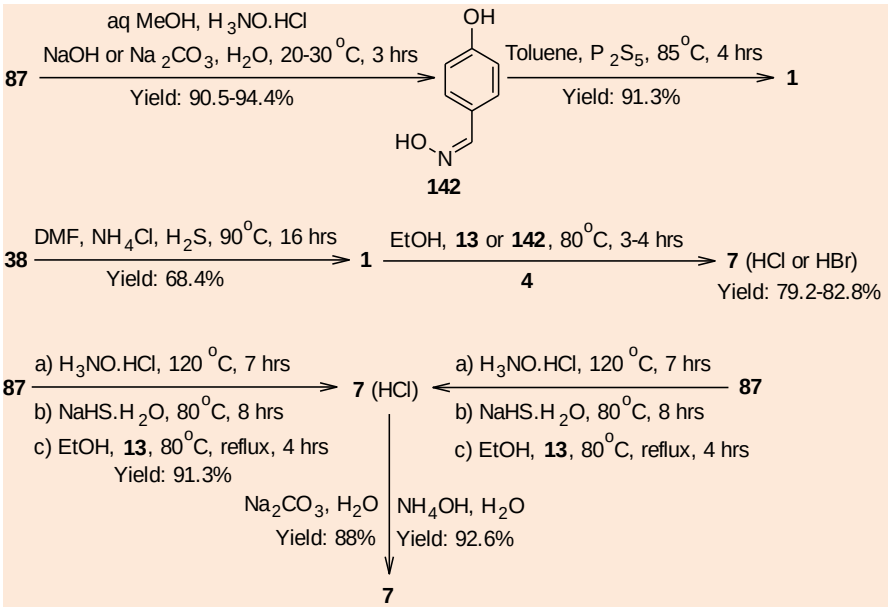
Scheme 43: Synthesis of **Fb** from **36** as per the disclosure by Zhang et al. [72]



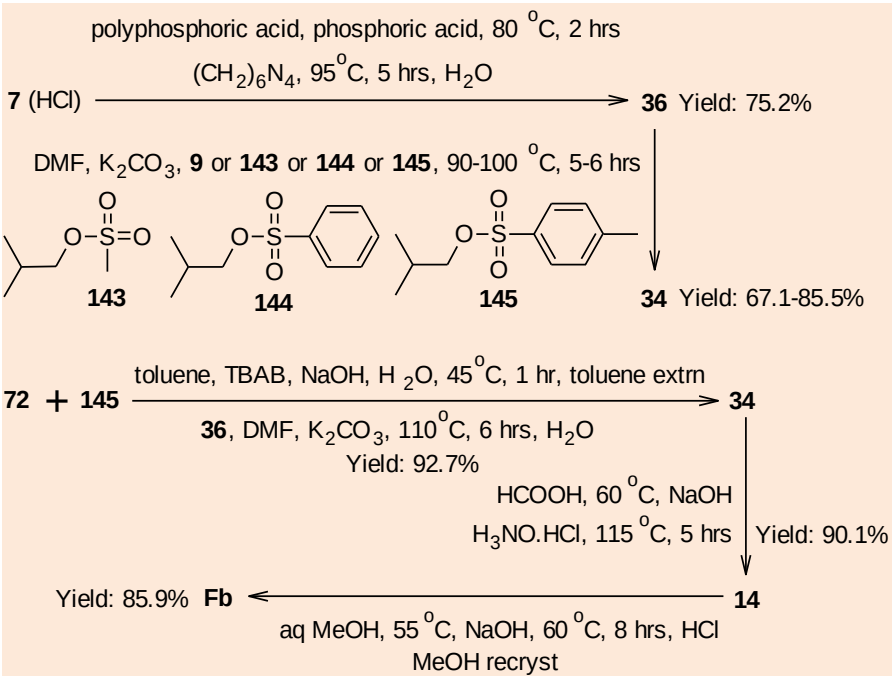
Scheme 44: Synthesis of **14** from **34** as per the disclosure by Zhou et al. [73]



Scheme 45: Synthesis of **7** from **87** as per the disclosure by Zhang et al. [75]

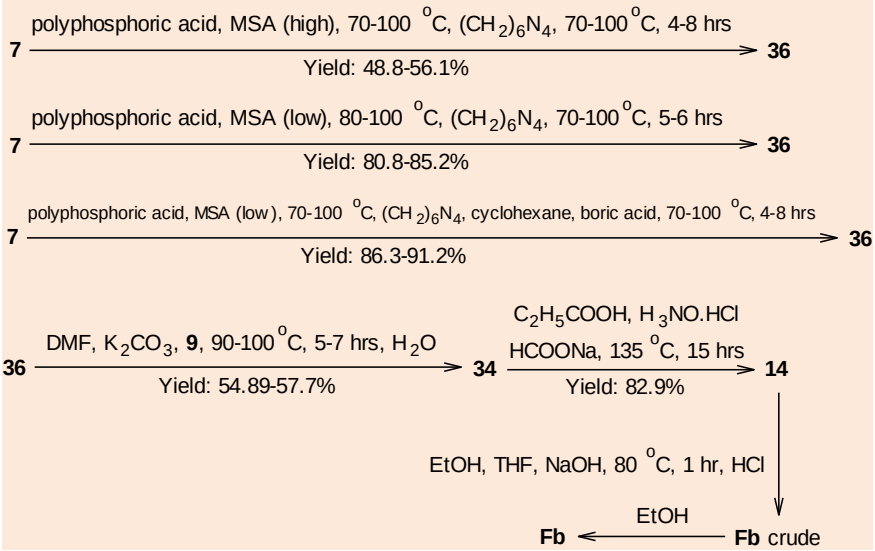


Scheme 46a: Synthesis of **7** from **87** or **38** as per the disclosure by Lyu et al. [78]

