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An efficient synthesis of neuroleptic drugs under microwave irradiation

Nandini R. Pai*, Deepnandan S. Dubhashi, Sandesh Vishwasrao, Deeptanshu Pusalkar

Chemistry, D.G. Ruparel College, Mahim, Mumbai, India

ABSTRACT

Microwave assisted organic reaction enhancement (MORE) is a simple, clean, fast, efficient, economic and environment friendly method developed for the synthesis of Trazodone hydrochloride, Aripiprazole and their key process intermediates. Using microwave irradiation, all the reaction could be completed in a very short duration (≤ 2 minutes) with desired increase in the yields (>10%) and purity of the compounds. Final proposed method is repeated three times to ensure its reproducibility and robustness. All the synthesized compounds were compared with products from conventional method by studying mixed melting point, Co-TLC, NMR and IR spectra.

Keywords: Microwave irradiation, Conventional method, Neuroleptic Drugs, Prescription drugs.

INTRODUCTION

In the recent years, microwave assisted organic reactions have emerged as a new tool in organic synthesis. Important advantages of this technique include highly accelerated rate of the reaction, reduction in reaction time with an improvement in the yield and quality of the product. Moreover the technique is considered as an important approach towards “Green Chemistry” because of its eco-friendly nature. Conventional methods of organic synthesis usually need longer heating time, elaborate and tedious apparatus set up, which result in higher cost of process and the excessive use of solvent/reagents leads to environmental pollution. [1] Microwave assisted reactions in solvent or solvent free conditions have gained popularity because of rapid reaction rate, cleaner reactions and ease of manipulation. [2] Microwaves are defined as electromagnetic waves with vacuum wavelengths ranging between 1 mm-1 m or, equivalently, with frequencies between 0.3- 300 GHz. Microwave dielectric heating uses the ability of some liquids and solids to transform electromagnetic radiation into heat to drive chemical reactions. This technology opens up new opportunities to the synthetic chemist in the form of new reactions that are not possible using conventional heating.

The interest in the microwave assisted organic synthesis has been growing during the recent years. Drug companies are exploiting microwaves in the area of organic/pharmaceutical synthesis for drug screening and discovery. [3-5] Scientists have demonstrated the potential of microwave -assisted organic synthesis using ionic liquids as solvent, co solvent, additives and/or catalyst. [6] Among the wide variety of drug molecules that have been explored for developing microwave assisted synthetic process include pharmaceutical drugs in various biological activities like analgesic, antihypertensive, central nervous system depressant, antiviral, bactericidal and fungicidal activities. [7-9]

In the course of our research efforts on synthetic process development of Trazodone hydrochloride and Aripiprazole; the leading neuroleptic prescription drugs; we observed that the conventional synthetic process [10, 11] of these drug molecule involves preparation of key process intermediates. This involves long hour reactions with elevated temperatures parameter leading to generation of unwanted byproducts and low product yields. Conventional synthetic method of Trazodone and Aripiprazole is also potentially slow reaction (>15 hours); involves high temperatures leading to undesired process efficiency on yield and quality. This calls for repeated purifications of the product to achieve desired purity and impurity levels prescribed within regulatory guidelines (<0.1%) for API.

The new microwave procedures were developed by considering two important parameters: minimum reaction time and minimum by-product formation leading to maximum yield of the pure product with desired quality. This was achieved by carrying out each reaction in two major ways. Firstly, optimization of the microwave power (intensity) was performed by conducting the reactions at different microwave powers/intensities (160, 350 and 500 W) setting for a fix time of two minutes. The microwave intensity giving the maximum yield was selected for optimizing the reaction time (Table 1). Each time, the product was isolated, the yield and quality of the product was compared with the one obtained by conventional method. Finally, by using the optimized microwave intensity and time, each reaction was repeated at least two times and the products were compared with the conventional products by studying their melting points, mixed melting points, TLC, Co-TLC, elemental analysis (Table 2), NMR and IR spectra (Table 3).

