An efficient synthesis of Anti-spasmodic drug Mebeverine hydrochloride

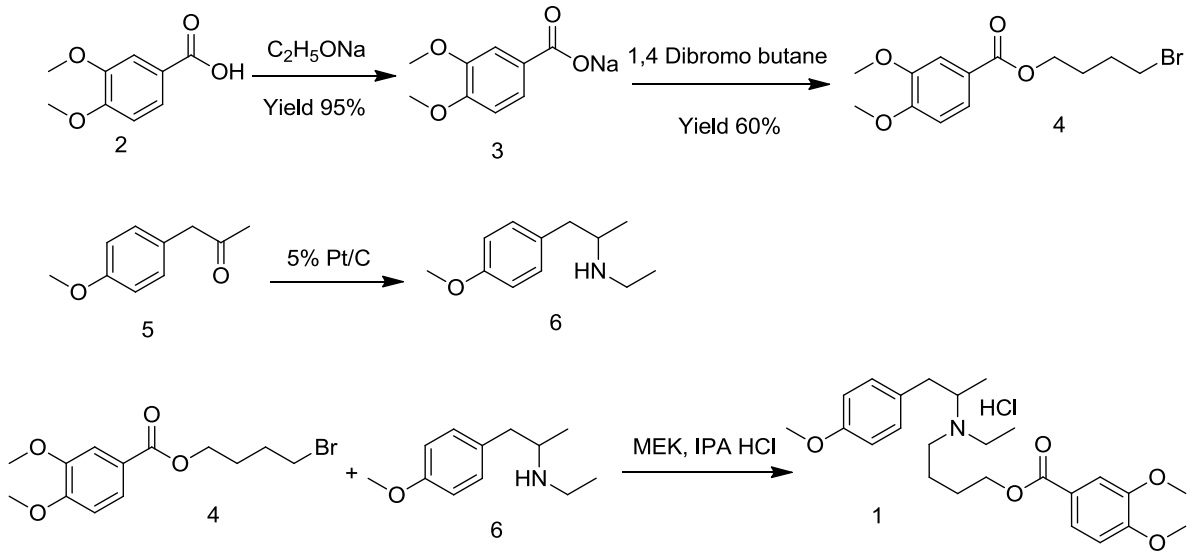
Abstract: An efficient synthetic process for an antispasmodic drug and active pharmaceutical ingredient of Mebeverine hydrochloride **1** is reported in this communication. It is used for stomach cramps and irritable bowel syndrome (IBS). The treatment for irritable bowel syndrome involves lot of drugs like (Dicyclomine hydrochloride, Linaclotide.etc) available in market, but Mebeverine hydrochloride (1) is most effective than any other drug. Earlier manufacturing **1** process reported yield < 46% and used high volumes of reagents and expensive catalyst. We developed new commercial process for **1** with economically, environmentally favored conditions. Proposed synthetic route contains three stages with overall yield of 77% and Purity by HPLC NLT 99.7%.

"Keywords": Anti-spasmodic, irritable bowel syndrome, efficient process, Economically favorable, Mebeverine hydrochloride

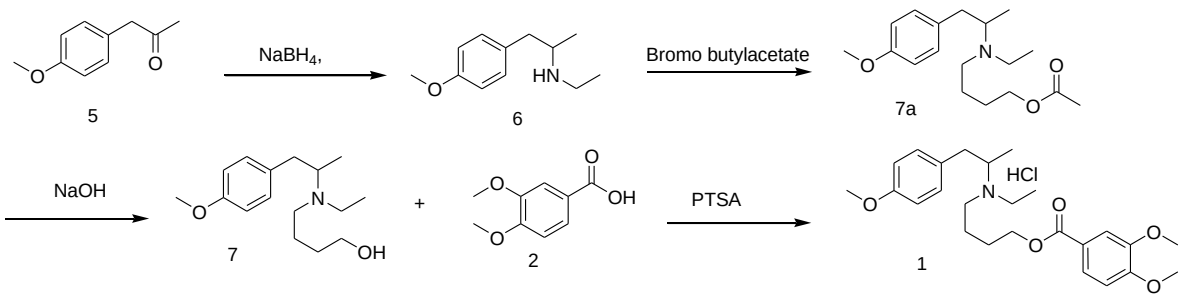
Introduction :