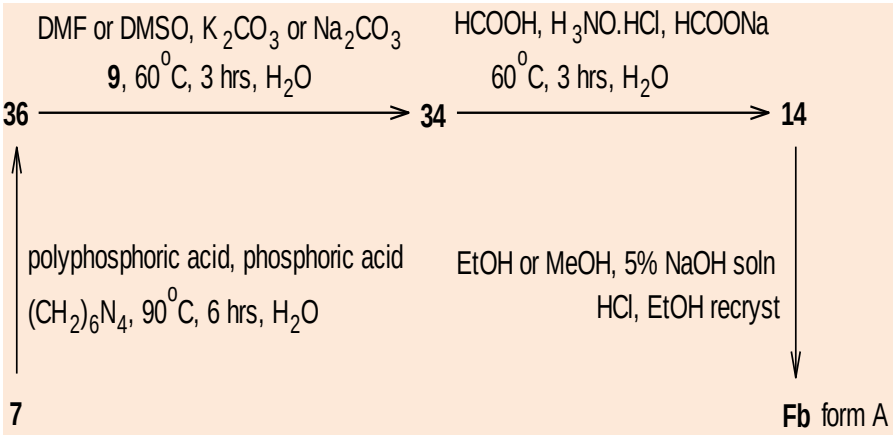


Scheme 46b: Synthesis of **Fb** from **7** as per the disclosure by Lyu & Guo [78]

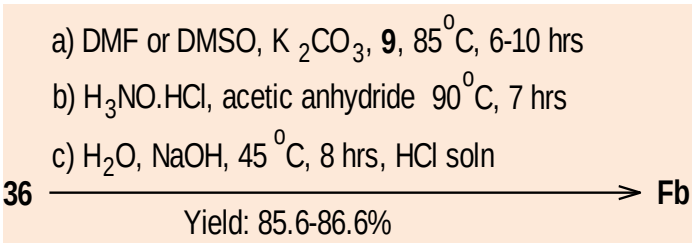
ISSN: 2789-1895 online
ISSN: 2958-3101 print



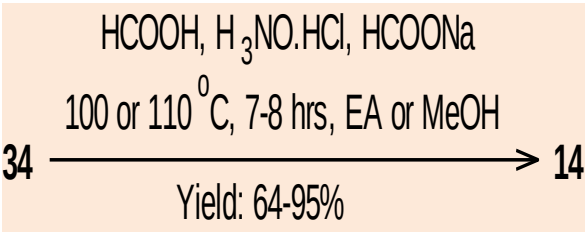
Scheme 47: Synthesis of **Fb** from **7** as per the disclosure by Tang et al. [79]



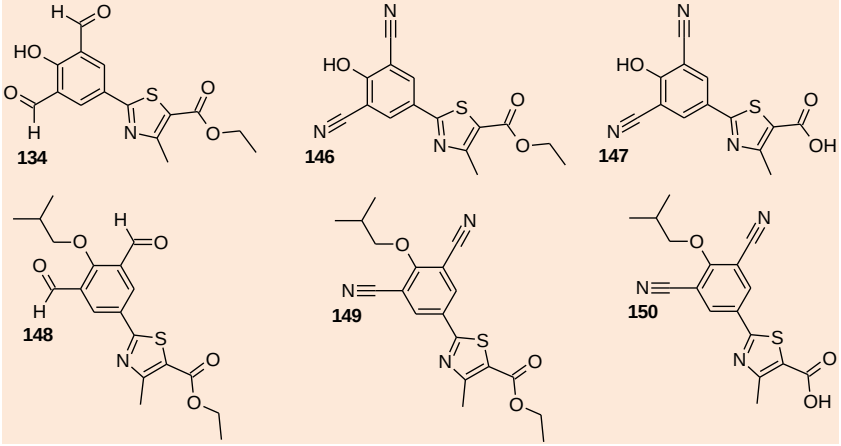
Scheme 48: Synthesis of **Fb** from **7** as per the disclosure by Lu [81]



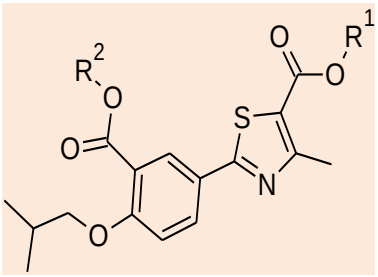
Scheme 49: Synthesis of **Fb** from **36** as per the disclosure by Liu & Su [82]



Scheme 50: Synthesis of **14** from **34** as per the disclosure by Sun et al. [83]

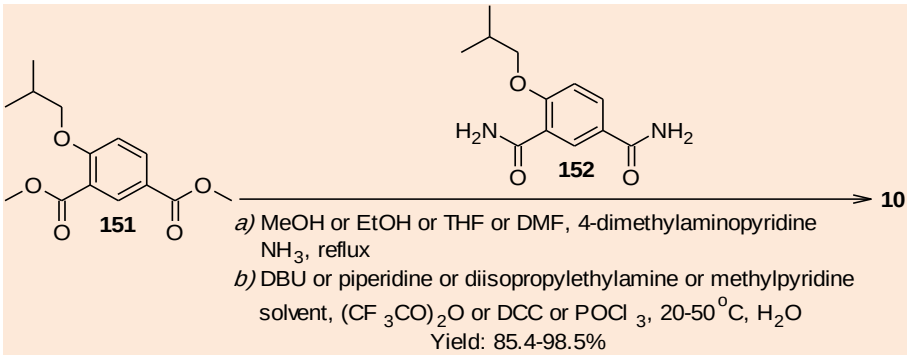


Scheme 51: Impurities of **Fb** as per the disclosure by Xu et al. [84]

