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Magic Bullet! Rebamipide, a Superior Antiulcer and Ophthalmic Drug and Its Large-Scale Synthesis in a Single Organic Solvent *via* Process Intensification Using Krapcho Decarboxylation

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Abstract: The Rebamipide (**1**) is a superior drug in healing of peptic ulcers, gastrointestinal bleeding and dyspepsia compared to existing drugs. In addition, it is also useful as ophthalmic drug for the treatment of dry eye syndrome. The process intensification was achieved by i) averting uncontrollable frothing using Krapcho decarboxylation instead of conventional acid hydrolysis where uncontrollable frothing became chaotic, ii) use of single organic solvent was minimized the organic waste generation, and iii) avoided antifoaming agents (n-octonol, acetophenone) and acetic acid. With these trifling modifications the overall yield of API was ≥83% with excellent purity of API (≥99.89%) and the process meets the metrics to "green" chemistry with E-Factor =11.5. The developed hassle free commercial process is viable for multi-kilogram synthesis of Rebamipide (**1**) as the key step, Krapcho decarboxylation is safe to run at 130-140 °C in DMSO and it was proved by DSC (differential scan calorimetry) thermal screening studies. The characterization data of intermediates **4**, **5**, **6** and **7**, process related impurities (**1a**, **1b 1c**, **8a** and **8b**) and API (**1**) is reported. The carryover and process related impurities were controlled efficiently. The present work can enhance the scope and world wide adoptability of Rebamipide (**1**) which is now limited to Asian countries.

Key words: Rebamipide, Process intensification, Frothing free, Ulcer healing, ophthalmic, E-factor

INTRODUCTION

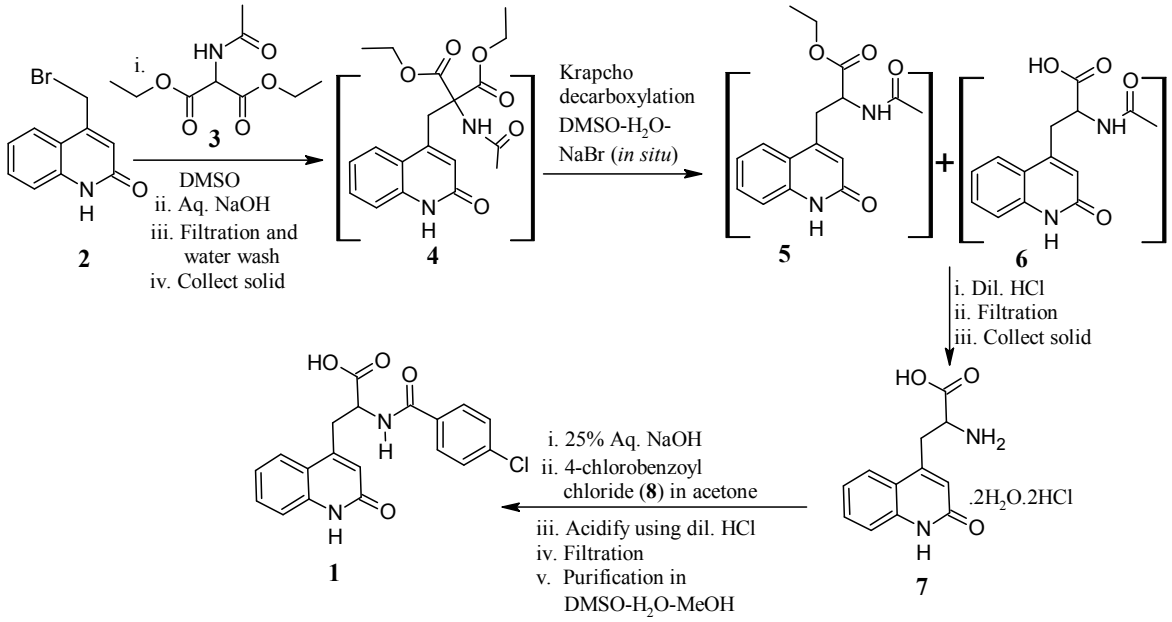
The peptic ulcer disease[1] is a disorder of the upper gastrointestinal tract caused by various noxious agents,[2] for example hypoacidity,[3] Helicobacter pylori[4] and use of certain drugs (captopril, gold salts, nicorandil, phenobarbitol, piroxicam), especially NSAIDS, such as ibuprofen and aspirin,[5] or other things that cause breaks in mucosa. The development of

ulcers can lead to serious complications such as bleeding, perforation, abdominal pain, burning sensation, vomiting, and a life-threatening condition that require emergency surgery.[6] Hence, there is a great demand for new drugs which prevent the formation of ulcers as the existing drugs are only inhibitors of gastric acid secretion and none of the available medications prevent the formation of peptic ulcer. The unresolved problem was solved with the invention of a magic bullet in 1980.[7] The magic bullet was named as Rebamipide which is superior drug to treat gastric ulcers, acute gastritis, exacerbated chronic gastritis, whereas other existing drugs are futile, for example Cetraxate.[8] It was also found that it can also be used as ophthalmic drug for the treatment of dry eye syndrome.[9] Rebamipide is chemically called as (±)–2–(4–Chlorobenzoylamino)–3–[2(1H)–quinolinon–4–yl] propionic acid. The precise mode of action of Rebamipide is unknown.[10-17]