Heterocyclic compounds play a significant role in the discovery of new drugs and drug like substances. Organic Synthesis is extensively used in the new drug discovery programs and new processes for already known drug substances using green and eco-friendly methodologies. In this context, we have been working in our laboratory to develop novel and commercially feasible synthetic methodologies for important drugs with a particular focus on environmentally benign conditions. Mebeverine.HCl is a heterocyclic compound which belongs to a group of medicines called Antispasmodics. This is used to treat symptoms of irritable bowel syndrome (IBS), the very common condition which causes spasms. There is a great demand for both developments of new antispasmodics agents and new manufacturing process for existing antispasmodic agents. Extensive literature search revealed that there is not much literature available for commercial synthesis of Mebeverine hydrochloride (1), hence we showed interest in developing a commercially feasible synthetic route. The reported method for preparation of Mebeverine hydrochloride(1) suffers from many disadvantages which include (i) overall low yield,(ii) inadequate optimization of reaction conditions, (iii) expensive reagents like Pt, hence there is a need to overcome the above mentioned drawbacks and also to develop an industrially viable process. The first synthesis of Mebeverine hydrochloride (1) was reported in 1965 as disclosed in the patent GB1009082A[2] Nandini[1] *et.al.* have reported the manufacturing process of Mebeverine hydrochloride **(1) a**s shown in Scheme-1.[1]Interesting biological activities for relevant compounds were also reported.[2] Synthesis starts with Veratric acid **(2)** as a key starting material. It was reacted with sodium methoxide to form sodium salt of Veratric acid (**3**) further reacted with 1,4 dibromobutane to get the compound (**4**). Reductive amination of 4-methoxy phenyl acetone (**5**) with aqueous ethylamine in presence of Pt/C and hydrogen pressure gives (**6**). Further reaction between compounds (**4)** & (**6)** in the presence MEK and *i*-PrOH HCl provides (**1).** The major disadvantages associated with this process are formation of dimer impurity of about 8-12% by HPLC during synthesis of (**4)** and use of highly expensive catalyst like Pt/C used for reductive amination with an overall yield of 34.0%. MVR Raju *et.al.* have recently disclosed commercial manufacturing process of Mebeverine hydrochloride (1).(Scheme -2).[3] Synthesis starts with 4-methoxy phenyl acetone (**5)** reacted with aqueous ethylamine in the presence of sodium borohydride to obtain (**6**) which was reacted with 4-bromo butyl acetate (**7a**) followed by hydrolysis to get compound (**7**), esterification between (**9**) and Veratric acid (**2**) in the presence of *Para* toluene sulphonic acid (*p*-TsOH) at 100-110°C followed by hydrochloride salt formation provided the target molecule Mebeverine hydrochloride (1). Disadvantages include formation of alcohol impurity by about 6-10 % by HPLC during reductive amination with an overall yield of 46.0%. Besides, there has been a great deal of interest on Mebeverine as revealed by recent litrerature.[4-8,]

[11]We report herein the results of our efforts to improve the process and overall yield of Mebeverine hydrochloride.



Scheme-1



Scheme-2

Material and Methods:

All the Chemicals, reagents and solvents used are of commercial grade. [1]HNMR and [13]C NMR data were recorded in SA-Varian 400MHz NMR. TMS as a reference standard, Chemical shifts values are reported in δ PPM and deteriorated solvents $CDCl_3$and DMSO.