EXPERIMENTAL SECTION

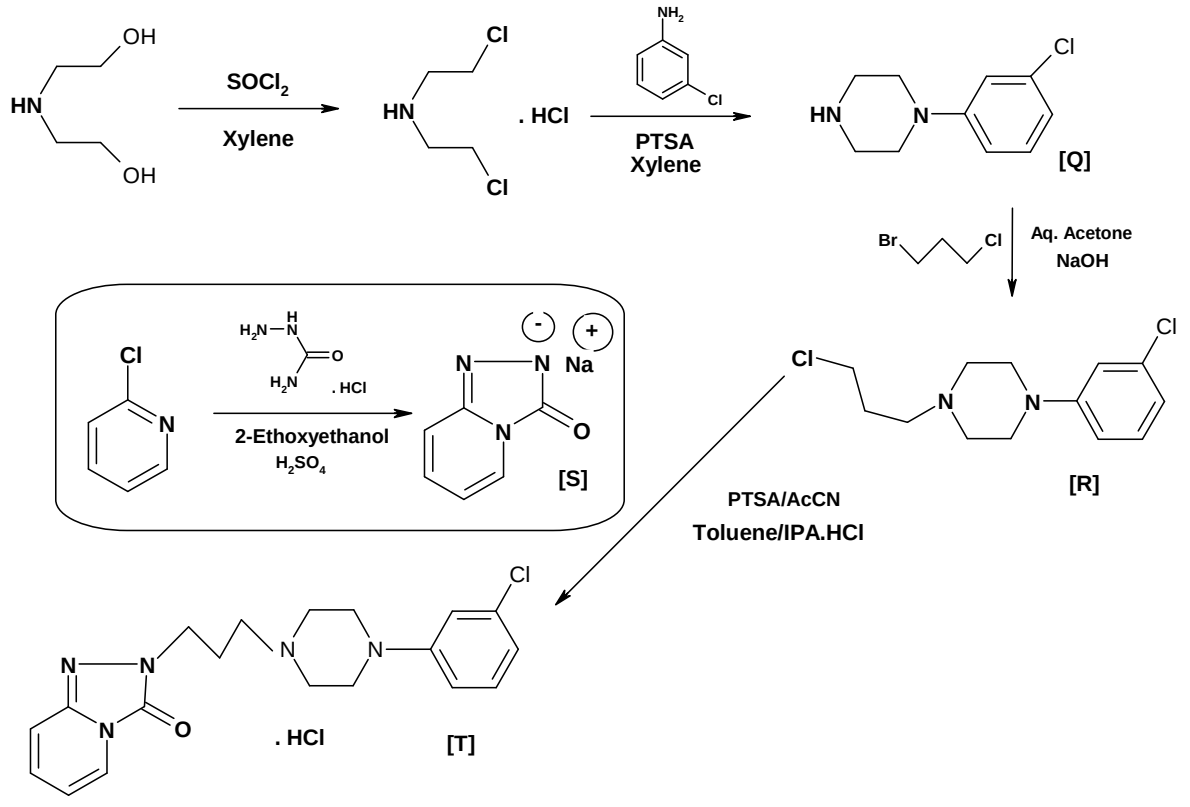
All the chemicals used were obtained from S. D. Fine Chem. Ltd. and E Merck Ltd., Mumbai while the reagents and solvents were of analytical grade. Heating was done in a microwave oven (LG-Healthcare System, MG-605 AP, and 900 w).The melting points were carried out in open capillary tube and were uncorrected. Thin layer chromatography was performed using silica gel coated on a glass plate. The reactions were monitored by TLC on a silica gel G coated glass plates using chloroform: methanol (8:2/9:1) solvent system. The purity of synthesized compounds was ascertained by HPLC.

Conventional synthesis of Trazodone and its intermediates were affected as outlined in Scheme 1. Conventional synthesis of Aripiprazole and its intermediates were affected as outlined in Scheme 2. The compounds were characterized by physical properties (M. P.), elemental analysis, FTIR and NMR spectral analysis.

Synthesis of Trazodone Hydrochloride

The Trazodone Hydrochloride drug molecule (Compound T), was prepared using the process described in Scheme 1, which involves simple condensation of 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine and 1, 2, 4-triazolo [4, 3-a] pyridine-3- (2H)-one intermediates [8].
In first part of the process bis-(2-chloroethylamine) hydrochloride (Compound P) is prepared by chlorination of diethanolamine with thionyl chloride in xylene, which is then condensed with 3-chloro aniline to get 1-(3-chlorophenyl)-piperazine hydrochloride intermediate (Compound Q). This is reacted with 3-bromo-3-chloropropane in alkaline aqueous acetone (50 %) gave various 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine intermediate (Compound R). In second part of the process, 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine is condensed with sodium salt of 1, 2, 4-triazolo [4, 3-a] pyridine-3- (2H)-one (Compound S) prepared in a single step process by reaction of 2-chloropyridine and semicarbazide hydrochloride in 2-ethoxyethanol afforded lead compound (Compound T), isolated as hydrochloride salt. The yields of 1-(3-chlorophenyl)-piperazine hydrochloride (Q), 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine (R) and of Trazodone Hydrochloride (T) reported in the literature and observed in the lab are 84-85%, 72-73%, 84-85% respectively. The intermediate 1, 2, 4-triazolo [4, 3-a] pyridine-3- (2H)-one (S) is obtained in >90 % yield and in desired purity. But the process involves long reaction hours (>12) and elevated temperature (145-150 ^{0}C).

Scheme 1: Reaction scheme for preparation of Trazodone Hydrochloride



Synthesis of Aripiprazole

The Aripiprazole drug molecule (Compound E), was prepared using the process described in Scheme 2, which involves simple condensation of 1-(2,3-dichlorophenyl) piperazine

(Compound B) and 7-(4- bromobutoxy)-3,4-dihydro-2(1*H*)-quinolinone intermediate (Compound D) [9].