Process intensification can be understood as a portfolio for the development of new process approaches resulting in "substantially smaller, cleaner, safer and more efficient process methods."[11,] Unfortunately, the reported methods for the production of Rebamipide (**1**) suffer from one or more disadvantages,[14–16] for example, expensive starting material and reagent, sudden bumping of reaction mass, fast refluxing conditions, requisite quick removal of by-products (ethanol, ethyl acetate and CO_2), increased utility cost and removal of traces amounts of some catalysts/reagents in API is difficult to meet the ICH guidelines, and huge organic waste generation. The extensive literature search revealed that uncontrollable frothing is chaotic during the synthesis of Rebamipide (**1**).[12, 13] The uncontrollable frothing or foaming or agglomerate or bubbles is one of the most problematic conditions not only in pharmaceutical industry, for example in production of Rebamipide,[14] but also in most of the other industries.[21] The major disadvantages include i) requirement of 10 times big reactor than usual with regard to batch size, ii) inefficiency of process involving expensive costs , iii) run-off of the reaction mass along with froth; iv) operational unfavourable and chaotic, v) reduction in product yield, and vi) sudden bumping of the reaction mass. The situation become worse when the reaction mass is handled at higher temperature. Hence, there is a great demand for the innovative process that is free from such uncontrollable frothing or bubbles in the production of Rebamipide drug. The messy problems were addressed in the present work by the application of Krapcho decarboxylation.[17]

The one–pot operation was reported first by Robinson nearly 100 years ago.[18] It has received great attention as it can minimize the number of reaction steps, cost, development time,

execution time, and environmental impact of synthesis.[19] In continuation of our interest in developing one–pot reactions[20] to meet the metrics to green chemistry, herein, we report a new synthetic method for the production of Rebamipide (**1**) starting from the reaction of 4–(bromomethyl)quinolin–2(1*H*)–one (**2**) with diethyl–(acetylamino) propanedioate (**3**) in presence of aqueous NaOH solution offered diethyl (acetylamino)[(2–oxo–1,2–dihydroquinolin–4–yl)methyl]propanedioate (**4**) followed by decarboxylation using Krapcho conditions [DMSO–H_2O–NaBr (*in situ*)] provided mixture of ethyl 2–(acetylamino) –3–(2–oxo–1,2–dihydroquinolin–4–yl)propanoate (**5**) as major and 2–(acetylamino)–3–(2–oxo–1,2–dihydroquinolin–4–yl)propanoic acid (**6**) as minor in DMSO as single organic solvent. The acid hydrolysis of compounds **5** and **6** offered compound **7** which further reacts with 4-chlorobenzoyl chloride (**8**) to produce Rebamipide (**1**) as shown in scheme 1.



Scheme 1: Synthesis of Rebamipide (**1**)

RESULTS AND DISCUSSION

In the initial stage of development, the synthesis of Rebamipide was carried out by aiming to develop frothing free cost-effective process as the reported literature methods suffer from few disadvantages at bulk scale as discussed in above sections. As a result, it is planned to focus on Krapcho decarboxylation[17] to avert conventional acid hydrolysis of compound **4** where uncontrollable frothing is hectic.[14] Accordingly, the Krapcho decarboxylation was preceded

well without any frothing in presence of DMSO–H_2O–NaBr (*in situ*). Secondly, we focused on optimization of unit operations, such as work–up(s), distillation(s), and filtration(s). For instance, we have avoided the isolation and work-up operations by the development of one–pot operation. Thirdly, we focused on impurity profile, for example source of carryover, process related impurities and development of control strategies for those impurities. The intermediates (**4**, **5**, **6** and **7**) and API (**1**) are soluble in DMSO, DMF and DMAc and they have poor solubility in other common organic solvents. This directs that the purification process could only be developed within certain confines to meet the specification criteria of API. Accordingly, DMSO–H_2O–MeOH solvent system was developed to remove the potential impurities. The desired quality and nature of API was achieved.

The hassle free and improved commercial process was designed and developed by aiming to achieve improved yields with desired quality (≥99.89%) of Rebamipide (**1**) drug as shown in Scheme 1. In each and every step, the reaction conditions were optimized well as discussed in below sections.