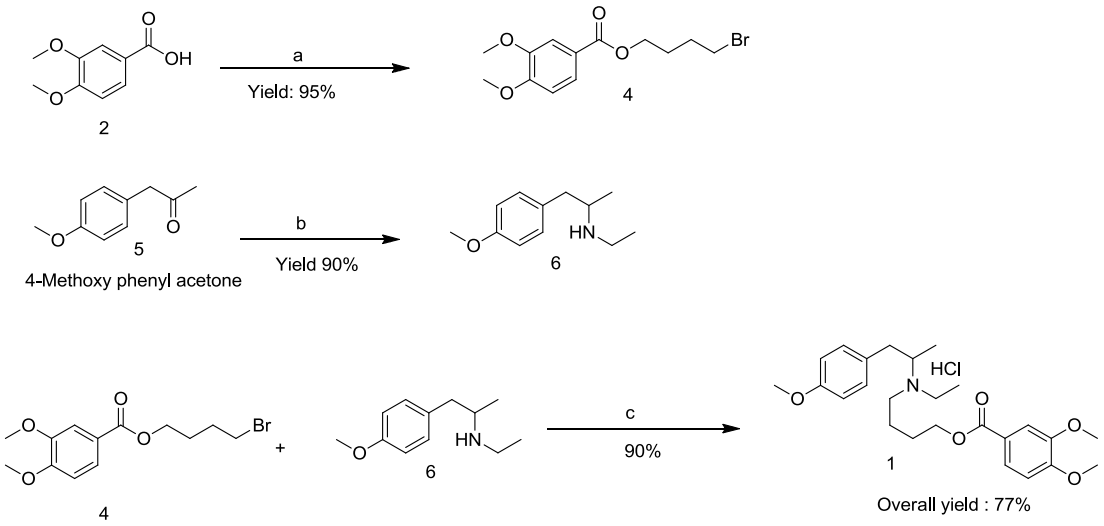
In [1] HNMR recorded, the chemical shifts and coupling constants of compound were determined. The Multiplicity of spectra identified by following: Singlet (s), Doublet (d), Triplet (t), quarter (q), multiplet (m), broad (br), Doublet of doublet (dd).

The ESI/MS experiments were performed on a Velos Pro ion trap mass spectrometer from Thermo Scientific(San Jose, CA, U.S.A.). Elemental analysis for C, H and N used instrument vario EL.

HPLC: Method of analysis of Mebeverine hydrochloride adopted from European pharmacopeia.

Results and discussion:

Based on the earlier reports that have shortcomings and limitations as described above and in order to overcome the drawback, we have pursued an alternative synthetic strategy which has resulted the final product in high yields and purity as shown in the scheme **3**. Hence, we report an improved synthetic route for Mebeverine hydrochloride (1) with high purity (≥99.7%), improved yields (77% of overall yield), easy workup and simple isolation of the product with commercial feasibility.



Reaction Conditions: (a) 4-Bromobutanol, *p*-TsOH, toluene at 105-110°C , (b) Aqueous ethylamine, Raney Ni, Hydrogen gas, Methanol at 40-50°C, (c) Acetone, 55-65°C

Scheme-3

Improved process of Mebeverine hydrochloride (1)

A modified process was designed and developed to achieve the improved yield of Mebeverine hydrochloride drug compared to existing processes as shown in scheme-3. Synthesis of target Mebeverine hydrochloride (**1**) starts with compound **2,** it was reacted with 4-bromo butanol to provide compound **4**, reductive amination of compound**5** with aqueous ethylamine in the presence of Raney Ni, Hydrogen gas provided compound **6.** Dehydrohalogenation by the reaction of compound **4** and **6** provided final Mebeverine hydrochloride (**1**). With an objective to develop a commercially viable process for the manufacture of Mebeverine hydrochloride (1**)** the reaction conditions were well optimized in each and every step as discussed below.

Improved Process Conditions for of 4-bromobutyl 3,4-dimethoxybenzoate (4):

Synthesis of compound 4 involves the esterification of compound **3**. The method reported by GB 1009082A involves use of high volumes of 1,4-dibromobutaneto react with compound **3** at 150°C.[1,10]This method suffers from formation of dimer. Hence, we conducted some experiments with different volumes of 1,4-dibromo butane and the obtained results are presented in Table 1.

