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A Simple and Commercially Viable Process for Improved Yields of Metopimazine, a Dopamine D_2-Receptor Antagonist

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Supporting Information

ABSTRACT: An efficient, practical, and commercially viable manufacturing process was developed with ≥99.7% purity and 31% overall yield (including four chemical reactions and one recrystallization) for an active pharmaceutical ingredient, called Metopimazine (**1**), an antiemetic drug used to prevent emesis during chemotherapy. The development of two in situ, one-pot methods in the present synthetic route helped to improve the overall yield of **1** (31%) compared with earlier reports (<15%). For the first time, characterization data of API (**1**), intermediates, and also possible impurities are presented. The key process issues and challenges were addressed effectively and achieved successfully.

INTRODUCTION

There is an increasing demand for antiemetic agents because of the most troublesome adverse effects of chemotherapy-induced nausea and emesis during cancer treatment.[1] However, the objective of complete prevention of emesis in all patients remains elusive. Therefore, there is a great demand for both development of (i) new antiemetic agents[2] and (ii) new manufacturing processes for existing antiemetic agents. Metopimazine is an existing dopamine D_2-receptor antagonist[3] with potent antiemetic properties.[4−6] It is chemically known as l-(3-[2-(methylsulfonyl)-10*H*-phenothiazin-10-yl]propyl)-4-piperidinecarboxamide (**1**), which belongs to nitrogen- and sulfur-containing tricyclic compounds (phenothiazine class of drugs) with interesting biological and pharmacological activities.[7] Recently, it has been found that Metopimazine plays a key role as an alternative to Ondansetron in the prevention of delayed chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderate to high emetogenic noncisplatin-based chemotherapy.[8−13] It has been used in France for many years for the prevention and treatment of nausea and vomiting under the brand name of Vogalene. Extensive literature search revealed that most of the reported methods for the preparation of **1** suffer from many disadvantages which include (i) overall lower yields (10−15%), (ii) use of toxic reagents and catalysts, (iii) inadequate discussion and optimization of reaction conditions, (iv) lack of study on impurity profile (evaluation of possible impurities, their control and also their elimination) in the process of Metopimazine (**1**), and (v) unavailability of characterization data of intermediates and possible impurities. To overcome the above-mentioned drawbacks and also to develop an industrially viable process, we planned to conduct a detailed study.

HISTORICAL DEVELOPMENT

In 1883, Bernthsen reported the first synthesis of 10*H*-dibenzo-(b,e)-1,4-thiazine, a phenothiazine.[14] Many methods for the synthesis of phenothiazines were reported.[15,16] Interestingly, only three types of synthetic routes were reported for the synthesis of Metopimazine (**1**), a drug which belongs to the phenothiazine family.

In 1959, the first synthesis and manufacture process of Metopimazine (**1**) was reported by Jacob et al.[17] (Scheme 1). The synthesis starts from the protection of 2-(Methylsulfanyl)-10*H*-phenothiazine (**2**) followed by selective oxidation of methyl sulfur and deprotection of **3** provided compound **4e**. Subsequent reaction of **4e** with 1-bromo-3-chloropropane provided intermediate **5**, which on condensation with 4-piperidinecarboxamide gave metopimazine (**1**). The major disadvantages associated with this process include (i) difficulties in handling of strong base ($NaNH_2$) in a large scale process, (ii) formation of byproducts due to high basicity of $NaNH_2$, and (iii) complications in removal of meta-chlorobenzoic acid, a byproduct generated during oxidation stage.

Later, in 1990, Sindelar et al.[18] reported a modified process (Scheme 2), which starts from synthesis of 4-(2-fluorophenylthio)-3-nitrophenylmethylsulfone (**2a**) by condensation of 2-fluorothiophenol and 4-chloro-3-nitrophenyl methyl sulfone. The reduction of compound **2a** to amine derivative (**2b**) followed by cyclization provided 2-(methylsulfonyl)-phenothiazine (**4e**). The subsequent condensation of compound **4e** with 1-(3-chloropropyl)-4-piperidinecarboxamide (**2c**) provided the target metopimazine (**1**). The major disadvantages include (i) harsh reaction conditions, (ii) lower yields were reported in most of the steps, and (iii) the process is lab-scale only (not commercial level).

In 2010, Satyanarayana Reddy et al.[19] reported a modified synthetic route (Scheme 3) which starts from either N-protection using acetyl chloride or N-alkylation using dihalopropane of 2-(methylsulfanyl)-10*H*-phenothiazine (**2**).

In one of the routes, protection of 2-(methylsulfanyl)-10*H*-phenothiazine (**2**) using acetyl chloride and then selective

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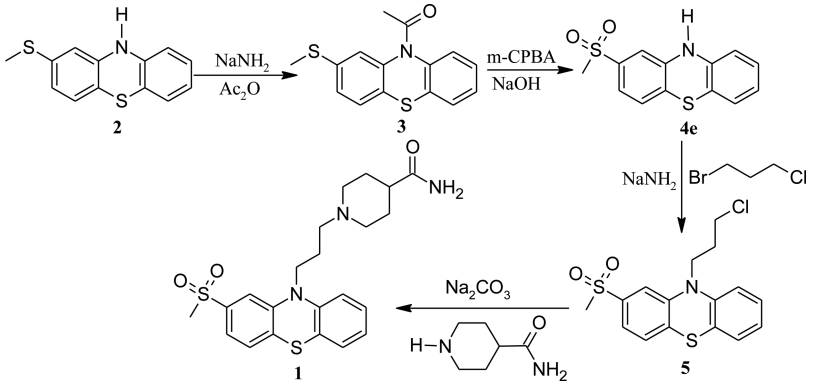
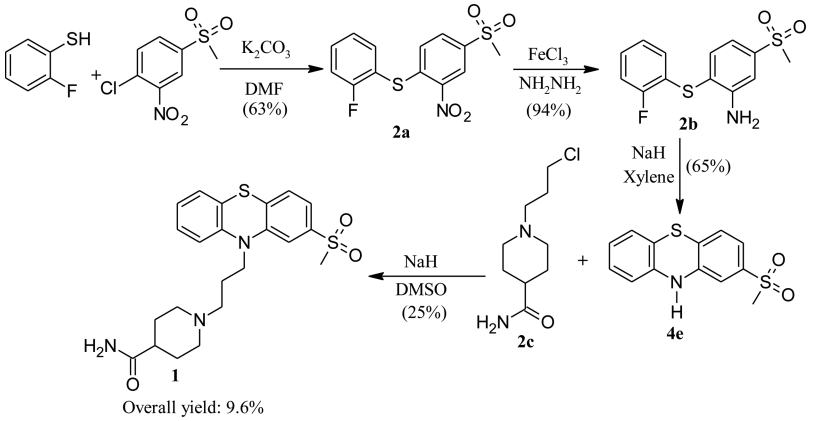
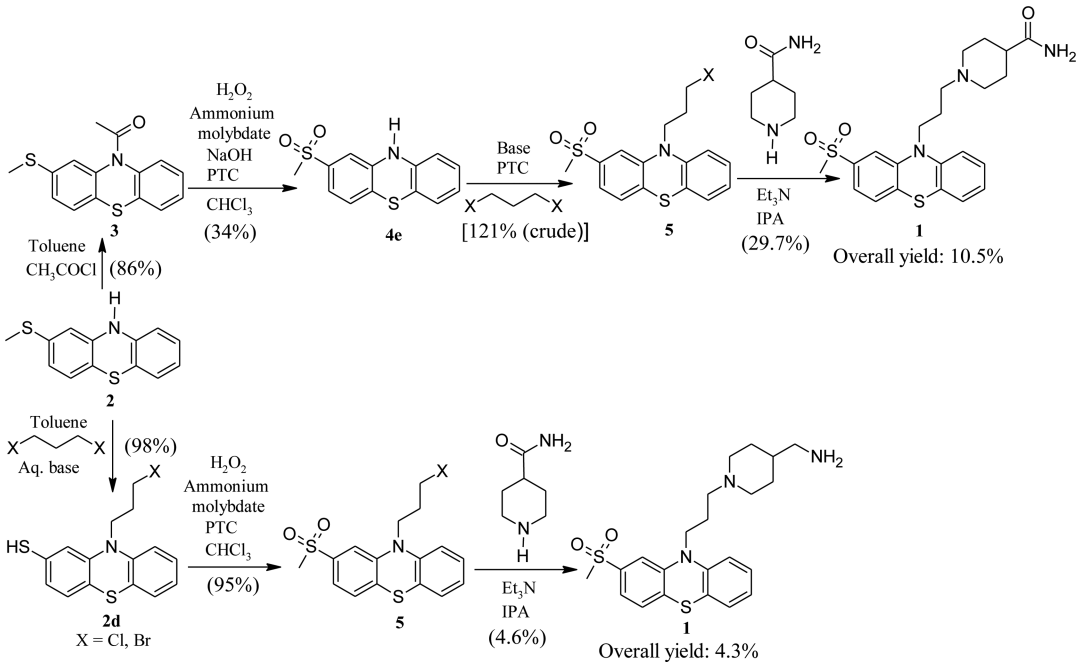
Scheme 1. First Synthesis of Metopimazine (1)



Scheme 2. Sindelar's Approach for the Synthesis of Metopimazine (1)