Ideal process conditions for the synthesis of diethyl(acetylamino)[(2–oxo–1,2–dihydroquinolin–4–yl)methyl]propanedioate (**4**): Initially, a reaction was carried out using 4-(bromomethyl)quinolin–2(1*H*)–one (**2**) with diethyl–(acetylamino)propanedioate (**3**) in presence of NaOH in DMF (as the compound **2** is soluble only in DMF, DMSO and DMAc) at 0–10 °C and the formation of compound **4** was 97% where as at 20–30 °C, slight low formation (94%) was observed (entry 1, Table 1). Most of the literature methods reported use of NaOH in DMF (anhydrous conditions).[21] If the same was followed at production scale, some amount of NaOH was settled down at the bottom of the reactor which leads to inconsistent results and also choking at the bottom valve of the reactor. To overcome the problem, the same reaction was carried out by dissolving NaOH in water (used 0.5 vol of water with respect to batch size) and obtained similar results (98%) (entry 1). The success of aqueous NaOH solution encouraged us to replace DMF with DMSO. The same reaction was carried out using DMSO at 20–30 °C and 98% formation of product **4** in presence of aqueous NaOH solution (entry 2) was observed. When the same reaction was carried out in DMAc, the formation was decreased (75% at 0–10 °C and 52% at 20–30 °C) (entry 3).

Further, the effect of various bases, for example KOH, Na_2CO_3, K_2CO_3 (aqueous solution) and Et_3N and piperidine was studied and obtained 78%, 11%, 19%, 22% and 20% formation of compound **4**, respectively (entries 4–8, Table 1).

The study disclosed that both DMF at 0–10 °C (entry 1, Table 1) and DMSO at 20–30 °C (entry 2 and Figure S6 in the Supporting Information) are the best solvents for maximum formation of compound **4** (~95%) in presence of aqueous NaOH solution. We have selected DMSO as preferable solvent for further studies of Krapcho reaction telescopically as the reaction proceeds well in DMSO.

Table 1: Effect of reaction conditions on formation of compound 4[a]

S. No.	Base	Solvent	Time (h)	Temp (°C)	Product	Product (% by HPLC)
1	NaOH	DMF	3	**0–10**	**4**	97
			2	**20–30**		94
	Aq. NaOH		3	**0–10**		98[c]
2	Aq. NaOH	DMSO[b]	3	**20–30**	**4**	98
3	Aq. NaOH	DMAc	1	**0–10**	**4**	75
				20–30		52
4	Aq. KOH	DMSO	1	**20–30**	**4**	78
5	Aq. Na_2CO_3	DMSO	6	**20–30**	**4**	11
6	Aq. K_2CO_3	DMSO	5	**20–30**	**4**	19
7[c]	Et_3N	DMSO	4	**20–30**	**4**	22
8[c]	Piperidine	DMSO	4	**20–30**	**4**	20

[a]**Reaction conditions**: Substrate **2** (10.0 mmol), compound **3** (11.0 mmol), Base (10.0 mmol), organic solvent (3.0 vol) and water (0.5 vol).
[b]Reaction conducted at 20-30 °C as DMSO freezing point is 19 °C.
[c]Water was not used.

New process conditions for the synthesis of ethyl 2–(acetylamino)–3–(2–oxo–1,2–dihydroquinolin–4–yl)propanoate (5) and 2–(acetylamino)–3–(2–oxo–1,2–dihydroquinolin–4–yl) propanoic acid (6): Initially, we attempted the conventional decarboxylation of compound **4** to prepare compound **7** directly using conc. HCl, an uncontrollable frothing was observed with 98% of product (**7**) formation (entry 1, Table 2).[14] The major problems faced during acid hydrolysis at production level include i) 10 times big reactor required than usual with respect to batch size, ii) run–off of the reaction mass along with foam, and iii) sudden bumping of the reaction mass cause operational unfavourable and chaotic. The situation became awful when the same reaction was carried out at higher temperature (>97 °C is compulsory).

Then, we conducted the same reaction using antifoaming agents (n-octonol, acetophenone and acetic acid) and the conversion is ≥94% (entries 2–4). The major issues associated with this method include sudden bumping of the reaction mass, unpredictable time line for the completion of the reaction, vigorous reflux conditions and removal of by–products of the reaction, and operational hazard at high temperature, organic waste generation, and their carryover up to API.

To get rid from these hassles, our attention turned towards Krapcho decarboxylation which was well documented in literature.[17] The Krapcho method is excellent when NaCN and KCN were used, but we have avoided them because of their heavy toxicity. Initially, a reaction was carried out using DMSO–H_2O–NaCl at 130–140 °C and the conversion was 97% (64% of compound **5** and 33% of compound **6**) (entry 6). The same reaction was carried out using NaBr instead of NaCl and the conversion was 96% (62% of compound **5** and 34% of compound **6**) (entry 7). The success of Krapcho reaction in DMSO–H_2O–NaBr system (entry 7) encouraged us to conduct the same experiment without addition of external NaBr as it was generated *in situ* during the conversion of compound **2** to compound **4** (scheme 1) and the formation of compound was good 95% (62% of compound **5** and 33% of compound **6** within 7 h (entry 8). It was observed that the unreacted substrate (**4**) (~2%) was converted to desired compound **7** during acid hydrolysis in the next stage.