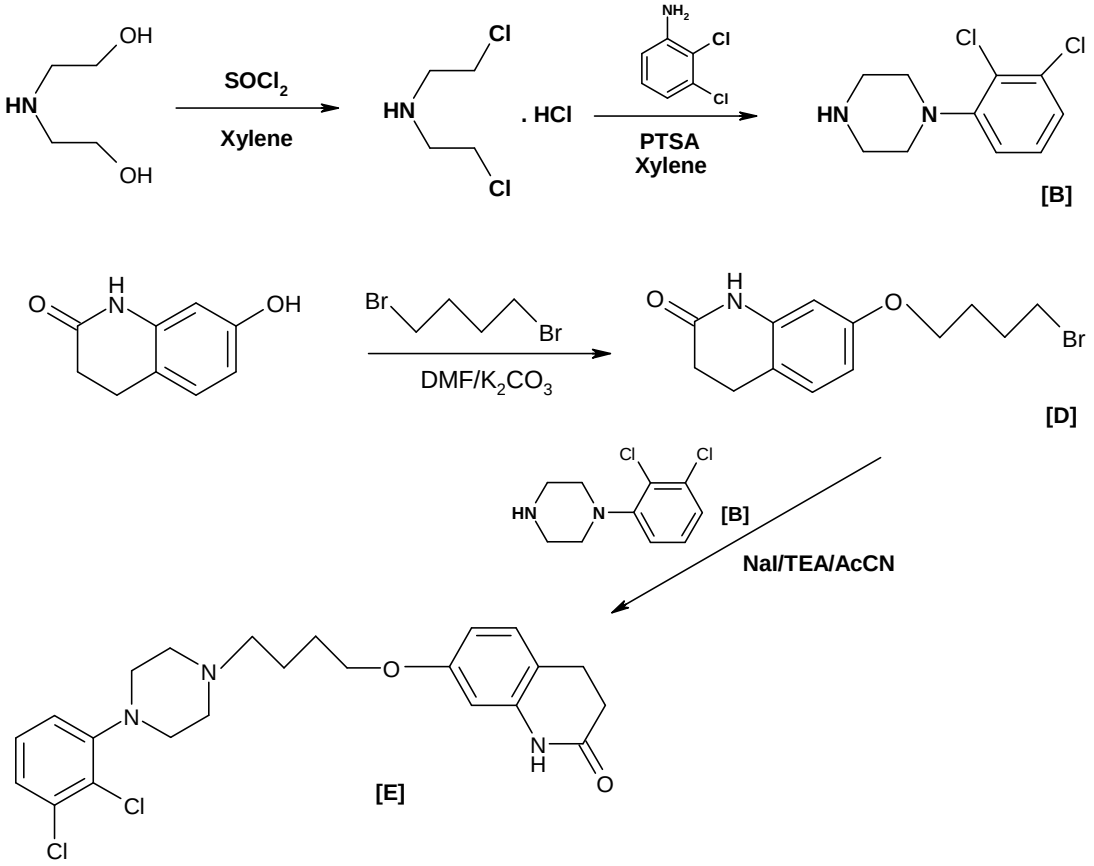
In first part of the process bis-(2-chloroethylamine) hydrochloride (Compound A) is prepared by chlorination of diethanolamine with thionyl chloride in xylene, which is then condensed with 2,3-dichloro aniline to get 1-(2,3-dichlorophenyl)-piperazine hydrochloride intermediate (B). The intermediate, 7-(4- bromobutoxy)-3, 4-dihydro-2(1*H*)-quinolinone (D) is prepared by condensation of 7-hydroxy-3, 4-dihydro-2(1*H*)-quinolinone (Compound C) with dibromobutane in DMF using potassium carbonate as base. The yields of 1-(2, 3-dichlorophenyl)-piperazine hydrochloride (B), 7-(4- bromobutoxy)-3,4-dihydro-2(1*H*)-quinolinone (D) and Aripiprazole (E) reported in the literature and observed in the lab are 81-82%, 62-65% and 84-85% respectively.

Synthesis of 1-(3-chlorophenyl)-piperazine hydrochloride (Compound Q)

- **Conventional Method**

The mixture of bis-(2-chloroethylamine) hydrochloride [P] (100 gm, 0.56 mol), 3-chloro-aniline (78.54 gm, 0.61 mol), *p*-toluenesulphonic acid (PTSA) (3 gm, 3%) in xylene (300 mL) was heated to reflux (140-145^{o}C, 20 h.) and progress of the reaction was monitored by TLC using Chloroform: methanol (8:2) solvent system. On completion the reaction mass was cooled to 30^{o}C and further chilled to 0-5^{o}C when product crystallizes as off-white crystals. The product is isolated by filtration and washed with chilled xylene (5^{o}C, 75 mL) followed by acetone (5^{o}C, 75 mL) for removal of aniline traces before drying in oven under reduced pressure (100 mm/Hg) at 40^{o}C for 8 hours. Product Yield: 110 gm, 84.6 %

Scheme 2: Synthetic route for the preparation of Aripiprazole



- **Microwave Method**

The mixture of bis-(2-chloroethylamine) hydrochloride [P] (10 gm, 0.056 mol), 3-chloro-aniline (7.85 gm, 0.061 mol), *p*-toluenesulphonic acid (PTSA) (0.3 gm, 3%) in xylene (30 mL) was placed in a conical flask, covered with glass funnel. The reaction mixture was irradiated with microwaves at different microwave intensities for different duration by following the pulse heating approach (irradiation in 30s increments). A beaker containing water was also kept in the oven to serve as a "heat sink". To monitor the progress of reaction, a TLC was run after every half minute of microwave irradiation using Chloroform: methanol (8:2) solvent system. After completion of reaction, the work up was done in a manner similar to the conventional procedure. Product Yield: 12.5 gm, 94.5 %