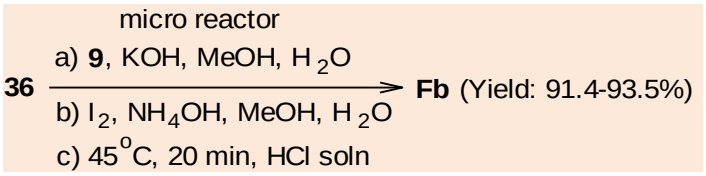


Scheme 52: Impurities of **Fb** as per the disclosure by Liu et al. [86].

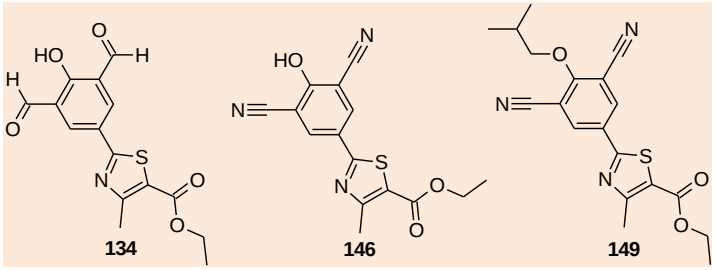
ISSN: 2789-1895 online
ISSN: 2958-3101 print



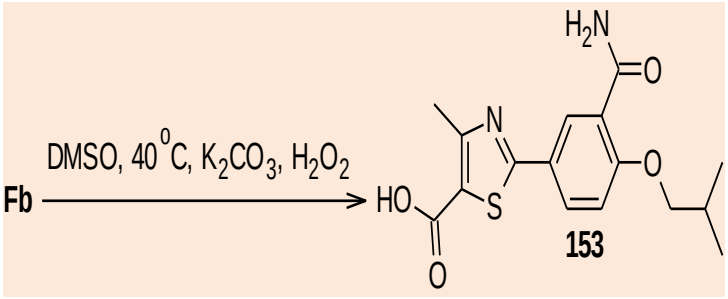
Scheme 53: Synthesis of **10** from **152** as per the disclosure by Song & Li [87]



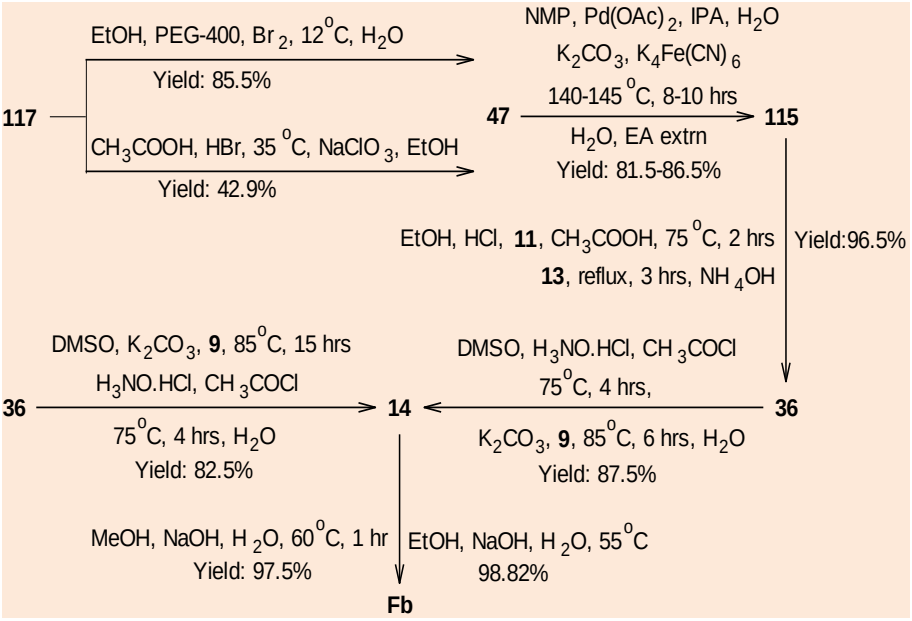
Scheme 54: Synthesis of **Fb** from **36** in a micro-reactor as per the disclosure by Lai et al. [88]



Scheme 55: Impurities of **Fb** as per the disclosure by Sun & Yang [90]

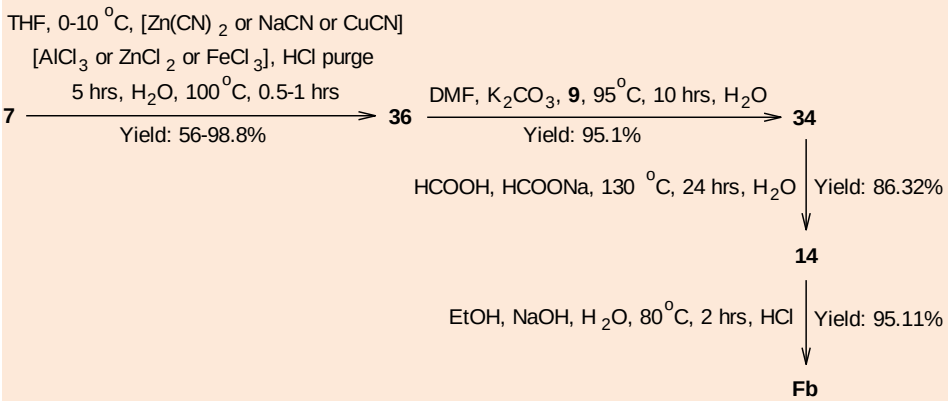


Scheme 56: Synthesis of **153** from **Fb** as per the disclosure by Chai et al. [91]