The study disclosed that Krapcho reaction [DMSO–H_2O–NaBr (*in situ*)] at 130–140 °C is good for maximum conversion (96%) and safe operation without frothing (entry 8, Table 2 and Figure S17 in the Supporting Information)

Table 2: **Effect of reaction conditions on decarboxylation of compound 4**.[a]

Entry	Conditions	Time (h)	Temp (°C)	Product	Selectivity (% by HPLC) 5:6:7	Remarks
1[b]	dil. HCl	11	>97	**7**	00:0.3:98	a. Uncontrollable frothing b. Sudden bumping c. run-off of the reaction mass along with foam
2[c]	dil. HCl and n-octonol	10–14	>97	**7**	00:02:96	a. Sudden bumping b. Vigorous reflux conditions c. Required quick

3[c]	dil. HCl and acetophenone	10–14	>97	**7**	00:03:94	removal of by-products azeotropically d. Carryover of antifoaming agents up to API e. More organic waste (in case of acetic acid) f. Unpredictable timeline
4[c, d]	dil. HCl and acetic acid	10–14	>99	**7**	00:0.1:98	
5	DMSO–H_2O	24	130–140	–	–	No reaction
6[e]	DMSO–H_2O-NaCl	10	130–140	**5** & **6**	64:33:00	a. Free from frothing helped to escape from frothing related troubles b. Conversion was good
7[e]	DMSO–H_2O–NaBr	8	130–140	**5** & **6**	62:34:00	
8[f]	DMSO–H_2O–NaBr (*in situ*)	7	130–140	**5** & **6**	62:33:00	

[a]**Reaction conditions**:
[b]Conventional process (15.0 vol of 20% HCl)
[c]Antifoaming agents are used (10.0 vol of 20% HCl and 0.5 vol of antifoaming agent)
[d]Acetic acid (10.0 vol of 20% HCl and 3.0 vol of acetic acid)
[e]Krapcho process was applied [DMSO (3.0 vol)–H_2O (0.5 vol)–NaCl (1.0 equiv)]
[f]Krapcho process was applied, one–pot operation

Evaluation of Process safety by Thermal Screening with DSC: The decomposition of DMSO at lower temperatures (<189 °C) is a common problem under reaction conditions compared to the boiling point temperature of DMSO alone. But, sometimes it cause serious explosion in chemical and pharmaceutical industry.[22] Hence, the reactions in DMSO need to carryout thermal screening using DSC and ARC etc. as a process safety issue. To ensure the safety of present developed process, we have planned to explore the decomposition of reactants/products in the present reaction conditions at 130-140 °C using DSC (differential scan calorimetry). It was found that there was no decomposition of either DMSO or reactants/products at this temperature (Figure 1). The exothermic onset decomposition at 186°C with heat evolution of 250 J/g of sample is due to decomposition of DMSO. The same trend was observed and found on bulk-scale synthesis.

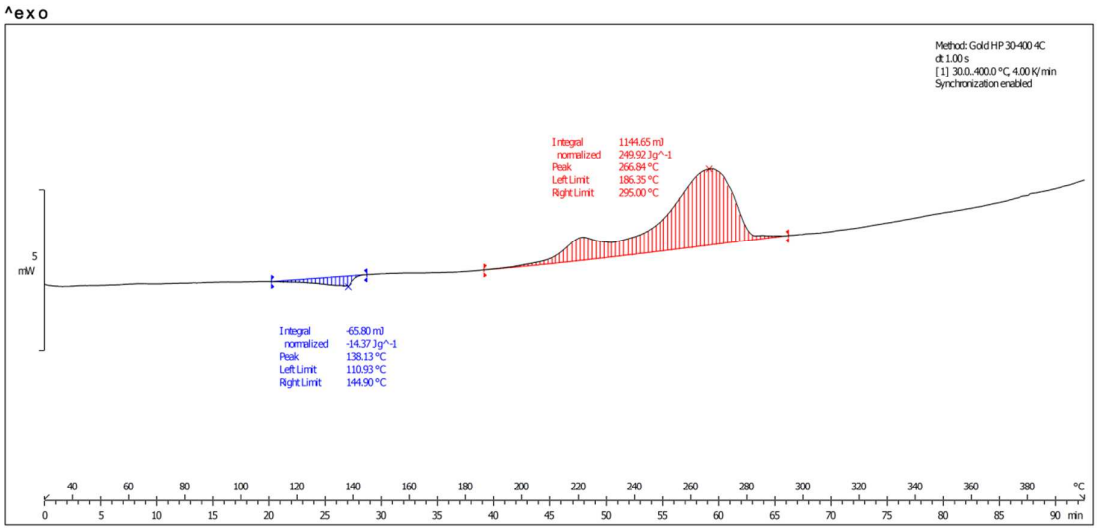


Figure 1: **Differential scan calorimetry (DSC) chart of Krapcho decarboxylation (4.5 mg reaction mixture)**

Optimum process conditions for the synthesis of 2-amino-3-(2-oxo-1,2-dihydroquinolin-4-yl)propanoic acid dihydrochloride dihydrate (**7**): The conventional ester hydrolysis and deprotection of compound(s) **5** and **6** was carried out at 80–90 °C[14] and obtained 95% of compound **7** (Figure S27 in the Supporting Information).