Synthesis of 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine (Compound R)

- **Conventional Method**

To the mixture of 1-(3-chlorophenyl)-piperazine hydrochloride [Q] (100 gm, 0.43 mol) in acetone (300 mL) and water (500 mL) was added sodium hydroxide (46 gm, 1.15 mol) followed by 1-bromo-3- chloropropane (143.6 gm, 0.911 mol) under stirring at 25-30^{o}C. The reaction was further stirred for 15 hours at same temperature and progress was monitored by TLC using chlorofom: methanol (8:2) solvent system. On completion the stirring was stopped and reaction mass was settled when two layers were obtained. The lower organic layer was separated and solvent evaporated under reduced pressure to isolate product as pale yellow oily product. Product Yield: 85.0 gm, 72.6 %

- **Microwave Method**

To the mixture of 1-(3-chlorophenyl)-piperazine hydrochloride [Q] (10 gm, 0.043 mol) in acetone (30 mL) and water (50 mL) was added sodium hydroxide (4.6 gm, 0.115 mol) followed by 1-bromo-3- chloropropane (14.36 gm, 0.091 mol) under stirring at 25-30^{o}C; was placed in a conical flask, covered with glass funnel. The reaction mixture was irradiated with microwaves at different microwave intensities for different duration by following the pulse heating approach (irradiation in 30s increments). A beaker containing water was also kept in the oven to serve as a "heat sink". To monitor the progress of reaction, a TLC was run after every half minute of microwave irradiation using chloroform: methanol (8:2) solvent system. After completion of reaction, the work-up was done in a manner similar to the conventional procedure. Product Yield: 10.5 gm, 88.5 %

Synthesis of1, 2, 4-triazolo [4, 3-a] pyridine-3- (2H)-one (Compound S)

- **Conventional Method**

A mixture of 2-chloropyridine (100 gm, 0.88 mol) and semicarbazide hydrochloride (200 gm, 1.79 mol) in 2-ethoxyethanol (200 mL) was heated to 145-150^{o}C for 12 hours. Progress of the reaction was monitored by TLC using benzene: ethyl acetate (7:3) solvent system. On completion the reaction mass was cooled to 60 ^{o}C and water (400 mL) was added. The solution further cooled to 0^{o}C and stirred for 0.5 hours. The precipitated product was isolated by filtration. Product Yield: 112.0 gm, 94.3 %

- **Microwave method**

A mixture of 2-chloropyridine (10 gm, 0.088 mol) and semicarbazide hydrochloride (20 gm, 0.179 mol) in 2-ethoxyethanol (20 mL) was placed in a conical flask, covered with glass funnel. The reaction mixture was irradiated with microwaves at different microwave

intensities for different duration by following the pulse heating approach (irradiation in 30s increments). A beaker containing water was also kept in the oven to serve as a "heat sink". To monitor the progress of reaction, a TLC was run after every half minute of microwave irradiation using benzene: ethyl acetate (7:3) solvent system. After completion of reaction, the work up was done in a manner similar to the conventional procedure. Product Yield: 11.5 gm, 97.0 %

Synthesis of Trazodone Hydrochloride (Compound T)

- **Conventional Method**

The mixture of 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine [R] (100 gm, 0.36 mol), 1, 2, 4-triazolo [4, 3-a] pyridine-3- (2H)-one [S] (66.1 gm, 1.15 mol) and para toluenesulphonic acid (PTSA) (3 gm, 3%) in acetonitrile (300 mL) was refluxed at 80-82^{o}C for 20 hours. Progress of the reaction was monitored by TLC using Chloroform: methanol (9:1) solvent system. On completion the reaction mass was cooled to 50^{o}C and filtered. The acetonitrile was recovered by atmospheric distillation (~80 %) and toluene (300 mL) was added to residual reaction mass when a clear solution was obtained. The toluene solution was further washed twice with 20% sodium hydroxide solution (2x 50 mL) followed by 2% brine solution (2x 50 mL) at 50^{o}C. To the toluene solution containing product as base, was added IPA HCl solution (15%, 80 mL) and pH adjusted between 2-2.5 when salt starts precipitating. The precipitated hydrochloride salt of target molecule was isolated by filtration and recrystallised from methanol (200 mL) to achieve white crystalline compound.
Product Yield: 126.0 gm, 85.0 %

- **Microwave method**

The mixture of 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine [R] (10 gm, 0.036 mol), 1, 2, 4-triazolo [4, 3-a] pyridine-3- (2H)-one [S] (6.6 gm, 0.115 mol) and para toluenesulphonic acid (PTSA) (0.3 gm, 3%) in acetonitrile (30 mL) was placed in a conical flask, covered with glass funnel. The reaction mixture was irradiated with microwaves at different microwave intensities for different duration by following the pulse heating approach (irradiation in 30s increments). A beaker containing water was also kept in the oven to serve as a "heat sink". To monitor the progress of reaction, a TLC was run after every half minute of microwave irradiation using Chloroform: methanol (9:1) solvent system. After completion of reaction, the work up was done in a manner similar to the conventional procedure.
Product Yield: 14.2 gm, 94.8 %

Synthesis of 1-(2, 3-dichlorophenyl)-piperazine hydrochloride (Compound B)