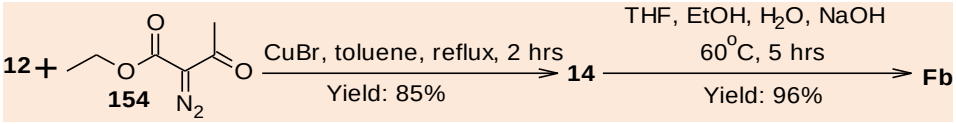


Scheme 57: Synthesis of **Fb** from **117** as per the disclosure by Ji et al. [92]

ISSN: 2789-1895 online
ISSN: 2958-3101 print



Scheme 58: Synthesis of **Fb** from **7** as per the disclosure by Leng et al. [93].



Scheme 59: Synthesis of **Fb** from **12** as per the disclosure by Manda et al. [95].

Table 4 provides the summary of research disclosures in accordance to their region-specific origin. Under the context, there are seven countries which had contributed towards the synthesis, process development, crystallographic study etc of **Fb** and its related scaffolds through various organizations/institutions/laboratories/individuals etc. Interestingly, China tops the chart with regard to research disclosures on **Fb**.

Table 4: Country-wise list of institutions/organizations/laboratories/individuals etc. behind the synthesis of **Fb** and its related compounds

Ref.	Research work was executed by or belongs to	Country
[10]	Ranbaxy Laboratories Ltd.	India
[11]	Hangzhou Zhuyangxin Pharmaceutical Co., Ltd.	China
[12]	Individual	China
[13]	Mylan Laboratories Ltd.	India
[14]	Mapi Pharma Ltd.	Israel
[15]	Hangzhou Zhuyangxin Pharmaceutical Co., Ltd.	China
[16]	Nanjing Huawe Medicine Technology Development Co., Ltd.	China
[17]	Natco Pharma Ltd.	India
[18]	Individual	China
[19]	Mylan Laboratories Ltd.	India
[20]	Anhui Youcare Kaiyue Pharmaceutical Co., Ltd.	China
[21]	China Resources Saike Pharmaceutical Co., Ltd.	China
[22]	Natco Pharma Ltd.	India
[23]	Guizhou Xinbang Pharmaceutical Co., Ltd.	China
[24]	Cadila Healthcare Ltd. & Zydus Lifesciences Ltd.	India
[25]	Jilin Sanshanen Technology Development Co., Ltd.	China
[26]	Jilin Institute of Chemical Technology	China
[27]	Interquim S. A.	Spain
[28]	Mapi Pharma Ltd.	Israel
[29]	Suzhou Chenghe Pharmaceutical and Chemical Co., Ltd.	China
[30]	Shenyang Pharmaceutical University	China
[31]	Teijin Pharma Ltd.	Japan
[32]	South China University Of Technology	China
[33]	Apeloa Pharmaceutical Co., Ltd. & Shanghai Puluochuangzhi Pharmaceutical Technology Co., Ltd. & Zhejiang	China
[34]	Beijing Lilesheng Pharmaceutical Technology Co., Ltd. & Fujian Zerui Pharmaceutical Co., Ltd.	China