Optimum process conditions for the synthesis of Rebamipide (**1**): The synthesis of Rebamipide (**1**) from compound **7** was carried out as per literature process.[12, 14] Accordingly, a reaction was carried out by dissolving compound **7** in 25% aqueous NaOH solution followed by addition of 4–chlorobenzoyl chloride (**8**) and desired compound **1** was formed about 98% (Figure S35 in the Supporting Information).

The HPLC purity of crude Rebamipide (**1**) did not fulfil the specifications stipulated for the API (Figure S36 in the Supporting Information). Hence, it was planned to develop efficient purification method to remove the impurities and to increase the purity of API (**1**). Accordingly, the crude compound **1** was dissolved in DMSO, DMF and DMAc at 60–70 °C and cooled the reaction mass up to room temperature followed by addition of water. The compound **1** was precipitated during addition of water. The major problems associated with this purification method include i) sticky nature of compound **1** and ii) very slow filtration (entries 1–3, Table 3). To overcome these problems at production scale, we have developed a new solvent system, mixture of DMSO–water–MeOH. The fast filtration and free flow solid nature was observed by the purification of this new solvent system.

The study disclosed that purification in a mixture of DMSO–water–MeOH (1:3:0.1 ratio) provided excellent purity (99.89%) with excellent yield (95%) (entry 4 and Figure S37 in the Supporting Information).

Table 3: Selection of suitable solvent system for the purification of Rebamipide (1).

Entry	Solvent system	Time[e] (h)	Product	Yield[f] (%)	Purity (% by HPLC)					
					1	**7**	**1c**	**8a**	**8b**	**Total unknown**
1[a, c]	DMSO–H_2O (1:3 ratio)	2.5	**1**	94	99.84	-	-	0.03	-	0.13
2[a, c]	DMF–H_2O (1:3 ratio)	2	**1**	93	99.82	0.01	-	0.06	-	0.11
3[a, c]	DMAc–H_2O (1:3 ratio)	2	**1**	88	99.80	0.03	-	0.03	-	0.14
4[b, d]	DMSO–H_2O–MeOH (1:3:0.1ratio)	0.5	**1**	95	99.89	-	0.02	0.03	0.02	0.04

Reaction conditions:

[a]Compound **1** (10.0 mmol) in solvent (3.0 vol) at 60–70 °C for 1 h, cooling to 20–30 °C, water (6.0 vol) was added, stirred for 1 h, and filtration of the solid.

[b]Compound **1** (10.0 mmol) in DMSO (3.0 vol) at 60–70 °C, clear solution, cooling to 20-30 °C, added to mixture of water-methanol (9.0 vol of water and 0.3 vol methanol), stirring for 1 h, and filtration of the solid.

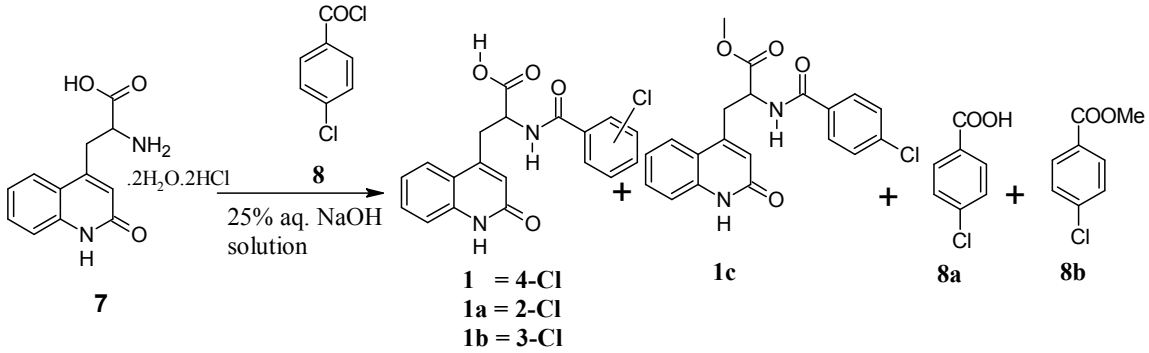
[c]Very slow filtration, sticky nature and wet weight 3 times with regard to input batch size.

[d]Fast filtration and the wet weight 1.5 times with regard to input batch size.

[e]Time duration for filtration

[f]Isolated yields

Formation of probable impurities: The formation of impurities was observed during the preparation of Rebamipide (**1**) from compound **7**. The impurities **1a** and **1b** were formed when 4–chlorobenzoyl chloride (**8**) contains trace amounts of either 2–chloro or 3–chlorobenzoyl chloride otherwise they are not formed in final API (entries 1–3, Table 3).