Table-1: Experiments with different volumes

S.No.	1,4-dibromobutane	Temp (° C)	Dimer (%)	yield (%)
1	6.0	150.0	10	60
2	10.0	150.0	5	65
3	3.0	150.0	25	40

In order to avoid the formation of dimer and to increase the yield, we have used 4- bromobutanol (1.2 eq) catalytic amount of *p*-TsOH(0.27 eq) and 5.0 v of toluene to get the compound with a dramatic improvement in the yield. The results obtained by using different dehydrating reagents are shown in the following Table 2.

Table-2: using different dehydrating reagents

S No	Dehydrating reagent	Solvent	Temp (°C)	Duration (h)	Yield(%)
1	*p*-TsOH	Toluene	110	10	95
2	H_2SO_4	Toluene	50	15	80
3	$SOCl_2$	DCM	40	2	90

Reaction Conditions: Compound 2 (1000.0 g), 4-Bromo butanol (1000.0g), *p*-TsOH (250.0 g),and toluene (10.0 L) at 105 to 115°C.

Improved Process Conditions for N-Ethyl-1-(4-methoxyphenyl) propan-2-amine (6)

Reported synthesis of compound **6** involves reductive amination between 4-methoxy phenyl acetone **5** and aqueous ethylamine (Scheme 1**)** is highly expensive for commercial manufacturing.[8] So we have focused our attention to develop the condition that is economically favorable for commercial application. The results obtained under different conditions are presented in Table 3.

Table-3: Results obtained with different conditions

SNo	Reagents	Aq. Ethyl amine	Solvent	Temp(°C)	Duration(h)	% Yield
1	$NaBH_4$	2.5	MeOH	-5°C	1	85
2	Raney Ni	1.5	MeOH	10-20°C	5	90
3	$NaCNBH_3$	2.5	MeOH	10-20°C	3	30
4	Pd/C	1.5	MeOH	25-35°C	5	0

Reaction conditions: Compound 4 (100.0 g), Aq.ethylamine (70%)(150.0 mL), Raney Ni (10.0 g) and Methanol (1000.0 mL) at 10-20°C in an autoclave with hydrogen pressure of 3-4 kg.

Improved Process Conditions for Mebeverine hydrochloride (1)

The reaction between compounds 4 and 6 as reported in scheme 1 was tried under different conditions to improve the yield and quality and the results obtained are tabulated as shown in the following table 4.

Table-4: Under different conditions and different solvents to improve the yield and quality.

S.No.	Solvent	Temp °C	%Yield	Purity	Time(h)
1	MEK	75-85	85.0	99.5	30
2	Acetone	50-60	90.0	99.5	20
3	MIBK	85-95	82.0	99.5	30
4	Toluene/Na_2CO_3	100-110	75	99.5	18
5	DMSO	100-110	70	99.5	20
6	DMF	100-110	-	-	-

Reaction conditions: compound 4 (100.0g), compound 6 (164.0 g) and acetone 300 mL at 10-20°C

Experimental Section:

Preparation of 4-Bromobutyl 3,4-dimethoxybenzoate (4)..

To a stirred solution of Veratric acid **2** (1.0 kg, 5.5mole) in toluene (5.0 L), 4-bromobutanol (1.0kg, 1.2 eq), *p*-TsOH(0.25 kg,0.27 eq) were added at 25-35°C, slowly the temperature of the reaction mass was increased to 105-115°C and maintained for 10-15 h. After the completion of the reaction, cooled to 25-35°C, water(5.0L) was added to the reaction mass and stirred for 30 min. Both layers were separated and evaporated the toluene under vacuum to get 4-Bromobutyl 3,4-dimethoxybenzoate (4).Weight :1.6 to 1.65kg;

Purity: NLT 98.0 % by GC;

^{1}H NMR(DMSO d_6, 300 MHz): 7.614 (d ,1H J 1.8), 7.586 (d, 1H, J 1.8), 7.069 (d, 1H J 8.4), 4.278 (t, 2H J 6.3), 3.84-3.81 (m ,6H), 3.63-3.55 (m, 6H).