Scheme 3. Satyanarayana Reddy's Approach for the Synthesis of Metopimazine (1)



oxidation of methyl sulfur of compound **3** followed by deprotection yield compound **4e** and subsequent N-alkylation using dihalopropane provided compound **5**. Then, the condensation of compound **5** with 4-piperidinecarboxamide provided the target Metopimazine (**1**). In another route, the synthesis starts from N-alkylation of **2** using dihalopropane followed by selective oxidation of **2d** provided intermediate **5**. Finally, condensation of compound **5** with 4-piperidinecarboxamide provided target Metopimazine (**1**) as depicted in above scheme. The notable drawbacks of this process include (i) use

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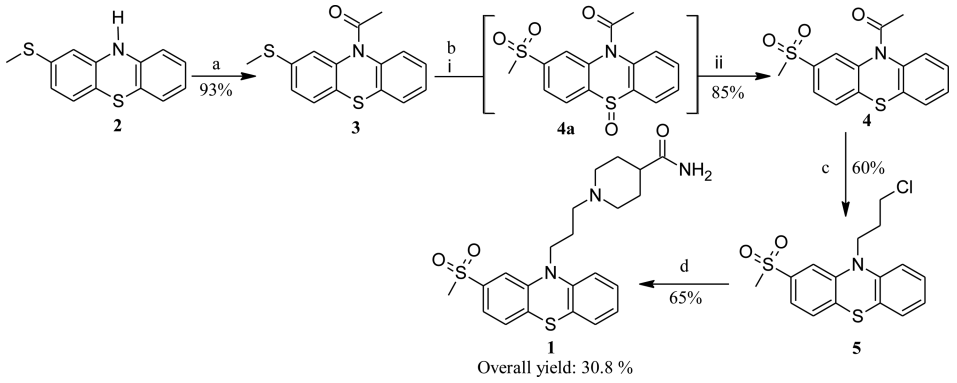
Scheme 4. Improved Process for the Synthesis of Metopimazine (1)[a]



[a]Reaction conditions: (a) acetyl chloride, toluene, 20−30 °C, 1 h; (b) (i) oxone, H_2O/acetonitrile (7:10 ratio) at 20−30 °C, 2 h, (ii) Zn powder, lactic acid, acetonitrile, 60−70 °C, 3h; (c) powdered KOH, 1-bromo-3-chloropropane, acetone, 50−60 °C, 3 h; (d) 4-piperidinecarboxamide, K_2CO_3, toluene−DMF (8:2 ratio), 90−100 °C, 8 h.

of ammonium molybdate, which causes health hazards; (ii) $CHCl_3$ was used as solvent (class 2); and (iii) lower yields of products were reported.

The following challenges are to be addressed to overcome the disadvantages of existing processes: (i) improved yields in each and every step; (ii) avoid the tedious workup procedures by enhancing the robustness throughout the synthesis by testing and optimization of critical parameters; (iii) reduce or replace toxic chemicals with green reagents or solvents; (iv) characterization of intermediates (**3**, **4**, and **5**) and process impurities; and (v) aiming to develop practical and commercial synthetic route with detailed study of impurities profile. Herein we report an improved synthetic route for the synthesis of Metopimazine (**1**) with high purity (≥99.7%), improved yields (31% of overall yield), easy workup, simple isolation, and purification of intermediates as well as final product.

RESULTS AND DISCUSSION

A modified process was designed and developed to achieve improved yields of Metopimazine drug compared with existing processes as shown in Scheme 4.

The synthesis of the target Metopimazine (**1**) starts by the protection of compound **2** using acetyl chloride and it provided compound **3**. Then, the oxidation of compound **3** using oxone provided compound **4a** and successive in situ selective reduction of compound **4a** using Zn-lactic acid provided compound **4** in one-pot. The deprotection and subsequent in situ N-alkylation of compound **4** in the presence of powdered KOH using dihalopropane in one-pot provided compound **5**. Finally, the condensation of compound **5** with 4-piperidine-carboxamide in the presence of K_2CO_3 provided the final Metopimazine (**1**) as shown in Scheme 4.

With an objective to develop a commercially viable process for the manufacture of **1**, the reaction conditions were well optimized in each and every step as discussed below.

Improved Process Conditions for 1-[2-(Methylsulfanyl)-10*H*-phenothiazin-10-yl]ethanone (3) Derivative. Synthesis of 1-[2-(methylsulfanyl)-10*H*-phenothiazin-10-yl]-ethanone (**3**) involves protection of compound **2**. Two methods were reported for protection of compound **2**. The method reported by Jacob et al.[17] involves N-acetylation using acetic anhydride in the presence of $NaNH_2$ without any quality profile. However, this method suffers from formation of byproducts due to high basicity of $NaNH_2$ and difficulties in handling of $NaNH_2$.

Recently, a new method was published in a patent[19] that reported N-acetylation using 8.0 equiv of acetyl chloride in toluene at 50−55 °C and provided compound **3** in 86.7% yield without any quality data. The isolation of compound **3** was carried out by adding cyclohexane, which is not preferable at production scale. The equivalents of acetyl chloride are also very high (8.0 equiv).

With an aim of reducing the acetyl chloride quantity, we conducted the same experiment with 1.0, 2.5, 5.0, 7.5, and 10 equiv of acetyl chloride both at 20−30 °C and 50−60 °C, and the obtained results were presented in Table 1. The study

Table 1. Effect of Acetyl Chloride Amount and Temperature on N-Acetylation[a]

entry	acetyl chloride (equiv)	time (h)	temp′ (°C)	yield (%)[b] of product **3**	product **3** (% by HPLC)
1	1	2	20−30	52	61
		2	50−60	41	56
2	2.5	1	20−30	93	95
		1	50−60	90	92
3	5	1	20−30	87	95
		1	50−60	79	89
4	7.5	1	20−30	85	94
		1	50−60	76	88
5	10	1	20−30	81	92
		1	50−60	72	86

[a]Reaction conditions: compound **2** (10 g, 0.04 mol), acetyl chloride, toluene (60 mL). [b]Isolated yield. [c]Remaining unreacted substrate.

establishes 2.5 equiv of acetyl chloride as the best option at 20−30 °C for maximum formation (95%) of compound **3** compared to at 50−60 °C (92%) (entry 2, Table 1 and Figure S5, Supporting Information). The same reaction either with low or high amount of acetyl chloride provided lower yields of compound **3** (entries 1, 3−5, Table 1). The same acetylation reaction was unsuccessful with inorganic (Na_2CO_3, K_2CO_3) and organic bases (Et_3N, piperidine) because of incompatibility of acetyl chloride with bases.[20] In this conversion, incremental scale-up and close monitoring of the reaction disclosed that the production is possible without difficulties.

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The purity of crude compound **3** is low (<95.5%). The compound **3** was isolated in different solvents to improve the quality by recrystallization in different solvents like methanol, ethanol, isopropanol, and ethyl acetate, and the obtained results were presented in Table 2. It was found that isopropanol was the best option to improve the quality (up to 97%) with good isolated yield (93%) (entry 3, Table 2, Figure S6, Supporting Information).

Table 2. Selection of Suitable Solvent for Isolation of Compound 3

entry	solvent	yield[b] (%)	purity (% by HPLC)
1	methanol	80	98
2	ethanol	82	98
3	isopropanol	93	97
4	ethyl acetate	72	93

[a]Reaction conditions: crude compound **3** (10 g, 0.034 mol) in solvent (30 mL), at reflux temperature (clear solution) for 30 min, cool to 10−15 °C, stir for 1 h, and filter the solid. [b]Isolated yield.

New Process Conditions for 1-[2-(Methylsulfonyl)-5-oxido-10*H*-phenothiazin-10-yl]ethanone (4) Derivative. The reported chemoselective oxidation methods provided low yields (up to 35%)[17] of compound **4** because the formation of 1-[2-(methylsulfonyl)-5-oxido-10*H*-phenothiazin-10-ylethanone (**4a**) [2-(methylsulfinyl)-10*H*-phenothiazin-10-yl]-ethanone (**4b**), 2-(methylsulfinyl)-10-oxo-10*H*-phenothiazin-10-ium (**4c**), and 1-[2-(methylsulfonyl)-5,5-dioxido-10*H*-phenothiazin-10-yl]ethanone (**4d**) are unavoidable byproducts (Scheme 5).

For example, in recent patent,[19] the selective oxidation of **3** using H_2O_2 was presented, but there were several difficulties. For example, (i) a large quantity of H_2O_2 was required; (ii) toxic metal catalysts are needed;[19] and (iii) huge amount of solvents are required for the purification of crude mass. In addition, the isolated yields were low (≤34%). In another patent,[17] *m*-CPBA (*meta*-chloro perbenzoic acid) was applied, and the obtained yield was low. The byproduct, meta-chlorobenzoic acid is difficult to remove and it affects the yield and purity of compound **4**. At the same time, the *m*-CPBA is expensive, and its storage is difficult.

We planned to develop a one-pot method which consists of preparation of compound **4a** exclusively by minimizing the formation of byproducts such as **4b**, **4c**, and **4d** and subsequent in situ reduction of compound **4a** to generate the desired compound **4** in high yield compared to literature reported low yields. Toward this direction, screening of a series of oxidizing agents in a variety of solvents was planned.