Scheme 2: Formation of probable impurities during the preparation of Rebamipide (1).

The formation of impurities **1c**, **8a** and **8b** was observed in final API (entries 1–3). The process related impurities **1c**, **8a** and **8b** were removed efficiently during purification in a mixture of DMSO–water–MeOH (1:3:0.1 ratio) system.

EXPERIMENTAL SECTION

The solvents and reagents were obtained from commercial sources and were used without any 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), qd (quartet 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.). The DSC study was performed in a Gold plated high pressure crucible at heating rate of 4 °C per minute on a METTLER TOLEDO (Greifensee, Switzerland).

Synthesis of 2–[(4–chlorobenzoyl)amino]–3–(2–oxo–1,2–dihydroquinolin–4–yl)propanoic acid (**1**): In a 50 L reactor, diethyl-(acetylamino)propanedioate (**3**) (5.0 kg, 23.0 mol) in DMSO (15 L) and 4–(bromomethyl)quinolin–2(1*H*)–one (**2**) (5.0 kg, 21.0 mol) were charged sequentially. The sodium hydroxide solution (0.84 Kg, 21.0 mol, dissolved in 2.5 L water) was added drop wise into the reaction mass at 20–30 °C and maintained for 2 h. After completion of the reaction as per reaction monitoring by HPLC, the temperature of the reaction mass was increased to 130–140 °C and maintained at the same temperature for 7 h. After completion of the reaction as per reaction monitoring by HPLC, the reaction mass was cooled to below 60 °C and slowly added water (12.5 L) followed by Conc. HCl (12.5 L). Again, the temperature of the reaction mass was raised to 80–90 °C and stirred for 2h. After completion of the reaction as per reaction monitoring by HPLC, the reaction mass was cooled to 20-30 °C and stirred for 1h at 20–30 °C. The solid was filtered, washed with cold 1N HCl (2.5 L) followed by water (1 L) and suck dried the material for 1h. The aqueous NaOH solution (2.94 kg of NaOH, 73.5 mol, dissolved in 25 L water) was taken in reactor and the wet material (**7**) was charged at 20–30 °C. The reaction mass was cooled to 5–10 °C and 4-chlorobenzoylchloride (**8**) (4.4 Kg, 25.2 mol) was added slowly into the reaction mass at 0–

10 °C and maintained at the same temperature for 30 minutes at 0-10 °C. After completion of reaction as per reaction monitoring by HPLC, the pH of the reaction mass was adjusted to pH 1.0–3.0 using HCl solution (~2.5 L) at 20–30 °C and maintained at the same temperature for 30 minutes. The reaction mass was filtered and washed with water (2.5 L). The obtained solid product **1** was dried under vacuum at 60−65 °C and obtained 6.85 kg (88% of yield) of compound **1** with HPLC purity of 99.31% (before purification).

Purification of compound 1: In a 50 L reactor, crude compound **1** (6.0 kg) was dissolved in DMSO (18 L) at 60–70 °C and stirred for 30 min at the same temperature. Then, the reaction mass was cooled up to 20–30 °C, filtered through sparkler and it was added slowly in to the mixture of water (54 L) and methanol (1.8 L) in 100 L reactor. The reaction mass was stirred for 1 h at 20–30 °C, filtered and washed with water (3 L) and obtained 5.7 kg (95%) of pure Rebamipide (**1**) after drying with an HPLC purity of 99.89%. The overall yield is 83.6% (after purification).

CHARACTERIZATION DATA

Diethyl– (acetylamino)[(2–oxo–1,2–dihydroquinolin–4–yl)methyl] propanedioate (4) : (Figures S1-S6). ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 11.76 (s, 1H, arom –NH–); 8.33 (s, 1H, aliphatic –NH); 7. 47–7.52 (m, 1H, arom H), 7.30 (d, 1H, *J* = 8.0 Hz, arom H), 7.16 (t, 1H, *J* = 7.6 Hz, arom H); 6.13 (s, 1H, arom H), 4.17–4.09 (m, 4H, 2 –CH_2–); 3.67 (s, 2H, –CH_2–), 1.8 (s, 3H, –CH_3), 1.16 (t, 6H, *J* = 7.2 Hz, 2 –CH_3).; ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 170.03, 166.81 (2C), 160.99, 145.64, 138.81, 130.40, 124.09, 123.04, 121.44, 119.42, 115.67, 66.56, 62.02 (2C), 32.88, 22.05, 13.72 (2C).; MS *m/z* (ESI): 375.12 $(M+H)^{+\cdot}$; HPLC purity: 98.34%