Preparation of N-Ethyl-1-(4-methoxyphenyl) propan-2-amine (6).. :

1.0 kg of 4-methoxy phenyl acetone and 100.0 g of Raney Ni were taken in 4.0 L of methanol in a pressure vessel. Resulting mixture was cooled to 10-15°C. At 10-15°C temperature slowly added the 1.5 L of aqueous mono ethylamine (70 %) into the reaction mass and maintained the reaction mass for 1h at 10-15°C. After completion of 1h maintenance applied 3-4 kg of hydrogen pressure then again maintained the reaction mass for 4h at 25-35°C under 2-3 kg of hydrogen pressure. Checked the 4-methoxy phenyl acetone content by HPLC or TLC (limit NMT 1.0 %). After Removing the hydrogen gas reaction mass filtered through hyflo and washed the hyflo bed with 5.0 L of methanol and evaporated methanol completely to get N-Ethyl-1-(4-methoxyphenyl) propan-2-amine(6). Weight :1.0-1.1 kg

Purity: NLT 95.0 % by HPLC;

^{1}H NMR(DMSO d_6, 300 MHz): 7.079(d, 2H J 8.4), 6.837 (d ,2H J 8.4), 3.718 (s, 3H), 2.79-2.32 (m, 5H), 0.974 (t, 3H), 0.882 (d, 3H J 6.0); ^{13}C NMR : 157.98, 132.03, 130.47, 113.95, 55.25, 54.82, 42.60, 41.36, 20.23, 15.82;

Mass (M+H): 194.2.

Preparation of Mebeverine hydro chloride (1).:

A solution of N-Ethyl-1-(4-methoxyphenyl) propan-2-amine (1.0 kg,1 eq) and 4-bromobutyl3,4-dimethoxybenzoate(1.64 kg, 1 eq) in acetone(3.0L) was heated to 55-65°C and maintained for 15-20 h. After completion of the reaction, slowly added the *i*-PrOH HCl (0.75L) at 10-15°C and maintained for 1h at 25-35°C. Precipitated solid product was filtered and washed with acetone and dried.

Weight:1.9-2.0 kg; Purity: 99.5% by HPLC;

Purification of Mebeverine Hydrochloride (1)..:

1.0 kg of Mebeverine hydrochloride was taken in 4.0 L of acetone at 25-35°C then the resulting mixture was heated to 50-60 °C for 30.0 min. after maintenance cooled to 0-5°C, filtered and obtained the product i.e. pure Mebeverine hydrochloride (1).Weight: 0.90 to 0.95kg;
Purity :NLT 99.7 % by HPLC

^{1}H NMR ($CDCl_3$, 400 MHz):12.1-12.2 (brs, 1H), 7.68 (dd, 1H J 1.6),7.53 (d, 1H J 1.6), 7.15 (d, 1H J 0.8), 6.88 (d, 1H J 8.4), 6.83 (d, 2H, J 8.4), 4.37 (t, 2H J 6.4), 3.93 (s, 6H), 3.78 (s, 3H), 3.56 (d, 2H J 10.8), 3.22-3.08 (m,4H), 2.54 (t, 1H), 2.14-2.13 (m, 2H), 1.89 (t, 2H), 1.56-1.54 (m, 3H), 1.24 (d, 3H J 6)
^{13}C NMR ($CDCl_3$, 100 MHz):9.88, 12.02, 21.19, 26.20, 36.20, 44.63, 45.95. 54.89, 55.72, 59.43, 63.07, 110.45, 111.62, 113.87, 122.02, 123.30, 127.68, 129.77, 148.31, 152.78, 158.40, 165.91.