- **Conventional Method**

The mixture of bis-(2-chloroethylamine) hydrochloride [A] (100 gm, 0.56 mol), 2, 3-dichloro-aniline (98 gm, 0.61 mol), *p*-toluenesulphonic acid (PTSA) (3 gm, 3%) in xylene (300 mL) was heated to reflux (140-145^{o}C, 27 h.) and progress of the reaction was monitored by TLC using chloroform: methanol (8:2) solvent system. On completion the reaction mass was cooled to 30^{o}C and further chilled to 0-5^{o}C when product crystallizes as off-white crystals. The product is isolated by filtration and washed with chilled xylene (5^{o}C, 75 mL) followed by acetone (5^{o}C, 75 mL) for removal of aniline traces before drying in oven under reduced pressure (100 mm/Hg) at 40^{o}C for 8 hours. Product Yield: 122 gm, 82.0 %

- **Microwave Method**

The mixture of bis-(2-chloroethylamine) hydrochloride [2] (10 gm, 0.056 mol), 2, 3-dichloro-aniline (9.8 gm, 0.061 mol), *p*-toluenesulphonic acid (PTSA) (0.3 gm, 3%) in xylene (30 mL) was placed in a conical flask, covered with glass funnel. The reaction mixture was irradiated with microwaves at different microwave intensities for different duration by following the pulse heating approach (irradiation in 30s increments). A beaker containing water was also kept in the oven to serve as a "heat sink". To monitor the progress of reaction, a TLC was run after every half minute of microwave irradiation using chloroform: methanol (8:2) solvent system. After completion of reaction, the work up was done in a manner similar to the conventional procedure. Product Yield: 14.2 gm, 94.6 %

Synthesis of 7-(4-Bromobutoxy)-2(1*H*)-quinolinone (Compound D)

- **Conventional Method**

A mixture of 7-hydroxy-2(1*H*)-quinolinone (163 g, 1.0 mol), 1, 4-dibromobutane (648 g, 3.0 mol), and K_2CO_3 (138 g, 1.0 mol) in DMF (2500 mL) were stirred for 4 h at 60 °C and then diluted with water (2500 mL). An organic layer was extracted with ethyl acetate (AcOEt), and the extract was washed, dried, and evaporated to dryness in vacuum. Recrystallization from EtOH gave the product as a white powder. Product Yield: 190 gm, 64%

- **Microwave Method**

A mixture of 7-hydroxy-2(1*H*)-quinolinone (16.3 g, 0.1 mol), 1, 4-dibromobutane (64.8 g, 0.3 mol), and K_2CO_3 (13.8 g, 0.1 mol) in DMF (100 mL) was placed in a conical flask, covered with glass funnel. The reaction mixture was irradiated with microwaves at different microwave intensities for different duration by following the pulse heating approach (irradiation in 30s increments). A beaker containing water was also kept in the oven to serve as a "heat sink". To monitor the progress of reaction, a TLC was run after every half minute of microwave irradiation using benzene: ethyl acetate (7:3) solvent system. After completion of reaction, the work up was done in a manner similar to the conventional procedure.
Product Yield: 23.3 gm, 78.5 %

Synthesis of Aripiprazole (Compound E)

- **Conventional method**

A mixture of 7-(4-Bromobutoxy)-2(1*H*)-quinolinone (297 g, 1.0 mol), NaI (234 g, 1.56 mol), triethylamine (173.7 g, 1.72 mol) and 1-(2, 3-dichlorophenyl)-piperazine hydrochloride (381 g, 1.43 mol), in acetonitrile (750 mL) was refluxed for 4 h with stirring. Progress of reaction was monitored by TLC; using benzene: ethyl acetate (7:3) solvent system. The reaction mixture was filtered, and the filtrate was evaporated to dryness in vacuo. The residue was extracted with CHCl3, and the extract was washed, dried, and evaporated in vacuo. Recrystallization from MeOH-CHCl3 gave the desired product as colorless needles. Product Yield: 407.0 g, 84 %

- **Microwave Method**

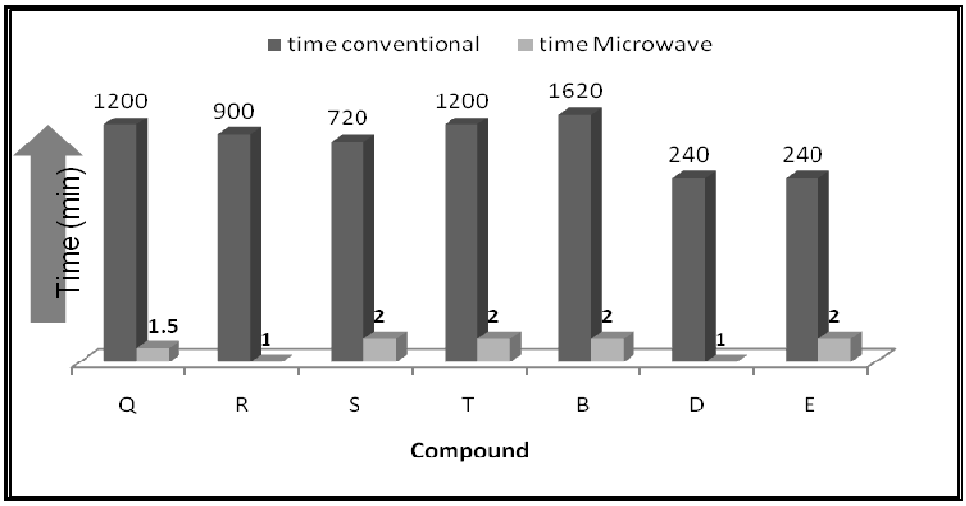
A mixture of 7-(4-Bromobutoxy)-2(1*H*)-quinolinone (29.7 g, 0.1 mol), NaI (23.4 g, 0.15 mol), TEA (17.3 g, 0.17 mol) and 1-(2, 3-dichlorophenyl)-piperazine hydrochloride (38.0 g, 0.14 mmol), in acetonitrile (50 mL) was was was placed in a conical flask, covered with glass funnel. The reaction mixture was irradiated with microwaves at different microwave intensities for different duration by following the pulse heating approach (irradiation in 30s