ISSN: 2789-1895 online
ISSN: 2958-3101 print

[35]	Chongqing Co., Ltd. of Hui Zhi Drug Research Institute. & Chongqing Shenghuaxi Pharmaceutical Co., Ltd.	China
[36]	Chongqing Kerui Pharmaceutical Group Co., Ltd.	China
[37]	Ranbaxy Laboratories Ltd. & Sun Pharmaceutical Industries Ltd.	India
[38]	Macleods Pharmaceuticals Ltd. & Pacific University	India
[39]	South China University of Technology & Guangdong Roth Pharmaceutical Co., Ltd.	China
[40]	Hetero Research Foundation	India
[41]	Anhui Qingyun Pharmaceutical and Chemical Co., Ltd. & Zhejiang Ao Xiang Medicine Co., Ltd.	China
[42]	Hangzhou Huadong Medicine Group Biological Engineering Research Institute Co., Ltd. & Hangzhou Zhongmei	China
[43]	Guangdong HEC Pharmaceutical	China
[44]	Weifang Hishine Pharmaceutical Co., Ltd. & Zhejianghuayi Pharmaceutical Co., Ltd.	China
[45]	Dr. Reddys Laboratories Ltd.	India
[46]	Graduate School of Science, Chiba University	Japan
[47]	Suzhou Jonathan New Materials Technology Co., Ltd.	China
[48]	Knowshine (Shanghai) Pharmachemicals Inc.	China
[49]	Zhejiang Huahai Pharmaceutical Co., Ltd.	China
[50]	School of Pharmacy & Jiangxi Science & Technology Normal University	China
[51]	Pharmathen S. A.	Germany
[52]	Zhejiang University	China
[53]	Sri Venkateswara University	India
[54]	Individual	China
[55]	Shandong Baoyuan Pharmaceutical Co., Ltd.	China
[56]	Qingdao Huanghai Pharmaceutical Co., Ltd.	China
[57]	Yangtze River Pharmaceutical Group Co., Ltd. & Jiangsu Coast Pharmaceutical Corporation Ltd.	China
[58]	Suzhou Hong Sen Pharmaceutical Ltd By Share Ltd.	China
[59]	CHA University, J2H biotech & Kyungpook National University	Korea
[60]	Zhejiang University	China
[61]	Wudi Reaction Pharma & Chemical Co., Ltd.	China
[62]	Teijin Pharma Ltd.	Japan
[63]	Tianjin Lisheng Pharmaceutical Co., Ltd.	China
[64]	Kamp Pharmaceuticals Co., Ltd.	China
[65]	Jiangxi with and Medicine Co Limited-Liability Co.	China
[66]	Beijing Voban Pharmaceutical Co., Ltd.	China
[67]	Qingyun Anhui Pharmaceutical Ltd, by Share Ltd.	China
[68]	Qingyun Anhui Pharmaceutical Ltd, by Share Ltd.	China
[69]	Hunan Fangsheng Pharmaceutical Co., Ltd.	China
[70]	Kunming Yuanrui Pharmaceutical Co., Ltd.	China
[71]	Harvest (Hunan) Pharmaceutical Technology Co., Ltd.	China
[72]	Fuan Pharmaceutical Group Pharmaceutical Co., Ltd., Chongqing Bosheng	China
[73]	Merro Pharmaceutical Co., Ltd., Dalian University of Technology	China
[74]	College of Chemical Engineering and Resource Recycling, Wuzhou University	China
[75]	Hubei Polytechnic University	China
[76]	Shandong Lenno Pharmaceutical Co., Ltd.	China
[77]	Wuhan Guanggu Asia-Pacific Medical Research Institute Co., Ltd.	China
[78]	Jinan Lide Medical Technology Co., Ltd. & Inner Mongolia Jingdong Pharmaceutical Co., Ltd.	China
[9]	Hangzhou Zhuyangxin Pharmaceutical Co., Ltd.	China
[80]	Hangzhou Zhuyangxin Pharmaceutical Co., Ltd.	China
[81]	Emeishan Hongsheng Pharmaceutical Co., Ltd.	China
[82]	Chongqing Changjie Pharmaceutical Co., Ltd. & Chongqing Shenghuaxi Pharmaceutical Co., Ltd.	China
[83]	Beijing Xinkaiyuan Pharmaceuticals Co., Ltd.	China
[84]	Wuhan Guanggu Asia-Pacific Medical Research Institute Co., Ltd.	China
[85]	Wuhan Guanggu Asia-Pacific Medical Research Institute Co., Ltd.	China

ISSN: 2789-1895 online
ISSN: 2958-3101 print

[86]	Wuhan Berek Pharmaceutical Technology Co., Ltd.	China
[87]	Lunan Pharmaceutical Group Co.	China
[88]	Fujian Haixi Pharmaceuticals Co., Ltd.	China
[89]	Zhejiang Tianyu Pharmaceutical Co., Ltd.	China
[90]	Langfang Normal University	China
[91]	Hanrui Pharmaceutical Jingmen Co., Ltd.	China
[92]	Jining Shengtai Pharmaceutical Co., Ltd.	China
[93]	Hubei Waterstone Bio Pharmaceutical Technology Co., Ltd.	China
[94]	Multination collaborative research initiative.	NA
[95]	CSIR-Indian Institute of Chemical Technology & Academy of Scientific and Innovative Research	India
[96]	Multination collaborative research initiative.	NA

Conclusion: This review segment (**Part II**) comprises the union of past research disclosures from 2013-2024 towards the synthesis of **Fb** and its closely associated compounds. In line with this, 87 scientific communications in the form of patents/journal articles were examined and the important aspects were sequentially tabulated with 59 supportive reaction schemes. The reaction schemes depicted were self-narrative in nature since all the reaction schemes were furnished with complete details of raw materials, reagents, solvents and catalysts. This initiative has been embedded with crisp insight on the past disclosures with an emphasis on the author/s details, work objectives, route of synthesis, yield, and country-wise work origin. Hence, this segment can push researchers to find new pathways or innovate with the existing routes to synthesize **Fb** in the near future with high yield and purity.