Initially, different types of oxidizing agents were applied for the oxidation of compound **3**, for example peracetic acid, *m*-CPBA, magnesium monoperoxyphthalate (MMPP) and oxone. The formation of compound **4a** with the above-mentioned oxidizing agents was 10%, 14%, 52%, and 85% in a mixture of H_2O/acetonitrile (7:10 ratio) (entries 1−4, Table 3). The

Table 3. Screening of Appropriate Oxidizing Agent for Oxidation[a]

				selectivity[b] by HPLC				
entry	oxidizing agent	time (h)	product	**4**	**4a**	**4b**	**4c**	**4d**
1	peracetic acid	4	**4a**	05	10	42	25	12
2	*m*-CPBA	3	**4a**	08	14	48	27	15
3	magnesium monoperoxy phthalate	5	**4a**	14	52	12	07	06
4	oxone	2	**4a**	0.2	85	0.8	0	12

[a]Reaction conditions: compound **3** (10 g, 0.034 mol), oxidizing agent (0.069 mol) in H_2O/acetonitrile (7:10 ratio) (170 mL) at 20−30 °C. [b]Remaining unreacted substrate.

formation of impurities increased with oxidizing agents other than oxone. For example, 12−48% of impurity **4b**, 7−27% of impurity **4c**, and 6−15% of impurity **4d** were formed along with 5−14% of desired compound **4** (entries 1−3). In addition, the formation of impurity **4d** was increased exponentially with increase of amount of oxidizing agent (more than 2.0 equiv). The study revealed that the formation of compound **4a** was good (85%) using oxone (entry 4, Table 3 and Figure S10, Supporting Information) compared to other oxidizing agents (entries 1−3). As a result, the oxone was selected for the optimization of other reaction conditions. In addition, oxone is a green oxidizing agent with good stability, easy to handle, nontoxic, and low cost.[21,22,23] Moreover, the byproducts of oxone (inorganic salts) are harmless to environment thus encouraging us to utilize it as a reagent for the present route of synthesis. Additionally literature also revealed that oxone can be efficiently used as an oxidizing agent in the conversion of sulfide to sulfone.[24]

Further, the effect of various solvents on the course of oxidation was studied; for example, dichloromethane, methanol, ethanol, THF, DMF, and DMSO provided compound **4a** in the range of 10−15% only (entries 1−6, Table 4). It is due to insolubility of oxone in these solvents. Hence, it was planned to study the effect of mixture of water and organic solvents. For example, in H_2O/dichloromethane and H_2O/ethyl acetate (in the presence of PTC), 67% and 38% of compound **4a** was formed, respectively (entries 7 and 8). In H_2O/dichloro-

Scheme 5. Formation of Possible Products during Oxidation of 3 Using Oxidizing Agents

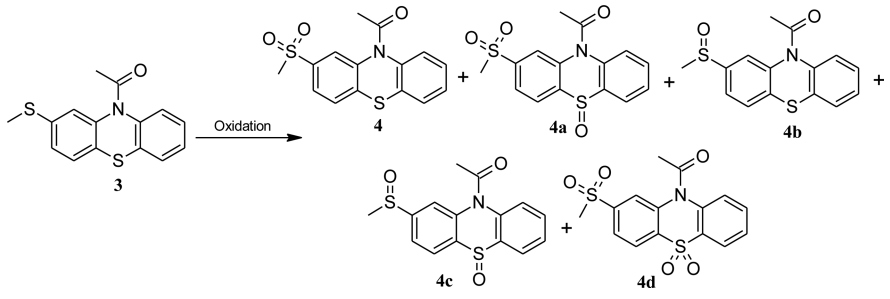

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Table 4. Selection of Suitable Solvent for Oxidation Using Oxone[a]

entry	solvent	time (h)	product	selectivity[b] by HPLC 4	4a	4b	4c	4d
1	dichloromethane	24	4a	05	10	02	01	02
2	methanol	24	4a	06	12	03	02	01
3	ethanol	24	4a	07	13	03	02	01
4	THF	24	4a	04	11	02	03	02
5[c]	DMF	24	4a	08	15	02	01	02
6[c]	DMSO	24	4a	07	14	02	02	01
7[d,e]	H_2O/dichloromethane	6	4a	11	67	05	06	09
8[d,e]	H_2O/ethyl acetate	8	4a	07	38	04	05	04
9[e]	H_2O/methanol	3	4a	02	52	03	04	39
10[e]	H_2O/ethanol	3	4a	02	55	02	04	35
11[e]	H_2O/THF	7	4a	03	46	03	05	04
12[e]	H_2O/acetonitrile	2	4a	0.2	85	0.8	0	12
13[f]	H_2O/DMF	3	4a	07	60	02	01	02
14[f]	H_2O/DMSO	4	4a	08	58	02	01	03

[a]Reaction conditions: compound **3** (10 g, 0.034 mol), oxone (42.7 g, 0.069 mol) in organic solvent (10 vol)/mixture of aqueous organic solvent at 20−30 °C. [b]Remaining unreacted substrate. [c]Solvent (3 vol). [d]In the presence of PTC (tetrabutyl ammonium bromide). [e]Mixture of solvents (7:10 ratio) (170 mL, 17 vol). [f]Mixture of solvents (8:2 ratio) (100 mL, 10 vol).

methane in the presence of PTC (tetra-butyl ammonium bromide), 67% of compound **4a** and 5% of impurity **4b** was formed (entry 7). The conversion (67%) was good, but the 5% of impurity **4b** was difficult to remove in further stages up to the limits of specification of API.

To improve the yield further, the same reaction was carried out in H_2O/methanol, H_2O/ethanol, H_2O/THF, and H_2O/acetonitrile (7:10 ratio) and 52%, 55%, 46%, and 85% of compound **4a** was formed (entries 9−12, Table 4), respectively. The oxidation in H_2O−methanol/ethanol, the formation of impurity **4d** increased up to 35% and 39% (entries 9 and 10). In H_2O/DMF and H_2O/DMSO (8:2 ratio), 60% and 58% of compound **4a** was formed, respectively (entries 13 and 14).

Interestingly, in the case of a mixture of H_2O−acetonitrile (7:10 ratio), 85% of compound **4a** and 0.8% of impurity **4b** was formed. The formation of impurity **4d** was increased to 12%, which easily gets removed during the purification process. The results reveal that mixture of H_2O−acetonitrile (7:10 ratio) is the best option for maximum conversion (85%) and exercise good control on potential impurities (entry 12, Table 4, and Figure S10, Supporting Information).

Then, the effect of temperature on the course of oxidation was studied in H_2O/acetonitrile (7:10 ratio); for example, oxidation at 20−30 °C provided 85% (**4a**) conversion in 2 h. With respect to the same reaction at >30 °C, the percentage of formation of impurity **4d** increased exponentially with the increase of temperature.

Finally the effect of load of oxone was studied on the course of oxidation; for example, 1.0, 2.0, and 3.0 equiv of oxone provided 40%, 85%, and 64% of compound **4a** (entries 1, 3, 4, Table 5). In the case of 1.0 equiv of oxone, 40% of compound **4a**, 43% of impurity **4b**, and 14% of impurity **4c** were formed (entry 1). Use of 2.0 equiv of oxone provided 85% of compound **4a** and impurity **4d** in 12% (entry 3). When 3.0 equiv of oxone was applied, low formation (64%) of compound **4a** and high (32%) formation of impurity **4d** was observed (entry 4). To reduce the load of oxone, 1.5 equiv of oxone was used; however, the conversion was low (55%), and the formation of impurities (27% of **4b** and 5% of **4c**) was increased (entry 2, Table 5). The study disclosed that 2.0 equiv of oxone is optimum for maximum formation (85%) of

Table 5. Effect of Load of Oxone[a]

entry	load of oxone (equiv)	time (h)	product	selectivity[b] by HPLC 4	4a	4b	4c	4d
1	1	1	4a	02	40	43	14	01
2	1.5	1.5	4a	04	55	27	5	08
3	2	2	4a	0.2	85	0.8	0	12
4	3	2.5	4a	05	64	0.4	0.5	32

[a]Reaction conditions: compound **3** (10 g, 0.034 mol), oxone in H_2O/acetonitrile (7:10 ratio) (170 mL) at 20−30 °C. [b]Remaining unreacted substrate.

compound **4a** and 12% of impurity **4d** in H_2O/acetonitrile (7:10 ratio) at 20−30 °C (entry 3, Table 5 and Figure S10, Supporting Information). The current study was also supported by a previous report from the literature.[24]

Then, we planned to conduct in situ reduction of compound **4a** to generate a desired compound **4** in one-pot using the process reported in the literature.[25] Accordingly, compound **4a**, Zn powder, and acetic acid in DMF were stirred at 60−70 °C, and a 68% isolated yield of compound **4** was obtained (entry 1, Table 6).