Ethyl 2–(acetylamino)–3–(2–oxo–1,2–dihydroquinolin–4–yl)propanoate (5): (Figures S7-S11). ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 11.71 (s, 1H, arom –NH–); 8.47 (d, 1H, *J* = 8.0 Hz, arom H); 7.76 (d, 1H, *J* = 8.4 Hz, arom H); 7.51 (t, 1H, *J* = 7.6 Hz, arom H); 7.33 (d, 1H, *J* = 8.0 Hz, arom H), 7.23 (t, 1H, *J* = 7.6 Hz, arom H), 6.38 (s, 1H, aliphatic –NH–), 4.54 (d, 1H, *J* = 4.8 Hz, –CH–), 4. 05-4.10 (m, 2H, –CH_2–), 3.27 (dd, 1H, *J* = 14.0 Hz and *J* = 5.6 Hz, –CH– geminal), 3.06 (dd, 1H, *J* = 14.0 Hz and *J* = 9.2 Hz, –CH– geminal), 3.01 (s, 3H, –CH_3), 1.14 (t, 3H, *J* = 6.8 Hz, –CH_3).; ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 171.26,

169.53, 161.31, 146.72, 138.94, 130.37, 124.00, 121.91, 121.89, 118.47, 115.83, 60.79, 51.56, 33.30, 22.23, 13.94.; MS *m/z* (ESI): 303.15 $(M+H)^{+.}$

2–(acetylamino)–3–(2–oxo–1,2–dihydroquinolin–4–yl)propanoic acid (6): (Figures S12-S17). ^{1}H NMR (400 MHz, D_2O, δ/ppm): 7.74 (d, 1H, *J* = 8.0 Hz, arom H), 7.47 (t, 1H, *J* = 6.8 Hz, arom H), 7.17–7.27 (m, 2H, arom H), 6.31 (s, 1H, arom H), 4.42 (dd, 1H, *J* =9.2 Hz, *J* = 4.0 Hz, –CH–), 3.38 (dd, 1H, *J* =13.6 Hz and *J* = 3.6 Hz, –CH–), 2.87 (dd, 1H, *J* =13.2 Hz, *J* = 10.0 Hz, –CH–), 1.74 (s, 3H, $–CH_3$).; ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 174.61, 169.07, 162.19, 149.67, 139.27, 130.24, 125.11, 121.94, 121.67, 119.89, 116.06, 54.60, 35.98, 23.26, 22.70.; MS *m/z* (ESI): 275.19 $(M+H)^{+.}$

2-amino-3-(2-oxo-1,2-dihydroquinolin-4-yl)propanoic acid dihydrochloride dehydrate (7): (Figures S18-S27). ^{1}H NMR (400 MHz, D_2O, δ/ppm): 7.90 (d, 1H, *J*= 8.0 Hz, arom H), 7.60 (t, 1H, *J*= 7.6 Hz, arom H), 7.49 (d, 1H, *J* = 8.0 Hz, arom H), 7.31 (t, 1H, *J*= 7.6 Hz, arom H), 4.20 (t, 1H, aliphatic –CH–), 3.39-3.50 (m, 2H, aliphatic $–CH_2–$).; ^{1}H NMR (400 MHz, DMSO-d_6, *δ/ppm*): 12.06 (br s, 1H, –COOH), 8.83 (br, 3H, $–NH_3^+Cl^-$), 7.93 (d, 1H, *J* = 8.0 Hz, arom H), 6.66–7.79 (m, 8H= 3H of arom H+5H of $2H_2O$ and HCl), 6.59 (s, 1H, arom H), 4.13 (d, 1H, *J* = 5.6 Hz, –CH–), 3.48–3.53 (m, 1H, –C**H**(H)– geminal), 3.36-3.41 (m, 1H, –CH(**H**)–, geminal).; ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 169.98, 161.33, 144.84, 139.16, 130.54, 124.27, 123.22, 122.03, 118.43, 115.96, 51.54, 32.51.; MS *m/z* (ESI): 233.05 $(M+H)^{+.}$; HPLC purity:

Rebamipide (1): (Figures S28-S35). ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 13.10 (br, 1H, –COOH), 11.66 (s, 1H, arom –NH–), 8.92 (d, 1H, *J* = 8.0 Hz, aliphatic –NH–), 7.82–7.85 (m, 3H, arom H), 7.49–7.56 (m, 3H, arom H) 7.32 (d, 1H, *J* = 8.4 Hz, arom H), 7.24 (t, 1H, *J*= 7.6 Hz, arom H), 6.45 (s, 1H, arom H), 4.71–4.77 (m, 1H, aliphatic –CH–), 3.47–3.52 (m, 1H,–C**H**(H)–, geminal), 3.20–3.26 (m, 1H, –CH(**H**)– geminal).; ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 172.90, 166.08, 161.94, 148.14, 138.98, 136.92, 132.64, 130.90, 129.61 (2C), 128.88 (2C), 124.40, 122.62, 121.86, 118.96, 116.33, 52.27, 33.23.; MS *m/z* (ESI): 371.15 $(M+H)^{+.}$