References

1. Tayar JH, Lopez-Olivo MA, Suarez-Almazor ME (2012) Febuxostat for treating chronic gout. Cochrane Database of Systematic Reviews. 11 (11): CD008653. doi: 10.1002/14651858.CD008653.pub2
2. Waller A, Jordan KM (2017) Use of Febuxostat in the management of gout in the United Kingdom. Therapeutic Advances in Musculoskeletal Disease. 9 (2): 55-64. doi: 10.1177/1759720x16682010
3. Collison J (2018) Stepping up febuxostat to treat gout flares. Nature Reviews. Rheumatology. 14 (1): 4. doi: 10.1038/nrrheum.2017.193
4. Sun R, Lu J, Li H, Cheng X, Xin Y, Li C (2020) Evaluation of febuxostat initiation during an acute gout attack: A prospective, randomized clinical trial. Joint, Bone, Spine: Revue Du Rhumatisme. 87 (5): 461-466. doi: 10.1016/j.jbspin.2020.03.017
5. Choi HK, Zhang Y, Dalbeth N (2022) When underlying biology threatens the randomization principle - initial gout flares of urate-lowering therapy. Nature Reviews. Rheumatology. 18 (9): 543-549. doi: 10.1038/s41584-022-00804-5
6. Shang Q, Du B, Mu L, Zhang L, Wang X, Lin T (2023) Clinical observation of Febuxostat in the treatment of gout patients with different body fat levels. Minerva Medica. 114 (3): 416-418. doi: 10.23736/S0026-4806.23.08499-9
7. Hainer BL, Matheson E, Wilkes RT (2014) Diagnosis, treatment, and prevention of gout. American Family Physician. 90 (12): 831-836.
8. Dakkak M, Lanney H (2021) Management of gout: Update from the American college of rheumatology. American Family Physician. 104 (2): 209-210.
9. James R, Paul BJ (2023) New and emerging therapies in gout. Rheumatology & Autoimmunity: 3 (2): 70-77. doi: 10.1002/rai2.12064
10. Sokhi SS, Nath A, Tandon N, Prasad M (2013) Polymorph of 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid. EP2542540A1. European Patent Office.
11. Shen R, Li Y, Tang J, He H, Yao C, Zhao F, Liu Y, Liu Q, Ma W (2013) Stable Febuxostat crystal. CN103396378A. China.
12. Ge C (2013) New preparation method of Febuxostat. CN102936230A. China.
13. Jetti RR, Bhogala BR, Beeravelli S (2013) Process for the preparation of Febuxostat polymorphs. WO2013076738A2. WIPO (PCT).

ISSN: 2789-1895 online
ISSN: 2958-3101 print

14. Mizhiritskii M, Marom E, Rubnov S (2013) Process and intermediates for the preparation of substituted 2-arylthiazole carboxylic acids. WO2013050996A2. WIPO (PCT).
15. Shen R, Li Y, Tang J, He H, Liu Y, Yao C, Ma W (2013) Drug chemical compound for gout. CN103467412A. China.
16. Zhang X, Bao J, Jiang Y, Xiao T, Xu F (2013) Preparation method of Febuxostat intermediate. CN103073465A. China.
17. Kompella AK, Gampa VK, Kusumba S, Adibhatla KSBR, Nannapaneni VC (2013) Stable crystal form of Febuxostat and process for the preparation thereof. WO2013088449A1.WIPO (PCT).
18. Zhou G, Liu X (2013) Synthetic method of Febuxostat. CN102964313A. China.
19. Vellanki SR.P, Sahu A, Raavi S, Nuchu R, Dandala R (2013) Process for the preparation of 2-arylthiazole derivatives. US2013303780A1. United States.
20. Zhou R (2013) Preparation method of Febuxostat. CN103058950A. China.
21. Lv H, Zou J, Yang Y (2013) Preparation method of high-purity Febuxostat. CN103012311A. China.
22. Kompella A, Gampa VGK, Adibhatla KSBR, Nannapaneni VC (2013) Process to prepare ethyl 4-methyl-2-(4-(2-methylpropyloxy)-3-cyanophenyl)-5-thiazolecarboxylate. US20130172571A1. United States.
23. Zhang G (2013) Preparation method and detection method of Febuxostat raw material. CN10303060A. China.
24. Dwivedi SD, Prasad A, Roy RU, Patel MR (2013) Substantially pure salts of Febuxostat and processes for preparation thereof. US2013190366A1. United States.
25. Luo Y, Zhang T, Su H (2013) Febuxostat pharmaceutical co-crystal and preparation method thereof. CN103044353A. China.
26. Luo Y, Qu X, Yang Y, Lian L, Cao X, Hou Y, Zhou G (2013) Novel Febuxostat pharmaceutical co-crystal and preparation method thereof. CN103058951A. China.
27. Salaet-Ferre J, Marquillas-Olondriz F (2013) Process for preparing the crystalline form II of Febuxostat. EP2593442A1. European Patent Office.
28. Marom E, Rubnov S (2013) Polymorphs of Febuxostat. US2013225830A1. United States.
29. Wang L, Xia Q, Chen J (2013) Method for synthesizing p-hydroxyl thiobenzamide. CN103396347A. China.
30. Wang S, Shi X, Lin Y (2013) 2-(3-cyano-4-alkoxy) phenyl-4-substituted thiazole-5-formic acid compound, composition as well as preparation methods and applications thereof. CN103333134A. China.
31. Komiyama M (2013) Method for producing phenyl-substituted heterocyclic derivative by means of coupling method using a palladium compound. CN103068807A. China.
32. Zhang L, Ren Y, Li J (2013) Preparation method for Febuxostat. CN103304512A. China.
33. Sun G, Zhou Y, Liu S, Chen J, Feng L, Ge M (2014) Preparation method of 2-(3-cyan-4-isobutoxyphenyl)-4-methylthiazole-5-formic acid A crystal. CN103739568A. China.
34. Zhang Y (2014) 2-[3-cyano-4-isobutoxy phenyl]-4-methylthiazole-5-formic acid crystal forms and preparation method thereof. CN103936689A. China.
35. Li N (2014) Preparation method of 3,4-substitituted thiobenzamide and application of 3,4-substitituted thiobenzamide in Febuxostat synthesis. CN104163782A. China.
36. Li Q, Liu R, Liu J, Li R, Cheng P, Wang X, Li F (2014) Synthetic method of Febuxostat. CN103910695A. China.
37. Pranab C, Asok N, Sarbjot SS, Mohan P (2014) Process for the preparation of Febuxostat. US8916713B2. United States.
38. Vallu VR, Desai KG, Patil SD, Agarwal R, Padi PR, Ghanta, MR (2014) Synthesis and characterization of process-related impurities of an anti-hyperuricemia drug-Febuxostat. Der Pharma Chemica. 6 (3): 300-311. Corpus ID: 98946187.
39. Zhang L, Huang Z, Li J (2014) Febuxostat polymorph and preparation method thereof. CN103788009A. China.
40. Parthasaradhi RB, Rathnakar RK, Muralidhara RD, Ramakrishna RM, Vamsi KB (2014) Process for Febuxostat. US20140112992A1. United States.
41. Huang Q, Huang H (2014) Preparation methods of compound 2-(3-formyl-4-isobutoxy phenyl)-4-methyl thiazole-5-ethyl formate and Febuxostat. CN103880775A. China.
42. Xie T, Xu Z, Zhou Y (2014) Febuxostat crystal form A and preparation method thereof. CN103588724A. China.
43. Chen G, Su Q (2015) Method for preparing 4-substituted thiobenzamide derivative. CN104610110A. China.
44. Lou H, Wang J, Chen T, Rao X (2015) Method for synthesizing high-purity ethyl 2-(3-aldehyde-4-isobutyloxyphenyl)-4-methylthiazole-5-formate. CN104529935A. China.
45. Praveen C, Sreenadha CK, Vijay KA, Chandra SV (2015) Preparation of Febuxostat. US8969582B2. United States.