There are a few disadvantages with this process at a commercial level. For example, the following are disadvantages: (i) the contamination of effluent with acetic acid and DMF; (ii) difficulty of removing DMF from the reaction mass; and (iii)

Table 6. Screening of Suitable Acid during Reduction[a]

entry	acid	time (h)	product	yield (%)[b]	selectivity[c] by HPLC 4	4a	4b	4d
1[d]	acetic acid	1	4	68	68	0.8	0.5	12
2[e]	lactic acid	3	4	85	83	0.1	0.4	11

[a]Reaction conditions: compound **4a** crude (10 g, 0.034 mol), Zn (3.76 g, 0.057 mol), lactic acid (20 mL) in solvent (70 mL, 7 vol) at 60−70 °C. [b]Isolated yield without purification. [c]Remaining unreacted substrate. [d]Reaction was carried out in DMF. [e]Reaction was carried out in acetonitrile.

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Scheme 6. Formation of Possible Products during Deprotection and In Situ N-Alkylation

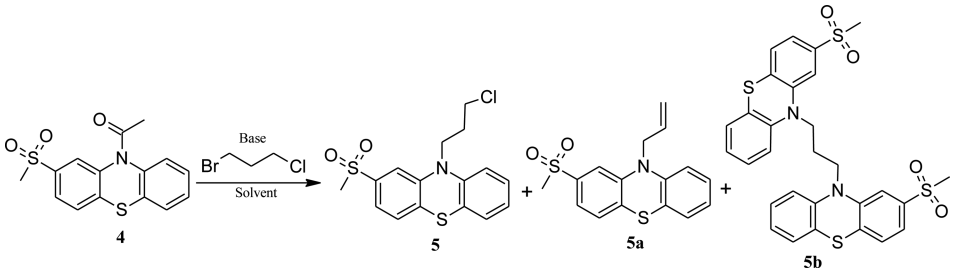

Table 7. Selection of Suitable Solvent for Deprotection and In Situ N-Alkylation[a]

					selectivity[c] by HPLC		
entry	solvent	time (h)	temp′ (°C)	product	5	5a	5b
1	dichloromethane	8	30−35	5	40	15	03
2	ethyl acetate	5	50−60	5	35	25	06
3	acetone	3	50−60	5	84	9	1.5
4		24	20−30	5	20	03	01
5		15	30−40	5	35	05	02
6		6	40−50	5	66	10	04
7	acetonitrile	4	50−60	5	42	31	08
8	THF	5	50−60	5	35	38	06
9[d]	DMSO	3	50−60	5	61	18	04
10[d]	DMF	2	50−60	5	64	20	05

[a]Reaction conditions: compound **4** (10 g, 0.031 mol), powdered KOH (5.26 g, 0.094 mol), 1-bromo-3-chloropropane (14.6 g, 0.094 mol) in solvent (10 vol) at 50−60 °C. [b]Isolated yield after isolation and purification in methanol. [c]Remaining unreacted substrate. [d]Solvent (3 vol).

large amount of water is required to isolate compound **4**. To overcome these issues, we replaced acetic acid with lactic acid and also DMF with acetonitrile. Accordingly, the same reaction was carried out in acetonitrile using Zn/lactic acid as selective reducing agent, and the conversion increased up to 83% (**4**) (entry 2, Table 6). In addition, the lactic acid is an environmentally benign, nonvolatile, and biodegradable green reagent.[26,27] The solvent, acetonitrile, was recovered after the completion of the reaction, and it is one of the added advantages over DMF.

With the help of the modified process, the inevitable compound **4a** that was formed in oxidation process was successfully converted into the desired compound **4** using a reduction process. This modification provided improved yield (85%) of compound **4** compared with previously reported chemoselective oxidation methods.[17−19] The study disclosed that the conversion of compound **4a** to compound **4** was good in Zn/lactic acid/acetonitrile system (entry 2, Table 6, and Figure S16, Supporting Information).

New Process Conditions for 10-(3-Chloropropyl)-2-(methylsulfonyl)-10*H*-phenothiazine (5) Derivative. The conversion of 1-[2-(methylsulfonyl)-5-oxido-10*H*-phenothiazin-10-yl]ethanone (**4**) to 10-(3-chloropropyl)-2-(methylsulfonyl)-10*H*-phenothiazine (**5**) in the presence of base using 1-bromo-3-chloropropane was achieved through deprotection followed by in situ N-alkylation as shown in Scheme 6.

The reaction of compound **4** in the presence of KOH using 1-bromo-3-chloropropane in dichloromethane at reflux temperature provided 40% of compound **5** through deprotection followed by in situ N-alkylation in one-pot (entry 1, Table 7) along with 15% of impurity **5a** and 3% of impurity **5b**. To improve the conversion further, the same reaction was carried out at 50−60 °C using ethyl acetate, acetone, acetonitrile, THF, DMSO, and DMF and 35%, 84%, 42%, 35%, 61%, and 64% of compound **5** was formed, respectively (entries 2, 3, and 7−10, Table 7). In ethyl acetate, acetonitrile, and THF, 35%, 42%, and 35% of compound **5** was formed (low conversion) and 25%, 31%, and 38% of impurity **5a** was formed, respectively (entries 2, 7, and 8). In acetone, 84% of compound **5** along with 9% of impurity **5a** and 1.5% of impurity **5b** were formed (entry 3). In DMSO and DMF, the formation of compound **5** was low, 61% and 64%, respectively, but the formation of impurities were more (18% and 20% of impurity **5a** and 4% and 5% of impurity **5b** were formed in DMSO and DMF, respectively; see entries 9 and 10). The solvent study confirmed that acetone is the best option for maximum formation (84%) of compound 5 (entry 3, Table 7 and Figure S40, Supporting Information). In solvents other than acetone (reported in Table 7), it was observed that the reaction did not proceed at 20−30 °C, and the formation of impurity **5a** increased exponentially with an increase of temperature >60 °C.

To study the effect of NaOH on the course of the reaction, the same reaction was carried out in the presence of NaOH, but the formation of compound **5** was low (68%) even after 6 h with increased formation of impurities (10% of **5a** and 8% of **5b**) compared with the reaction in KOH.

When we studied the effect of temperature on the course of reaction (e.g., 20−30 °C, 30−40 °C, and 40−50 °C in acetone) 20%, 35%, and 66% of compound **5** was formed, respectively (entries 4−6, Table 7). The study disclosed that the optimum temperature for maximum formation (84%) of compound **5** was 50−60 °C (entry 3, Table 7 and Figure S40, Supporting Information)

Then, the effect of load of powdered KOH on the course of the reaction was studied in acetone (e.g., 1.0, 2.0, 3.0, and 4.0 equiv of powdered KOH), 4%, 20%, 84%, and 69% of compound **5** was formed, respectively. In 1.0 equiv of KOH, low formation of compound **5** was observed. The deprotection

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of compound **4** was completed, but N-alkylation was not proceeding because of insufficient KOH. In the case of 2.0 equiv of KOH, the same situation was observed, but the formation of **5** was increased (20%) slightly. When the same reaction was allowed to occur in the presence of 4.0 equiv of KOH, the formation of **5** decreased (69%) as the formation of impurities increased (20% of **5a** and 4% of **5b**). The study revealed that 3.0 equiv of powdered KOH in acetone provided the maximum formation of **5** (84%) along with 9% of impurity **5a** and 1.5% of impurity **5b** (Figure S40, Supporting Information).

The formation of a potential impurity (**5a**) was at a high level (9%) (entry 3, Table 7), which severely affects the required quality of the obtained API. Hence, its removal is mandatory up to the level of not more than 2.5%. Therefore, we planned to improve the quality of compound **5** by isolating it in different solvents (e.g., acetone, methanol, ethanol, acetonitrile, and ethyl acetate), and the obtained results were presented in Table 8 (entries 1−5). The study disclosed that methanol was the best option to isolate the desired compound **5** and also to remove the potential impurity **5a** up to the process capability level (<2.5%) (entry 2, Table 8 and Figure S41, Supporting Information).

Table 8. Selection of Suitable Solvent for Isolation of Compound 5[a]

				purity (% by HPLC)		
entry	solvent	yield[b] (%)	product	**5**	**5a**	**5b**
1	acetone	65	**5**	89	05	01
2	methanol	60	**5**	96	02	1.2
3	ethanol	64	**5**	91	04	01
4	acetonitrile	66	**5**	90	06	01
5	ethyl acetate	68	**5**	89	07	01

[a]Reaction conditions: crude compound **5** (10 g, 0.031 mol) in solvent (100 mL) at reflux temperature for 30 min, cool to 20−30 °C, stir for 1 h and filter the solid. [b]Isolated yield.

New Process Conditions for the Preparation of 1-(3-[2-(Methylsulfonyl)-10*H*-phenothiazin-10-yl]propyl)-4-piperidinecarboxamide (1), Metopimazine. The synthesis of final Metopimazine (**1**) was achieved by the reaction of compound **5** with 4-piperidinecarboxamide in the presence of base as shown in Scheme 7. (Note: The 4-piperidinecarboxylic acid is a common impurity in 4-piperidinecarboxamide). This impurity content should be less than 2%; if it is beyond 2%, the formation of both impurity **1a** and **1b** increase exponentially.

Initially, a reaction of compound **5** with 4-piperidinecarboxamide was carried out in dichloromethane in the presence of K_2CO_3 at reflux temperature, and the reaction was unsuccessful (entry 1, Table 9). The same reaction was carried out in ethyl acetate, acetone, and methanol at reflux temperature, but the reaction was unsuccessful (entries 2−4). It is due to inadequate temperature. If the same reaction was conducted in toluene at reflux temperature, then 50% of compound **1** and 1% of impurity **1a** and 2% of impurity **1b** were formed (entry 5).