increments). A beaker containing water was also kept in the oven to serve as a "heat sink". To monitor the progress of reaction, a TLC was run after every half minute of microwave irradiation using benzene: ethyl acetate (7:3) solvent system. After completion of reaction, the work up was done in a manner similar to the conventional procedure.
Product Yield: 46.1 gm, 95.2 %

RESULTS AND DISCUSSION

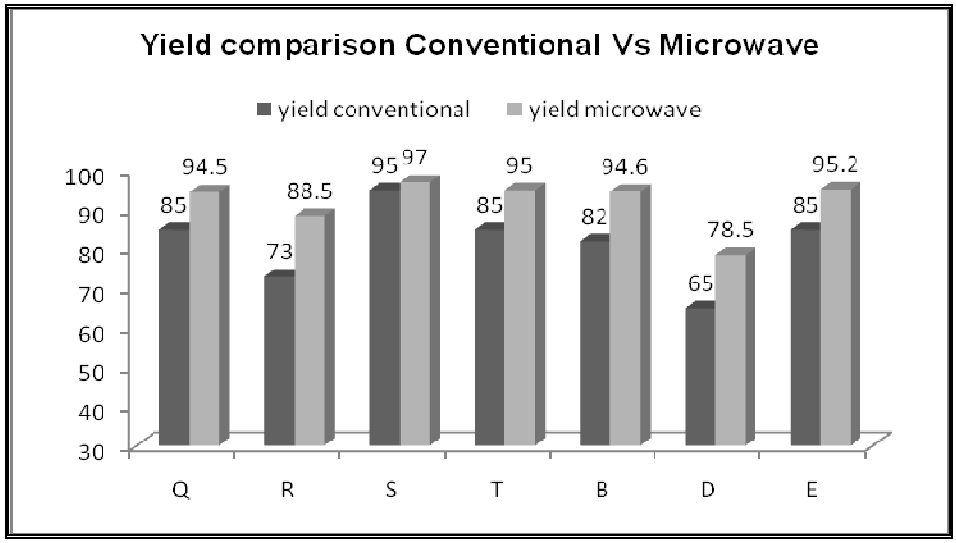
A new microwave process for the rapid and efficient synthesis of Trazodone hydrochloride, Aripiprazole and their process intermediates has been developed. The microwave heating effectively reduced the reaction time from >10-15 hours to few minutes (≤ 2) as presented in Figure 1.

Figure 1: Comparison of Synthesis Time- Conventional against Microwave Process



By using microwave irradiation technique, all the compounds were prepared in yields that were appreciably more than the conventional methods (Table 1) as shown in Figure 2.

Figure 2: Comparison of yield profile-Conventional against Microwave



From the in-process results, it was observed that levels of byproduct formation during the reaction was considerably less in microwave process against conventional method; which may be the reason for higher yields obtained with microwave irradiation. Highest yield improvement was observed for compound D, compare to the conventional method (>77 % against 62-65 %). The process also reduced consumption of DMF solvent by ~ 60%. Encouraging yield enhancement was also observed for compound R from >85 % in microwave process against 72-73 % using conventional method.

Table 1: Microwave intensity and reaction time optimization data

Sr. No.	Compound	Conventional Process Yield(%)	Microwave Intensity (W)	Yield* %	Optimum Intensity (W)	Reaction Time (min.)	Yield** %
1	Compound Q	84-85	160	88.5	500	1	92.8
			350	91.3		**1.5**	**94.5**
			500	94.4		2	85.6
2	Compound R	72-73	**160**	86.5	160	**1**	**88.5**
			350	84.5		1.5	87.0
			500	79.2		2	80.5
3	Compound S	94-95	160	95.0	350	1	93.1
			350	96.0		1.5	95.8
			500	90.0		**2**	**97.0**
4	Compound T	84-85	160	91.5	500	1	93.2
			350	93.2		1.5	94.1
			500	94.0		**2**	**94.8**
5	Compound B	81-82	160	89.0	350	1	91.6
			350	93.0		1.5	93.5
			500	90.5		**2**	**94.6**
6	Compound D	62-65	**160**	72.5	160	**1**	**78.5**
			350	67.8		1.5	73.0
			500	58.3		2	69.4
7	Compound E	84-85	160	90.4	350	1	92.5
			350	94.3		1.5	94.6
			500	89.0		**2**	**95.2**

**Average of three separate reaction after microwave irradiation for 2 min.*
***Average of two readings*

The yields of drug molecules Trazodone (Compound T) and Aripiprazole (Compound E) also showed increase by >7 %. While the microwave process for the Compound S showed no measurable benefits over product yield and quality; it considerably reduced the process time to ~2 minutes against 12-13 hours and eliminated need of high temperature (145-150^{o}C) as in conventional process. The desired compounds synthesized by microwave process were compared against products of conventional synthesis to confirm their formation. The physical, elemental and spectroscopic analysis data is presented in Table 2 and Table 3.