Mass(M+H): 430.2;
Elemental analysis: C: 66.23%, H:7.639%, N: 2.94 %

Process Comparison:

Improved process Vs Reported process (Der Pharma Chemica, 2010, 2(2):366-378)

Name of the compound	Improved process (Scheme-3)	Reported process (Scheme-1)
Preparation of Compound 4	Preferred the 4-Bromobutanol for the preparation of compound 4. To avoid the formation of dimer impurity.	1,4 Dibromobutane used for synthesis of Compound 4. Observed Dimer impurity.
Preparation of Compound 6	Reduction of imine (-C=N-) to amine usedRany Ni and Hydrogen gas. It economically favorable reagent for commercialization.	Reduction of imine (-C=N-) to amine used Pt/C and Hydrogen gas. It is highly expensive reagent. It is not suitable for commercialization.
Preparation of Compound 1	A stirred solution of compound No.4 and compound No.6 in acetone at 55-65 °C for 15 to 20 h. And also optimized purification in acetone to avoid the drying before purification stage.	Preparation of compound in MEK at 75-80°C for 30 h.

Note: All the reactions are well established and practically proved

Conclusion

In the present work, we have reported an efficient process for Mebeverine hydrochloride and practically demonstrated as disclosed in the experimental part. All the intermediates were characterized by ^{1}HNMR, ^{13}CNMR and Mass. The major advantages of present process include (i) improved overall yield, (ii) well optimized conditions and economically favorable reagents.

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Conflict of interest

The authors do not have conflict of interest on the results disclosed in the publication of the present results of the study.

References:

[1]. Nandini R.pai and Deepnandan S. Dubhashi. Synthesis and Preliminary pharmacological evolution of Veratric acid ester 4-[ethyl-{2-4-methoxy phenyl-1-methyl ethyl} amino] butan-1-ol derivatives. Der Pharma chemica, **2(2)**, 366-378, **(2010)**

[2]. N. V. Philips 'GloeilampenFabrie-Ken. Improvements in or relating to the production of esterified amino-alcohols. Patent No. GB 1009082A

[3]. Adolf Lindner; Durk Moed Hendrik; Houtenlaan Van; Johannes Asma Willem; TeunisKralt. Substituted tertiary amino compounds having valuable pharmacological properties. US3254112

[4]. M. R.Raju; M. Ashok Srinivasa Raju; M.Anand; G Vamsi Krishna; V S R N Phani Kumar; S. Raghu ram; Y Satyanarayana; C H L D Sateesh; D Srini Vasa Rao; K Chandra Mouli; A Ramakrishnam Raju; S Seshagiri Rao. Process for the preparation of Mebeverine hydrochloride. Ind Patent 201841023171.

[5]. N.V. Philips; Gloeilampen-fabrieken. Improvements in or relating to substituted amines. GB 893088A, DE1126889 (1962)

[6]. Impagnatiello, R. and Benedini, WO Patent 007230(2009)

[7]. Tennis Kralt; Hendrik Durk Moed; and Willem Johannes Asma, all of Van Houtenlaan, Weesp, Netherlands, and Adolf Lindner. Method of relieving spasmodic conditions and pharmaceutical composition useful there for. US Patent 3265577 (1966)

[8]. Andrea A.;Tommaso, F.; Nunzio, I.; Giuseppe, M.;Serena,M.;Donatella,P.;Oriana, T.;Glenn, W. K.;Maria, L. B.;Stefano, S.;Violetta, C.; J.Med. Chem.**60(4)** 1598-1604,**(2017)**

[9]. A. Allen and R Ely. Synthetic methods of amphetamine.

[10]. Palaniappan, S., & Ram, M. S. (2002). Esterification of carboxylic acids with alcohols catalyzed by polyaniline salts. Green Chemistry, **4(1),** 53–55, **(2002)**

[11]. Seham S Abdulhady[1] * and Khaled M Hosny I brahim[2]. Preparation and evaluation of Mebeverine hydrochloride as mucoadhesive buccal tablet for local anesthesia. Tropical journal of pharmaceutical research august **16(8),** 1805-1812, (**2017)**