The same reaction was carried out in alcoholic solvents and also in acetonitrile at reflux temperature, and the formation of compound **1** was low (43−47%) along with 1−2% of impurity **1a** and 1−3% of impurity **1b** (entries 6−9, Table 9). Interestingly, in DMAc, the conversion was very low (30%) with 1% of impurity **1a** and 2% of impurity **1b** (entry 10). However, in the case of DMSO and DMF, 51% and 63% of compound **1** was formed, respectively (entries 11 and 12) in the presence of K_2CO_3 at 90−100 °C. In DMSO and DMF, 2% of impurity **1a** and 1% and 12% impurity **1b** was formed, respectively. It is found that in DMF, the conversion was good (63%) (entry 12). It was observed that both in toluene (entry 5) and DMF (entry 12), the conversion was good compared to other single solvents (entries 1−4 and 6−11). This encouraged us to study the effect of mixture of toluene and DMF. For example, in the mixture of toluene−DMF in 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1 ratio, 63%, 68%, 70%, 72%, 81%, and 73% of compound **1** was formed, respectively (entries 13−17 and 24, Table 9). With a decrease in the DMF ratio (e.g., a decrease from 6 to 2), the formation of impurity **1a** decreased from 5% to 1.5%, and impurity **1b** also decreased from 11% to 8% (entries 13−17). Interestingly, a further decrease of the DMF ratio leads to an increase of impurities (3% of **1a** and 10% of **1b**; see entry 24).

The study revealed that the formation of compound **1** (81%) was good, and the impurities profile (1.5% of **1a** and 8% of **1b**) is also tolerable in 8:2 ratio of toluene−DMF mixture (entry 17, Table 9 and Figure S59, Supporting Information).

Then, the effect of base on the course of reaction was studied (e.g., Na_2CO_3, Et_3N, and piperidine in toluene/DMF (8:2 ratio)), and the conversion was 67%, 31%, and 37%, respectively (entries 18−20, Table 9). The formation of impurities in the presence of K_2CO_3 was low (1.5% of **1a** and 8% of **1b**) compared with Na_2CO_3 and Et_3N. In presence of piperidine, the conversion was not acceptable (37%), but the formation of impurities was considerably lower (1% of **1a** and 2% **1b**). The investigation revealed that K_2CO_3 is a suitable base for the maximum conversion (81%) with acceptable impurities profile (entry 17, Table 9 and Figure S59, Supporting Information).

Then, the effect of temperature on the course of reaction was studied in toluene/DMF (8:2 ratio). Accordingly, a reaction of

Scheme 7. Formation of Possible Products during N-Alkylation of Compound 5

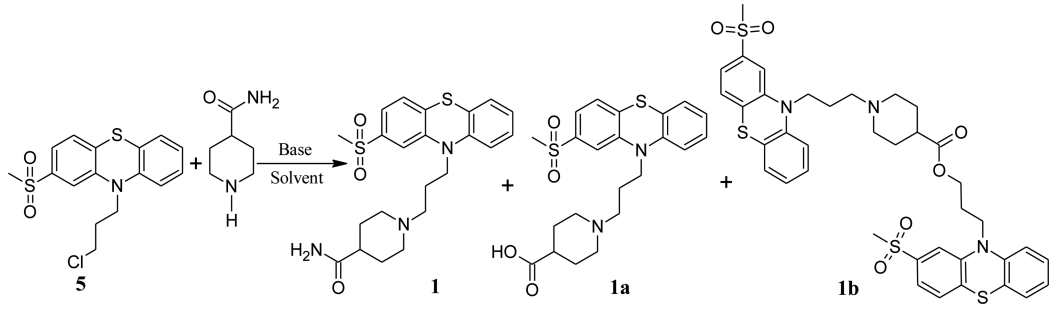

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Table 9. Effect of Solvent for the Synthesis of Metopimazine (1) from Compound 5[a]

entry	solvent	time (h)	temp′ (°C)	base	product	selectivity[b] by HPLC 1	1a	1b
1	dichloromethane	24	reflux	K_2CO_3	1			
2	ethyl acetate	24	reflux	K_2CO_3	1			
3	acetone	24	reflux	K_2CO_3	1			
4	methanol	24	reflux	K_2CO_3	1			
5	toluene	24	reflux	K_2CO_3	1	50	01	02
6	ethanol	24	reflux	K_2CO_3	1	43	02	03
7	Isopropanol	24	reflux	K_2CO_3	1	45	02	01
8	*n*-butanol	11	90−100 °C	K_2CO_3	1	47	01	02
9	acetonitrile	24	reflux	K_2CO_3	1	44	02	03
10	DMAc	7	90−100 °C	K_2CO_3	1	30	01	02
11	DMSO	10	90−100 °C	K_2CO_3	1	51	02	01
12	DMF	7	90−100 °C	K_2CO_3	1	63	02	12
13	toluene/DMF (4:6 ratio)	6	90−100 °C	K_2CO_3	1	63	05	11
14	toluene/DMF (5:5 ratio)	6	90−100 °C	K_2CO_3	1	68	04	10
15	toluene/DMF (6:4 ratio)	7	90−100 °C	K_2CO_3	1	70	03	09
16	toluene/DMF (7:3 ratio)	8	90−100 °C	K_2CO_3	1	72	02	08
17	toluene/DMF (8:2 ratio)	8	90−100 °C	K_2CO_3	1	81	1.5	08
18		12	90−100 °C	Na_2CO_3	1	67	04	07
19		24	90−100 °C	Et_3N	1	31	04	04
20		24	90−100 °C	piperidine	1	37	01	02
21		24	20−30 °C	K_2CO_3	1			
22		24	50−60 °C	K_2CO_3	1	42	01	02
23		24	70−80 °C	K_2CO_3	1	53	01	03
24	toluene/DMF (9:1 ratio)	8	90−100 °C	K_2CO_3	1	73	03	10

[a]Reaction conditions: compound **5** (10 g, 0.028 mol), 4-piperidinecarboxamide (5.43 g, 0.042 mol), base (0.07 mol) in solvent (100 mL, 10 vol). [b]Remaining unreacted substrate.

Table 10. Selection of Suitable Solvent for Purification of Compound 1[a]

entry	solvent	(%)	product	purity by HPLC yield[b] 1	1a	1b	5	5a	5b	unknown
1	toluene/DMF (8:2 ratio)	65	1	99.7	0	0	0.01	0.01	0.06	0.05
2	toluene/methanol (8:2 ratio)	60	1	99.0	0.2	0.5	0.02	0.03	0.1	0.15
3	toluene/ethyl acetate (8:2 ratio)	64	1	98.4	0.5	0.8	0.02	0.05	0.2	0.16
4	methanol/DMSO (8:2 ratio)	66	1	99.0	0.2	0.5	0.02	0.03	0.1	0.15

[a]Reaction conditions: crude compound **1** (9.5 g, 0.031 mol) in mixture of solvents (8:2 ratio) (50 mL, 5 vol) at 60−70 °C for 1 h, cool to 20−30 °C, stir for 30 min, and filter the solid. [b]Isolated yield.

compound **5** with 4-piperidinecarboxamide in the presence of K_2CO_3 was carried out at 20−30 °C, but the reaction did not proceed (entry 21, Table 9). With respect to the same reaction at 50−60 °C and 70−80 °C, the conversion was 42% and 53%, respectively (entries 22 and 23). The formation of impurity **1b** (2−3%) was lower and unreacted substrate **5** (5−15%) was higher when the reaction was conducted at <90 °C. The conversion was decreased (60−70%) and the formation of impurity **1a** (4−8%) and impurity **1b** (15−20%) was increased when the reaction was carried out at >100 °C. The study disclosed that 90−100 °C is the optimum temperature for maximum conversion (81%) (entry 17, Table 9 and Figure S59, Supporting Information).

Finally, the effect of base concentration was studied. In the presence of 1.0, 2.0, 3.0, and 4.0 equiv of K_2CO_3, 52%, 66%, 75%, and 72% of compound **1** was formed, respectively. In 1.0 equiv of K_2CO_3, 40% of the unreacted compound **5** was formed, and formation of impurities was usual even after 24 h. The same reaction was completed in 12 h with 2.0 equiv of K_2CO_3, but 6−7% of substrate **5** was unreacted. In the case of 3.0 and 4.0 equiv, the formation of impurity **1a** was increased up to 15−25%. Hence, it is planned to conduct the same reaction using 2.5 equiv of K_2CO_3, the reaction completed in 8 h with 1.5% of impurity **1a** and 8% of impurity **1b**. The study disclosed that maximum formation (81%) of compound **1** was observed in the presence of 2.5 equiv of K_2CO_3 in toluene/DMF (8:2 ratio) at 90−100 °C (Figure S59, Supporting Information).

The purity of crude Metopimazine (**1**) did not comply with the specifications of API. Hence, it was planned to isolate in different solvents to improve the quality, to remove potential impurities such as **1a** and **1b** and also other carryover impurities. Initially, the purification was conducted using a single-solvent system (toluene, methanol, isopropanol, and ethyl acetate), but the impurities were not eliminated completely. Then, a mixture of solvents such as toluene/DMF, toluene/methanol, toluene/ethyl acetate, and methanol/DMSO (8:2 ratio) (entries 1−4, Table 10) were used, and the obtained results were presented in Table 10. The study disclosed that toluene−DMF (8:2 ratio) is the best option for the purification to achieve the desired quality of Metopimazine

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(API) (**1**) (entry 1, Table 10 and Figure S60, Supporting Information).