2–(2–chlorobenzamido)–3–(2–oxo–1,2–dihydroquinolin–4–yl)propanoic acid (1a): (Figures S38-S42). ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 11.68 (s, 1H, arom –NH–), 8.88 (d, 1H, *J* = 8.4 Hz, arom H), 7.83 (d, 1H, *J* = 8.0 Hz, aliphatic –NH–), 7.18–7.54 (m, 7H, arom H), 6.49 (s, 1H, arom H), 4.68–4.74 (m, 1H, aliphatic –CH–), 3.46–3.51 (m, 2H, $–CH_2–$, geminal), 3.07–3.13 (m, 1H, –CH–, geminal).; ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm):

172.87, 166.75, 161.82, 147.37, 139.47, 136.7, 131.43, 130.72, 130.43, 130.14, 129.27 (2C), 127.45 (2C), 124.47, 122.61, 122.37, 119.02, 116.29, 52.04, 33.53.; MS *m/z* (ESI): 371.14 $(M+H)^{+.}$

2–(3–chlorobenzamido)–3–(2–oxo–1, 2–dihydroquinolin–4–yl)propanoic acid (1b): (Figures S38-S47). ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): (Figures S43-S47). 13.12 (s, 1H, –COOH), 11.70 (s, 1H, arom –NH–), 9.02 (d, 1H, *J* = 8.0 Hz, aliphatic –NH–), 7.84–7.86 (m, 1H, arom H), 7.79 (d, *J* = 8.0 Hz, arom H), 7.62 (dq, 1H, *J* = 8.0 Hz and *J* = 2.0 Hz, arom H), 7.51 (t, 1H, *J* = 7.6 Hz, arom H), 7.34 (d, 1H, *J* = 8.0 Hz, arom H), 7.23-7.27 (m, 1H, arom H), 6.47 (s, 1H, arom H), 4.73–4.79 (m, 1H, aliphatic –CH–), 3.48–3.53 (m, 1H, –CH–, geminal), 3.27 (dd, 1H, *J* = 14.4 Hz and *J* = 10.8, –CH–, geminal).; ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 172.54, 165.04, 161.34, 147.36, 138.96, 135.60, 133.21, 131.41, 130.42, 130.33, 127.09, 126.14, 124.03, 121.93, 121.68, 118.54, 115.87, 51.96, 32.79.; MS *m/z* (ESI): 371.07 $(M+H)^{+.}$

Methyl–2–(4–chlorobenzamido)–3–(2-oxo–1, 2–dihydroquinolin–4–yl)propanoate (1c): (Figures S48-S52). ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 11.70 (br, 1H, –COOH), 9.08 (d, 1H, *J* =8.0 Hz, arom –NH–), 7.81–7.84 (m, 3H, arom H), 7.49–7.57 (m, 3H, arom H), 7.33 (d, 1H, *J* = 8.4 Hz, arom H), 7.21–7.26 (m, 1H, arom H), 6.45 (s, 1H, arom H), 4.78–4.83(m, 1H, aliphatic –CH–), 3.69 (s, 3H,–CH_3), 3.46-3.51 (m, 1H, –CH(**H**)–, geminal), 3.25–3.32 (m, 1H, –C**H**(H)–, geminal).; ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 171.58, 165.44, 161.27, 147.12, 138.92, 136.51, 132.1, 130.39, 129.30 (2C), 128.49 (2C), 124.01, 121.97, 121.71, 118.52, 115.92, 52.30, 51.96, 32.54.; MS *m/z* (ESI): 385.11 $(M+H)^{+.}$

CONCLUSION

In the present work, we have developed bulk scale synthesis of Rebamipide (**1**) using Krapcho method using DMSO–H_2O–NaBr (*in situ*) system at 130–140 °C to arrest the chaotic uncontrollable frothing. Several process issues were addressed effectively and efficiently to achieve the goal of development of multikilogram–scale process for production of Rebamipide (**1**). New intermediates (**5** and **6**) were isolated and characterized for the first time. The major advantages of the present developed commercial process include i) excluding the use of antifoaming agents as well as conventional process for decarboxylation. In addition, it was found that Krapcho reaction was useful to arrest the uncontrollable frothing, ii) avoided step–by–step process to save process time cycle, drying and analysis, utility cost and averting the loss of compound during isolation of intermediates and

purification, iii) purification of API in DMSO–H_2O-methanol solvent system was utilized to remove the impurities and to achieve desired quality (≥99.89%) and nature, and iv) E–Factor of the developed process is 11.5 (excluded water) which meets the metrics to "green" chemistry. We are hopeful that the use of Krapcho reaction conditions in the present work may be helpful in the development of efficient processes for other drugs also as it is safe to run at 130-140 °C (confirmed by DSC thermal screening studies). Our mission and vision is that the present work can help in adoption and use of Rebamipide (**1**) as safe antiulcer and ophthalmic drug worldwide which is now limited to Asian countries.

ASSOCIATED CONTENT

Copies of relevant ^{1}H, ^{13}C NMR, and mass spectra, powder XRD data, and HPLC chromatograms can be found in supporting information.

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