The in-process analysis indicated improved impurity profile (less byproduct formation) during the process especially in synthesis of Compound R and Compound D by conventional method which generates dimer impurity in the range of 8-10 %. These impurities were observed at the level of <2% in microwave process and should be instrumental in enhanced yields obtained. An improved quality and impurity profile of Trazodone hydrochloride and Aripiprazole drug molecules was observed on HPLC chromatogram compared to the conventional products which eliminated repeated purifications.

Table 2: Physical data and elemental analysis results of compounds

Compd.	Synthetic Method	M. P. ^{0}C	R_f	Mol. Formula	Found (Calcd.) %			Purity %
					C	H	N	
Compound Q	Conventional	-	0.78	-	-	-	-	99.78
	Microwave	-	0.77	-	-	-	-	99.60
Compound R	Conventional	-	0.80	-	-	-	-	97.49
	Microwave	-	0.80	-	-	-	-	99.67
Compound S	Conventional	-	0.41	-	-	-	-	99.81
	Microwave	-	0.42	-	-	-	-	99.82
Compound T	Conventional	223-225	0.60	$C_{19}H_{22}ClN_5O$ .HCl	55.8787 (55.8824)	5.6395 (5.6373)	17.1541 (17.1569)	99.89
	Microwave	224-225	0.60		55.8791 (55.8824)	5.6334 (5.6373)	17.1605 (17.1569)	99.90
Compound B	Conventional	-	0.79	-	-	-	-	98.43
	Microwave	-	0.80	-	-	-	-	99.08
Compound D	Conventional	-	0.62	-	-	-	-	96.74
	Microwave	-	0.62		-	-	-	99.16
Compound E	Conventional	109-112	0.80	$C_{23}H_{27}Cl_2N_3O_2$ .HCl	56.9687 (56.9659)	5.7759 (5.7792)	8.6716 (8.6687)	99.85
	Microwave	109-111	0.80		56.9655 (56.9659)	5.7829 (5.7792)	8.6724 (8.6687)	99.95

Table 3: Characterization data of compounds (Conventional and Microwave method)

Compound	Process	Test	Results
Compound Q	Conventional	IR	3050 (aromatic C-H stretching), 2900 (aliphatic C-H stretching), 1589.23 (aromatic C=C), 1300 (C-N sretching), 750(C-Cl stretching).
		NMR	ð 3.54-3.41 (m, 4H, -CH_2 of piperazine), 3.93 (s,4H, -CH_2 of piperazine), 6.68-6.81 (d, 1H, Ar-H), 6.95-6.94 (d, 1H, Ar-H), 7.02-7.01 (s, 1H, Ar-H), 7.26-7.22 (t,1H, Ar-H)
	Microwave	IR	3200 (aromatic C-H stretching), 2923 (aliphatic C-H stretching), 2486 (N-H stretching), 1595.63 (aromatic C=C), 1256.69 (C-N sretching), 751 (C-Cl stretching).
		NMR	ð 3.35-3.25 (m, 8H, -CH_2 of piperazine), 6.95-6.90 (d, 1H, -Ar-H), 7.15-7.04 (m, 3H, -ArH)
Compound R	Conventional	IR	3062.75 (aromatic C-H stretching), 2916.17 (aliphatic C-H stretching), 1500 (aromatic C=C stretching), 1334.65 (C-N stretching), 775 (C-Cl stretching)
		NMR	ð 2.28-2.21(m, 2H, -CH_2), 3.27-3.06 (m, 6H, CH_2, -CH_2 of piperazine), 3.57-3.54 (t, 2H,-CH_2 of piperazine), 3.77-3.73 (m, 2H, ,-CH_2 of piperazine), 3.89-3.86 (t, 2H, -CH_2),6.97-6.85 (m,2H, Ar-H) ,7.05-7.04 (s,1H, Ar-H),7.28-7.22 (t,1H, Ar-H) ,10.87(S,1H, N-H)
	Microwave	IR	3071.45 (aromatic C-H stretching), 2947.54 (aliphatic C-H stretching), 1594.52 (aromatic C=C stretching), 1380.03 (C-N stretching), 766.90 (C-Cl stretching)
		NMR	ð 2.09-2.00 (m, 2H, -CH_2), 2.66-2.59 (t, 6H, -CH_2, CH_2 of piperazine), 3.25-3.23 (t, 4H, -CH_2 of piperazine), 3.65-3.61 (t, 2H, -CH_2), 6.83-6.80 (m, 1H, Ar-H) , 6.97-6.95 (m,1H, Ar-H), 7.10-7.02 (t, 1H, Ar-H) , 7.25-7.13 (s,1H, Ar-H)
Compound S	Conventional	IR	3106 (aromatic C-H stretching), 1721 (C=O stretching), 1637 (C=N stretching), 1541 (aromatic C=C stretching), 1353 (C-N stretching)
		NMR	ð 6.24-6.21 (t, 1H, Ar-H), 6.68-6.65 (t, 1H, Ar-H), 6.97-6.95 (d, 1H, Ar-H), 7.58-7.56 (d, 1H, Ar-H)
	Microwave	IR	3105 (aromatic C-H stretching), 1714 (C=O stretching), 1636