ISSN: 2789-1895 online
ISSN: 2958-3101 print

46. Tamura T, Moriyama K, Tog H (2015) Facile one-pot transformation of Arenes into aromatic nitriles under metal-cyanide-free conditions. European Journal of Organic Chemistry. 9: 2023-2029. doi: 10.1002/ejoc.201403672
47. Li Z, Li S (2015) Preparation method of 2-(3-cyano-4-hydroxyl) phenyl-4-methyl-5-thiazole ethyl formate. CN104478824A. China.
48. Cui Y, Feng X (2015) Preparation method of Febuxostat intermediate. CN104418823A. China.
49. Wang Q, Jin C, Zhang W Wang P (2016a) Method for preparing Febuxostat through one-pot process. CN106187940A. China.
50. Wang Q, Guo Y, Wang M, Zhu W, Xu S (2016) Synthesis of 3-bromo-4-isobutyloxyphenyl carbothioamide. Proceedings of the 2015 2nd International Conference on Machinery, Materials Engineering, Chemical Engineering and Biotechnology. 794-797. doi: 10.2991/mmeceb-15.2016.157
51. Koftis TV, Neokosmidis E, Trakossas S, Panagiotidis T, Andreou T, Varvogli AA (2016) A novel process for the preparation of Febuxostat. CN105452228A. China.
52. Kang Y, Gu J, Hu X (2016) Syntheses, structure characterization and dissolution of two novel cocrystals of Febuxostat. Journal of Molecular Structure. 1130: 480-486. doi: 10.1016/j.molstruc.2016.10.044
53. Reddy MVB, Srinivasulu D, Sudhana SM, Srikanth B, Raju CN (2016) Inhibition of LPS-induced no production in RAW264.7 cell lines: synthesis and molecular modeling of α-ketophosphonates of Febuxostat. Phosphorus, Sulfur, and Silicon and the Related Elements. 191 (1): 144-149. doi: 10.1080/10426507.2015.1050018
54. Wei C (2017) Method for controlling Febuxostat intermediate impurity. CN106366048A. China.
55. Zhao X, Xia C, Zhang M (2017) Synthesis method of ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate. CN106518802A. China.
56. Liu C, Wu L, Liu F, Ji C, Li Y (2017) Compounding method for gout suppressant Febuxostat. CN106892879A. China.
57. Shi L, Chen X, Zhang H, Chen L, Gu C, Zhou H, Xu Z, Liu X, Yin B (2017) Preparation method for pharmaceutical crystal form of Febuxostat. CN106565627A. China.
58. Zhai J, Fan C (2017) Process method for synthesizing thioamide. CN106928108A. China.
59. An J-H, Lim C, Ryu H, Kim J, Kim H, Kiyonga A, Park M, Suh Y-G, Park G, Jung K (2017) Structural characterization of febuxostat/l-pyroglutamic acid cocrystal using solid-state 13C-NMR and investigational study of its water solubility. Crystals. 7 (12): 365. doi: 10.3390/cryst7120365
60. Kang Y, Gu J, Hu X (2017) Syntheses, structure characterization and dissolution of two novel cocrystals of Febuxostat. Journal of Molecular Structure. 1130. 480-486. doi. 10.1016/j.molstruc.2016.10.044
61. Gong J, Liu L, Zhao W (2018) Preparation method of Febuxostat intermediate. CN108440443A. China.
62. Komiyama M, Tsuchiya H, Teramoto M, Yajima N, Kurokawa M, Minamizono K, Tsuchiya N, Kato Y, Sato Y, Dohi M (2018) Process development of Febuxostat using palladium- and copper-catalyzed C–H arylation. Organic Process Research & Development. 22 (9): 1306-1311. doi: 10.1021/acs.oprd.8b00164
63. Shi L, Zhang Y, Huo Z, Song K, Jiang G (2018) Synthesis method for transforming impurity 3-formyl Febuxostat into Febuxostat. CN108299335A. China.
64. Zeng P, He X, Wu J, Liu D, Cheng Z (2018) Febuxostat compound and preparation method. CN107540630A. China.
65. Zhou L, Huang W, Zeng W, Xu H, Kang L, Feng Y, Lin Y (2018) Preparation method of Febuxostat intermediate, and application thereof in preparation of Febuxostat. CN108358866A. China.
66. Zhang W, Xing W, Luo L (2018) Synthesis method of Febuxostat isomeride. CN108084112A. China.
67. Huang H, Huang Q, Li K, Shi Y (2019) Preparation method of Febuxostat. CN109293597A. China.
68. Huang H, Huang Q, Li K, Zhang H (2019) Febuxostat intermediate synthetic method. CN109574952A. China.
69. Zhang Q, Chen B, Yan Z (2019a) Preparation method of high-purity Febuxostat. CN109912531A. China.
70. Wang G, Xu C, Niu S, Zhu X (2019) Preparation method of Febuxostat. CN109320474 A. China.
71. Yan J, Song S, Liu H, Yuan J (2019) One pot method' synthesis method for Febuxostat intermediate. CN109503513A. China.
72. Zhang Y, Hong R, Yuan M, Ding D, Zhang X, Che Y, Luo H (2019) New preparation method of Febuxostat. CN110229117A. China.
73. Zhou Y, Qu J, Chen H, Xi H, Zhang C (2019) Synthesis method of Febuxostat and intermediate thereof. CN109503512A. China.
74. Gao L, Zhang X-R, Chen Y-F, Liao Z-L, Wang Y-Q, Zou X-Y (2019) A new febuxostat imidazolium salt hydrate: Synthesis, crystal structure, solubility, and dissolution study. Journal of Molecular Structure. 1176, 633-640. doi: 10.1016/j.molstruc.2018.08.098
75. Zhang Y, Sui N, Jiao P, Chen X, Ma Z, Xu L (2019) One-pot synthetic method of ethyl 2-(4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate. CN109354584A. China.