EXPERIMENTAL SECTION

The solvents and reagents were obtained from commercial sources and were used without purification. Nuclear magnetic resonance (NMR) spectra of the synthesized compounds were recorded on Ascend Bruker 400 (Bruker, Fallanden, Switzerland) instrument and operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR using either $CDCl_3$ or DMSO-d_6 solvent and tetramethylsilane (TMS) as internal standard. Spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), and m (multiplet) as well as brs (broad singlet). The ^{1}H chemical shift values were reported on δ scale in ppm, relative to TMS (δ = 0.00 ppm) and in the ^{13}C chemical shift values were reported relative to DMSO-d_6 (δ = 39.5 ppm). The ESI/MS experiments were performed on a Velos Pro ion trap mass spectrometer from Thermo Scientific (San Jose, CA, U.S.A.).

Synthesis of 1-[2-(Methylsulfanyl)-10*H*-phenothiazin-10-yl]ethanone (3). In a 2 L RB flask, 2-(methylsulfanyl)-10*H*-phenothiazine (**1**) (200 g, 0.81 mol) in toluene (1200 mL, 6 vol) was charged, and acetyl chloride (160 g, 2.02 mol) was added slowly at 20−30 °C. The reaction mass was stirred at 20−30 °C for 1 h. After completion of the reaction as per reaction monitoring by HPLC, the reaction mass was cooled to 0−5 °C and water (800 mL, 4 vol) was added slowly. Then, the temperature of the reaction mass was increased to 20−30 °C. The layers were separated, and the organic layer was collected and washed with 5% aqueous $NaHCO_3$ solution (15 g in 300 mL water). Again the layers were separated, and the organic layer was collected. The organic layer was washed with water (600 mL, 3 vol). The organic layer was collected and the solvent was evaporated under vacuum at 45 °C. Isopropanol (600 mL) was added to the crude mass, and the temperature was increased to reflux (clear solution). At reflux temperature, the reaction mass was stirred for 15 min and then cooled to 10−15 °C and maintained for 1 h. The solid was filtered and washed with (100 mL, 0.5 vol) isopropanol. The compound was dried under vacuum at 60−65 °C for 8 h.

Off-white solid, yield. 93% (218 g), mp 223−226 °C.

^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 7.49 (d, 1H, arom H, J = 7.6 Hz), 7.46−7.42 (m, 2H, arom H), 7.36−7.32 (m, 2H, arom H), 7.28−7.22 (m, 1H, arom H), 7.13 (dd, 1H, arom H, J = 8.0 and 1.6 Hz), 2.51 (s, 3H, $-SCH_3$), 2.23 (s, 3H, $-COCH_3$).

^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 168.36, 139.19, 138.52, 137.74, 132.05, 128.07, 127.97, 127.78, 127.44, 127.19, 126.94, 124.60, 124.51, 22.71, 14.88.

MS m/z (ESI): 288.04 $(M + H)^{+\cdot}$

Kilogram Scale. The same reaction carried out in kilogram scale with compound **1** (6.5 kg, 26.49 mol, 1.0 equiv), acetyl chloride (5.2 kg, 66.2 mol, 2.5 equiv), toluene (39 L, 6 vol), and obtained 6.98 kg of compound **3** (Yield: 91.8%).

Synthesis of 1-[2-(Methylsulfonyl)-10*H*-phenothiazin-10-yl]ethanone (4). In a 3 L RB flask, 1-[2-(methylsulfanyl)-10*H*-phenothiazin-10-yl]ethanone (**3**) (150 g, 0.52 mol) was charged at 20−30 °C in acetonitrile (1500 mL, 10 vol). The oxone [641.3 g, 1.04 mol] in water (1050 mL, 7 vol) was added slowly. The reaction mass stirred at 20−30 °C for 2 h. After completion of the reaction as per reaction monitoring by HPLC, the reaction mass was quenched with sodium thiosulfate solution (75 g in 300 mL water, 2 vol). Dichloromethane (DCM) (750 mL) was added and stirred for 10 min. Layers were separated, the organic layer was collected in the same pot, and the solvent was evaporated under vacuum. To the crude mass (**4a**), Zn powder (56.5 g, 0.86 mol) in acetonitrile (1050 mL, 7 vol) and lactic acid (300 mL, 2 vol) were added and stirred at 60−70 °C for 3 h. After completion of the reaction as per reaction monitoring by HPLC, the reaction mass was cooled to 20−30 °C. Charged dichloromethane (750 mL, 5 vol) as the compound **4** has poor solubility in acetonitrile. The reaction mass stirred for 30 min and filtered through Hyflo bed at 20−30 °C. The filtrate was transferred into a 2 L RB flask, and the solvent was removed under reduced pressure at 40−45 °C. The reaction mass was cooled to 20−30 °C and water (750 mL, 5 vol) was added slowly and then stirred for 30 min. The precipitated solid was filtered and washed with water (300 mL, 2 vol). The solid product **4** was dried in hot air oven at 50 °C for 10 h.

Off-white solid, yield. 85% (142 g), mp 90−97 °C.

^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 8.13 (s, 1H, arom H), 7.86−7.81 (m, 2H, arom H), 7.69 (d, 1H, arom H, J = 7.6 Hz), 7.60 (d, 1H, arom H, J = 8.0 Hz), 7.48−7.44 (m, 1H, arom H), 7.38−7.34 (m, 1H, arom H), 3.25 (s, 3H, $-S-CH_3$), 2.17 (s, 3H, $-COCH_3$), 1.8 (s, 3H, $-COCH_3$ of acetic acid impurity).

^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 168.43, 139.48, 138.66, 138.55, 137.95, 130.80, 128.69, 128.06, 127.88, 127.45, 127.40, 125.70, 125.06, 43.43, 22.54.

MS m/z (ESI): 320.05 $(M + H)^{+\cdot}$

Characterization Data of 1-[2-(Methylsulfonyl)-5-oxido-10*H*-phenothiazin-10-ylethanone (4a). ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 8.37 (s, 1H, arom H), 8.10−8.05 (m, 2H, arom H), 7.93 (dd, 1H, arom H, J = 6.4 and 2.0 Hz), 7.64−7.56 (m, 3H, arom H), 3.14 (s, 3H, $-SO_2-CH_3$), 2.40 (s, 3H, $-COCH_3$). MS m/z (ESI): 336.01 $(M + H)^{+\cdot}$

Kilogram Scale. The same reaction carried out in kilogram scale with compound **3** (6.3 kg, 21.92 mol, 1.0 equiv) in acetonitrile [63 L, 10 vol], oxone [26.93 kg, 43.8 mol, 2.0 equiv] in water (44.1 L, 7 vol), dichloromethane (31.5 L), Zn powder (2.36 kg, 36.0 mol, 1.65 equiv) in acetonitrile (44.1 L, 7 vol) and lactic acid (12.6 L, 2 vol) and obtained 5.91 kg of compound **4** (yield: 84.4%).

Synthesis of 10-(3-Chloropropyl)-2-(methylsulfonyl)-10*H*-phenothiazine (5). In a 2 L RB flask, 1-[2-(methylsulfonyl)-10*H*-phenothiazin-10-yl]ethanone (**4**) (100 g, 0.313 mol) in acetone (1000 mL, 10 vol) and powdered KOH (52.6 g, 0.94 mol) was added. (Note: The color of the reaction mass was changed from gray yellow to dark pink.) Then, 1-bromo-3-chloropropane [148 g, 0.94 mol] was added slowly at 20−30 °C. The reaction mass temperature was increased to 50−60 °C and was stirred at the same temperature for 3 h. After completion of the reaction as per reaction monitoring by HPLC, the reaction mass was cooled to 20−30 °C, and water (500 mL, 5 vol) was added. The formed product was extracted using dichloromethane (500 mL, 5 vol). The organic solvent was collected and evaporated under vacuum. To the obtained crude mass, methanol (500 mL, 5 vol) was added. The reaction mass temperature was increased to 60−65 °C and was maintained for 30 min. Then, the reaction mass was cooled to 20−30 °C, and it was stirred for 1 h at 20−30 °C. The reaction mass was filtered and washed with methanol (50 mL, 0.5 vol). The obtained compound **5** was dried in vacuum oven at 50 °C for 10h.

Yellow color solid, yield. 60% (67 g), mp 122−127 °C.

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^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 7.49 (dd, 1H, arom H, J = 8.0 Hz and1.6 Hz), 7.40 (d, 1H, arom H, J = 1.6 Hz), 7.32−7.28 (m, 1H, arom H), 7.24−7.22 (m, 1H, arom H), 7.17 (dd, 1H, arom H, J = 7.6 and 1.2 Hz), 7.04−7.0 (m, 1H, arom H), 6.96 (d, 1H, arom H, J = 8.0 Hz), 4.15 (t, 2H, $-NCH_2-$, J = 6.4 Hz), 3.68 (t, 2H, $-CH_2Cl$, J = 6.0 Hz), 3.06 (s, 3H, $-SO_2CH_3$), 2.26 (quintet, 2H, $-CH_2-$).

^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 145.29, 143.53, 140.24, 131.13, 128.16, 127.75, 127.46, 123.52, 122.81, 120.98, 116.51, 113.43, 43.67, 43.43, 42.52, 29.04.

MS m/z (ESI): 354.04 $(M + H)^{+\cdot}$

Kilogram Scale. The same reaction carried out in kilogram scale with compound **4** (5.5 kg, 17.2 mol, 1.0 equiv) in acetone (55 L, 10 vol), powdered KOH (2.893 kg, 51.6 mol, 3.0 equiv), and 1-bromo-3-chloropropane (8.14 kg, 51.7 mol, 3.0 equiv) obtained 3.73 kg of compound **5** (yield: 61.2%).

Synthesis of 1-(3-[2-(Methylsulfonyl)-10*H*-phenothiazin-10-yl]propyl)-4-piperidinecarboxamide (1), Metopimazine. In a 2 L RB flask, a mixture of 10-(3-chloropropyl)-2-(methylsulfonyl)-10*H*-phenothiazine (**5**) (100 g, 0.282 mol), 4-piperidinecarboxamide (54.21 g, 0.42 mol), and K_2CO_3 (97.63 g, 0.706 mol) in toluene-DMF (8:2 ratio) (1000 mL, 10 vol) was stirred at 90−100 °C for 8 h. After completion of the reaction as per reaction monitoring by HPLC, the mixture was cooled to 25−30 °C. Toluene (1000 mL, 10 vol) was added to the reaction mass, and the mixture was stirred for 30 min. The reaction mass was filtered and washed with toluene (100 mL, 1 vol). Water (1000 mL, 10 vol) was added to the wet material and stirred for 1 h at 20−30 °C, and the solid was filtered and dried at 60−65 °C for 5 h. The crude material (95 g) in toluene/DMF (8:2 ratio) (500 mL, 5 vol) was stirred at 60−70 °C for 1 h. Then, the reaction mass was cooled to 20−30 °C and stirred for 30 min. The formed solid was filtered and washed with toluene (100 mL, 1 vol). The obtained compound (**1**) was dried in a hot air oven at 50 °C.

Pale yellow color solid, yield. 65% (82 g), DSC 189 °C.

^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 7.44 (d, 1H, arom H, J = 8.8 Hz), 7.37 (d, 2H, arom H, J = 8.0 Hz), 7.24 (t, 1H, arom H, J = 7.6 Hz), 7.16 (m, 2H, $-NH_2$), 7.1 (d, 1H, arom H, J = 8.4 Hz), 6.99 (t, 1H, arom H, J = 7.6 Hz), 6.68 (s, 1H, arom H), 3.99 (t, 2H, $-NCH_2$, J = 6.4 Hz), 3.23 (s, 3H, $-S-CH_3$), 2.8−2.73 (m, 2H, $-CH_2-$), 2.36 (t, 2H, $-CH_2-$, J = 6.8 Hz), 2.02−1.96 (m, 1H, −CH−), 1.84−1.78 (m, 4H, $2-CH_2-$), 1.61−1.58 (m, 2H, $-CH_2-$), 1.48−1.44 (m, 2H, $-CH_2-$).

^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 176.52, 145.41, 143.5, 140.12, 130.47, 128.03, 127.50, 127.25, 123.23, 122.16, 120.59, 116.38, 113.24, 54.82, 52.97, 44.64, 43.47, 41.7, 28.59, 23.52.

MS m/z (ESI): 446.21 $(M + H)^{+\cdot}$

Powder XRD Data. The crystalline form of Metopimazine was characterized by PXRD (Powder XRD), and it showed peaks at 4.43, 8.81, 9.84, 11.37, 13.21, 16.57, 17.64, 19.09, 19.72, 19.99, 20.62, 21.68, 22.07, 24.39, 24.77, 26.42, 27.76, 30.82, 32.02 degrees 2θ.

Kilogram Scale. The same reaction carried out in kilogram scale with compound **5** (3.5 kg, 9.89 mol, 1.0 equiv), 4-piperidinecarboxamide (1.9 kg, 14.8 mol, 1.5 equiv) and K_2CO_3 (3.42 kg, 24.74 mol, 2.5 equiv) in toluene/DMF (8:2 ratio) (35 L, 10 vol) and obtained 2.81 kg of Metopimazine API (**1**) (Yield: 63.8%); HPLC purity: 99.9% and the related substances and individual unknown impurities are within the limit of the specifications.

Synthesis and Characterization Data of Possible Impurities. All the possible impurities were identified, synthesized, and characterized. The details are as below.

Synthesis of 1-[2-(Methylsulfinyl)-10*H*-phenothiazin-10-yl]ethanone (4b). In a 2 L RB flask, 1-[2-(methylsulfanyl)-10*H*-phenothiazin-10-yl]ethanone (**3**) (50 g, 0.174 mol) was charged at 20−30 °C in dichloromethane (500 mL, 10 vol). Then, oxone (13.24 g, 0.087 mol, 0.5 equiv) in water (750 mL, 15 vol) and PTC (tetrabutyl ammonium bromide) (5.6 g, 0.0173 mol, 0.1 equiv) were added. The reaction mass was stirred at 30−40 °C for 6 h. After completion of the reaction as per TLC, the reaction mass was cooled to 20−30 °C and was quenched in sodium thiosulfate solution (25.0 g in 100 mL water, 2 vol). Layers were separated, the organic layer was collected, and the solvent was evaporated under vacuum. The crude mass was purified over column filled with silica gel (60−120 mesh) using 20% ethyl acetate in hexane. The solid product **4b** was dried in hot air oven at 50 °C. Weight = 8.8 g.

^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 7.94 (s, 1H, arom H), 7.76 (d, 1H, arom H, J = 8.4 Hz), 7.67 (d, 1H, arom H, J = 8.0 Hz), 7.62−7.58 (m, 2H, arom H), 7.46−7.42 (m, 1H, arom H), 7.36−7.32 (m, 1H, arom H), 2.78 (s, 3H, $-SO-CH_3$), 2.17 (s, 3H, $-COCH_3$).

^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 168.37, 145.59, 138.96, 138.21, 134.87, 131.33, 128.50, 127.97, 127.59, 127.41, 127.24, 122.48, 122.01, 43.15, 22.62.

MS m/z (ESI): 303.98 $(M + H)^{+\cdot}$

Synthesis of 1-[2-(Methylsulfinyl)-5-oxido-10*H*-phenothiazin-10-yl]ethanone (4c). In a 1 L RB flask, 1-[2-(methylsulfanyl)-10*H*-phenothiazin-10-yl]ethanone (**3**) (25g, 0.087 mol) was charged at 20−30 °C in dichloromethane (250 mL, 10 vol). Then, oxone (53.4 g, 0.087 mol, 1.0 equiv) in water (375 mL, 15 vol) and PTC (tetrabutyl ammonium bromide) (2.8 g, 0.0087 mol, 0.1 equiv) were added. The reaction mass was stirred at 30−40 °C for 6 h. After completion of the reaction as per TLC, the reaction mass was cooled to 20−30 °C and was quenched in sodium thiosulfate solution (12.5 g in 50 mL water, 2 vol). Layers were separated, the organic layer was collected, and the solvent was evaporated under vacuum. The crude mass was purified over column filled with silica gel (60−120 mesh) using 20% ethyl acetate in hexane. The solid product **4c** was dried in hot air oven at 50 °C. Weight = 12 g.

^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 8.18 (br, 1H, arom H), 8.00 (t, 1H, arom H, J = 7.2 Hz), 7.89 (t, 1H, arom H, J = 8.0 Hz), 7.85 (d, 2H, arom H, J = 8.0 Hz), 7.67 (t, 1H, arom H, J = 7.2 Hz), 7.60 (t, 1H, arom H, J = 7.2 Hz), 2.82 (s, 3H, $-SO-CH_3$), 2.33 (s, 3H, $-COCH_3$).

^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 168.48, 150.20, 142.12, 139.57, 132.11, 131.54, 129.16, 128.25, 125.03, 123.10, 123.02, 122.62, 122.56, 43.57, 23.71.

MS m/z (ESI): 320.07 $(M + H)^{+\cdot}$

Synthesis of 1-[2-(Methylsulfonyl)-5,5-dioxido-10*H*-phenothiazin-10-yl]ethanone (4d). In a 1 L RB flask, 1-[2-(methylsulfanyl)-10*H*-phenothiazin-10-yl]ethanone (**3**) (10g, 0.034 mol) was charged at 20−30 °C in acetic acid (100 mL, 10 vol). Then, 30% solution of H_2O_2 (100 mL) was added slowly. The reaction mass stirred at 20−30 °C for 24 h. After completion of the reaction as per TLC, the reaction mass was filtered and washer with water (20 mL, 2 V). The crude mass was purified over column filled with silica gel (60−120 mesh) using 20% ethyl acetate in dichloromethane. The solid product **4d** was dried in vacuum oven at 50 °C. Weight = 2.3 g.