ISSN: 2789-1895 online
ISSN: 2958-3101 print

76. Bao M, Hu J, He J, Hu M, Liu J, Liu P (2019) Preparation method of Febuxostat A crystal form. CN109776448A. China.
77. Xu Y, Yuan W, Wang H (2020) Preparation method of large-particle-size Febuxostat A crystals. CN111004191A. China.
78. Lyu G, Guo R (2020) New preparation method of Febuxostat intermediate. CN110790720A. China.
79. Tang J, Ma W, He H, Guo Y, Zhao F, Zhang Q (2020) Febuxostat and intermediates and synthesis thereof. CN111072591A. China.
80. Tang J, Ma W, He H, Guo Y, Zhao F, Zhang Q (2020) Method for synthesizing Febuxostat and intermediate thereof. CN111039891A. China.
81. Lu C (2020) Synthesis process of Febuxostat. CN111499593A. China.
82. Liu J, Su J (2020) Method for continuously preparing Febuxostat. CN111285821A. China.
83. Sun X, Yu K, Ge Z, Dai X (2020) Improved method for synthesizing Febuxostat key intermediate. CN112142685A. China.
84. Xu Y, Yuan W, Zhang X (2020) High-yield synthesis method of certain specific impurity of Febuxostat. CN110878064A. China.
85. Xu Y, Zhang X, Wang H (2020) Preparation method of a special impurity of Febuxostat. CN110642804A. China.
86. Liu Q, Yao S, Xiao W, Wang S (2020) Synthesis method of Febuxostat impurity. CN111303071A. China.
87. Song C, Li W (2021) Preparation method of Febuxostat intermediate. CN113620832A. China.
88. Lai Y, Zhang F, Wang R (2021) Method for continuously producing Febuxostat by using micro-reaction device. CN113072519A. China.
89. Peng L, Huang F, Wang Z, Zhu G, Tu Y (2021) Preparation method of Febuxostat A crystal form. CN112390766A. China.
90. Sun Y, Yang W (2021) Preparation method of Febuxostat impurity. CN112961119A. China.
91. Chai J, Zhang X, Li T, Li K (2022) Preparation method of 2-(3-carbamyl-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid. CN115093379A. China.
92. Ji H, Chen S, Kan J (2023) Preparation method of Febuxostat. CN115772137A. China.
93. Leng Z, Zhang Z, Yan W, Xiao C, Jiang G, Zhou W (2023) Preparation method of Febuxostat and aldehyde ester intermediate thereof. CN115572272A. China.
94. Ungur DT, Santiso-Quinones G, Pop MM, Tamas TL, Guguta C, Stam D, Mija A, Iordache CA (2023) Febuxostat-p-toluenesulfonic acid multi-component crystal: Characterization, crystal growth and elucidation of the salt/co-crystal nature. Crystals. 13 (5): 836. doi: 10.3390/cryst13050836
95. Manda J, Sridhar B, Subba Reddy BV (2024) Cu(I)-mediated modular approach for the synthesis of febuxostat and its analogues. Tetrahedron. 164 (134167): 134167. doi: 10.1016/j.tet.2024.134167
96. Ungur, DT, Lanza A, Stam D, Guguta C, Iordache C, Fruth V, Santiso-Quinones G, Pop MM (2024) Crystal structure of Febuxostat marketed polymorph determined by electron diffraction and reinforced by X-ray crystallography. CrystEngComm. 26 (32): 4295-4304. doi: 10.1039/d4ce00518j

Acknowledgments: The author thanks the management of SDM Educational Society, Ujire, for the motivation and support to complete this review segment. I would like to thank all my beloved students for enriching this review article by raising their frank questions during the article budding phase.
Conflict of interest: The author declares the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Ethical issues: Including plagiarism, informed consent, data fabrication or falsification, and double publication or submission were completely observed by the author.