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^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 8.53 (s, 1H, arom H), 8.30 (d, 1H, arom H, J = 8.0 Hz), 8.16 (dd, 1H, arom H, J = 8.0 and 1.6 Hz), 8.09−8.03 (m, 2H, arom H), 7.84 (t, 1H, arom H, J = 6.8 Hz), 7.68 (t, 1H, arom H, J = 7.6 Hz), 3.35 (s, 3H, $-SO_2-CH_3$), 2.36 (s, 3H, $-COCH_3$).

^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 168.71, 144.98, 140.30, 139.57, 138.11, 134.41, 133.77, 128.62, 128.47, 127.06, 126.47, 125.21, 124.26, 43.50, 23.93.

MS m/z (ESI): 308.00 $(M + H)^{+\cdot}$

Synthesis of 2-(Methylsulfonyl)-10-(prop-2-en-1-yl)-10*H*-phenothiazine (5a). In a 100 mL RB flask, 1-[2-(methylsulfonyl)-10*H*-phenothiazin-10-yl]ethanone (**4**) (5 g, 0.015 mol) in acetone (50 mL, 10 vol) and powdered KOH (2.63 g, 0.047 mol) were added at 20−30 °C. (Note: The color of the reaction mass was changed from gray yellow to dark pink.) Then, allyl bromide (4.3 g, 0.035 mol) was added slowly at 20−30 °C. The reaction mass stirred at 50−60 °C for 3 h. After completion of the reaction as per TLC, the reaction mass was cooled to 20−30 °C. The dichloromethane (100 mL, 20 vol) was added to the crude reaction mass, and it was stirred for 30 min. The solid was filtered and it was dried in vacuum oven at 50 °C.

^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 7.41 (dd, 1H, arom H, J = 8.0 and 1.6 Hz), 7.34 (d, 1H, arom H, J = 8.0 Hz), 7.27 (s, 1H, arom H), 7.20−7.16 (m, 1H, arom H), 7.12 (dd, 1H, arom H, J = 7.6 and 1.2 Hz), 6.95 (q, 2H, arom H, J = 7.6 Hz), 5.99−5.93 (m, 1H, $-CH{=}CH_2$), 5.31 (dd, 1H, J = 12 Hz and J = 1.2 Hz, $-CH{=}CH_2$), 5.20 (dd, 1H, J = 18.4 Hz and J = 1.2 Hz, $-CH{=}CH_2$), 4.58 (t, 2H, $-CH_2-$, J = 2.0 Hz), 3.18 (s, 3H, $-SO_2CH_3$).

^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 144.38, 143.03, 139.86, 132.57, 129.08, 128.03, 127.10, 126.79, 123.28, 120.83, 120.59, 117.49, 116.07, 113.16, 50.21, 43.51.

MS m/z (ESI): 316.98 $(M + H)^{+\cdot}$

Preparation of 2-Methanesulfonyl-10-[3-(2-methanesulfonyl-10*H*-phenothiazin-10-yl) propyl]-10*H*-phenothiazine (5b). The mother liquor of 10-(3-chloropropyl)-2-(methylsulfonyl)-10*H*-phenothiazine (**5**) was taken and concentrated. The crude mass was purified over column filled with Silica gel using 10% ethyl acetate in hexane, and the desired impurity **5b** was collected.

^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 7.27−7.24 (m, 4H, arom H), 7.50−7.00 (m, 4H, arom H), 6.96 (dd, 2H, arom H, J = 7.6 and 1.2 Hz), 6.84 (t, 2H, arom H, J = 7.6 Hz), 6.77 (d, 2H, arom H, J = 8.0 Hz), 4.07−4.01 (m, 4H, 2 $-CH_2-$, aliphatic), 2.95 (s, 6H, $-CH_3$, $-SO_2CH_3$), 2.10−2.05 (m, 2H, $-CH_2-$).

^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 146.06, 143.10, 139.42, 133.47, 127.84, 127.76, 127.64, 124.43, 123.66, 121.11, 116.41, 113.88, 53.44, 44.59, 43.46, 23.30, 19.17.

MS m/z (ESI): 595.10 $(M + H)^{+\cdot}$

Synthesis of 1-(3-[2-(Methylsulfonyl)-10*H*-phenothiazin-10-yl]propyl)-4-piperidine Carboxylic Acid (1a). In a 100 mL RB flask, Metopimazine (**1**) (5 g, 0.011 mol), concn HCl (12.5 mL) were stirred at 70−80 °C for 10 h. After completion of the reaction as per TLC, the mixture was cooled to 20−30 °C, and water (50 mL, 5 vol) was added. Then dichloromethane (100 mL, 20 vol) was added. The layers were separated, and the organic layer was collected and washed with water (10 mL, 2 vol). The organic layer was collected, dried over Na_2SO_4, and the solvent was evaporated under vacuum. The ethyl acetate was added (15 mL, 3 vol) to the crude compound, and the mixture was stirred for 1 h at 20−30 °C. The solid was filtered and washed with ethyl acetate (5 mL, 1 vol). The solid **1a** was dried under vacuum at 30−35 °C for 8 h.

^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 7.49−7.43 (m, 3H, arom H), 7.28 (t, 1H, arom H, J = 7.2 Hz), 7.24−7.21 (m, 1H, arom H), 7.14 (d, 1H, J = 8.4 Hz), 7.03 (t, 1H, arom H, J = 7.6 Hz), 4.07 (t, 2H, $-NCH_2-$, J = 6.8 Hz), 3.26 (br s, 6H, −alky H), 3.00 (br, 2H, $-CH_2-$), 2.75 (br s, 2H, $-CH_2-$), 2.46 (br s, 1H, −CH−), 2.08 (br s, 2H, $-CH_2-$), 1.92 (m, 2H, $-CH_2-$), 1.79 (br m, 2H, $-CH_2-$).

^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 175.33, 145.81, 143.93, 140.71, 131.56, 128.66, 128.23, 127.96, 124.04, 123.27, 121.47, 117.11, 114.06, 55.39, 53.99, 51.50, 44.59, 43.99, 38.38, 25.94, 21.95, 21.55.

MS m/z (ESI): 447.08 $(M + H)^{+\cdot}$

Bis-{(1-(3-[2-(Methylsulfonyl)-10*H*-phenothiazin-10-yl]propyl)-4-piperidine carboxamide)} (1b). In a 2 L RB flask, a mixture of 10-(3-chloropropyl)-2-(methylsulfonyl)-10*H*-phenothiazine (**5**) (10 g, 0.0282 mol), 4-piperidinecarboxylic acid (5.47 g, 0.042 mol), and K_2CO_3 (9.76 g, 0.07 mol) in toluene/DMF (8:2 ratio) (1000 mL, 10 vol) was stirred at 90−100 °C for 8 h. After completion of the reaction as per TLC, the reaction mass was cooled to 20−30 °C. Then, toluene (100 mL, 10 vol) was added and stirred for 30 min. The reaction mass was filtered and washed with toluene (20 mL, 2 vol). The crude material was collected and purified over column filled with Silica gel using 5% ethyl acetate in dichloromethane.

^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 7.45−7.36 (m, 6H, arom H), 7.23 (t, 2H, arom H, J = 8.0 Hz), 7.17 (t, 2H, arom H, J = 6.8 Hz), 7.09 (t, 2H, J = 7.6 Hz), 6.99 (m, 2H, arom H), 4.07 (m, 4H, $-NCH_2$), 3.98 (t, 2H, $-CH_3$, J = 7.6 Hz), 3.21 (s, 6H, $-CH_2-$), 2.62 (br s, 2H, $-CH_2-$), 2.32 (br, 2H, −CH−), 2.17 (br t, 2H, $-CH_2-$, J = 10.8 Hz), 1.99 (br t, 2H, $-CH_2-$, J = 6.4 Hz), 1.88−1.75 (br m, 4H, $-CH_2-$), 1.60 (br, 2H, $-CH_2-$), 1.34 (q, 2H, $-CH_2-$, J = 10.4 Hz).

^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 174.32, 145.43, 145.28, 143.57, 143.44, 140.19, 140.12, 130.94, 130.52, 128.09, 128.05, 127.64, 127.55, 127.38, 127.29, 123.42, 123.26, 122.60, 122.22, 120.85, 120.63, 116.44 (2C), 113.35, 113.31, 61.09, 54.65, 52.36 (2C), 44.57 (2C), 43.46, 43.43, 43.14, 27.87 (2C), 25.10, 23.48.

MS m/z (ESI): 764.14 $(M + H)^+$.

CONCLUSIONS

In the present work, we have demonstrated the commercially viable and practical process for the preparation of Metopimazine (**1**), an antiemetic drug. Important intermediates (**3**, **4**, and **5**) and impurities (**4b−d**, **5a**, **5b** and **1a**, **1b**) were well characterized by ^{1}H, ^{13}C NMR and Mass spectral data. The major advantages of the present process include (i) improved commercial process with well optimized reaction conditions, (ii) use of green chemicals, (iii) operational friendly process (simple, scalable and practical) with improved yields (overall yield ≈31%) compared to previously reported processes (<15%). In the present process (i) two new impurities (**5b** and **1b**) are found and reported with characterization data; (ii) the concept of green chemistry was achieved partially with the use of green reagents like oxone and lactic acid. In addition, the present work is highly helpful in commercialization of the Metopimazine drug throughout the world which is now limited to France.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.7b00052.

Copies of relevant ^{1}H, ^{13}C NMR and mass spectra and also HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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