			(C=N stretching), 1541 (aromatic C=C stretching), 1350 (C-N stretching)
		NMR	ð 6.51-6.52 (m, 1H, Ar-H), 7.20-7.15 (d, 2H, Ar-H), 7.77-7.75 (d, 1H, Ar-H)
Compound T	Conventional	IR	3000 (aromatic C-H stretching), 2954 (aliphatic C-H stretching), 1704 (C=O stretching), 1650 (C=N stretching), 1600 (aromatic C=C stretching), 1350 (C-N stretching), 750 (C-Cl stretching)
		NMR	ð 2.16-2.12 ppm (t, 2H, -CH_2), 2.64-2.60 (t, 2H, -N CH_2), 2.73 (s, 4H, -CH_2-N-CH_2), 3.09 (s, 4H, CH_2-N-CH_2), 4.12-4.07 (t, 2H,-CH_2-N), 6.51-6.46 (m,1H, -ArH), 7.02-6.93 (m, 2H,-ArH), 7.09-7.08 (d, 2H, -ArH), 7.26-7.17 (m, 1H, -ArH), 7.34-7.31 (d, 1H, -ArH), 7.76-7.74 (d, 1H, -ArH)
	Microwave	IR	2954 (aliphatic C-H stretching), 1704 (C=O stretching), 1650 (C=N stretching), 1600 (aromatic C=C stretching), 1434 (C-H bending), 1350 (C-N stretching), 750 (C-Cl stretching)
		NMR	ð 2.28-2.26 ppm (t, 2H, -CH_2), 3.09 (t, 2H, -N CH_2), 3.23-3.20 (s, 5H, -CH_2-N-CH_2), 3.38 (s, 3H, CH_2-N-CH_2), 3.53-3.51 (t, 2H,-CH_2-N), 6.64-6.63 (m,1H, -ArH), 6.86-6.84 (m, 1H,-ArH), 6.95-6.93 (d, 1H, -ArH), 6.96 (s, 1H, -ArH), 7.22-7.85 (d, 3H, -ArH), 7.85-7.87 (d, 1H, -ArH)
Compound B	Conventional	IR	3396 (N-H stretching), 3063 (aromatic C-H stretching), 2965 (aliphatic C-H stretching), 1578-1418 (aromatic region), 1313 (C-N stretching), 777(C-Cl stretching).
		NMR	ð 3.33-3.18 (m, 8H, -CH_2 of piperazine), 7.20-7.15 (d, 1H, Ar-H), 7.35-7.28 (m, 2H, Ar-H), 9.51 (s, 1H, -NH)
	Microwave	IR	3055 (aromatic C-H stretching), 2900 (aliphatic C-H stretching), 1573 (aromatic C=C stretching), 1342 (C-N stretching) , 786 (C-Cl sretching)
		NMR	ð 3.20-3.17 (m, 4H, -CH_2 of piperazine), 3.34-3.31 (s, 4H, -CH_2 of piperazine), 7.06-7.01 (t, 1H, Ar-H), 7.13-7.11 (d, 1H, Ar-H), 7.27-7.22 (t, 1H, Ar-H)
Compound D	Conventional	IR	3337 (N-H stretching), 3035 (aromatic C-H stretching), 2932 (aliphatic C-H stretching), 1676 (C=O stretching), 1594-1414 (aromatic region), 1178 (C-N stretching), 764(C-Cl stretching).
		NMR	ð 1.81-1.75 ppm (m, 2H, -CH_2), 1.96-1.87 (m, 2H, CH_2), 2.40-2.35 (t, 2H, CO-CH_2 of carbostyryl), 2.77-2.72 (t, 2H, -CH_2 of carbostyryl), 3.58-3.54 (t, 2H,-CH_2), 3.91-3.87 (t, 2H,-CH_2), 6.40-6.39 (m,1H, -ArH), 6.47-6.43 (m, 1H,-ArH), 7.02-7.00 (d, 1H, -ArH), 9.95 (s, 1H, -NH)
	Microwave	IR	3332 (N-H stretching), 3101 (aromatic C-H stretching), 2839 (aliphatic C-H stretch), 1674 (C=O starching), 1596 (aromatic C=C stretching), 1180 (C-O stretching), 624 (C-Br stretching)
		NMR	ð 1.82-1.79 ppm (m, 2H, -CH_2), 1.96-1.91 (m, 2H, CH_2), 2.40-2.37 (t, 2H, -CH_2 of carbostyryl), 2.79-2.74 (t, 2H, -CH_2 of carbostyryl), 3.61-3.56 (t, 2H,-CH_2), 3.93-3.89 (t, 2H,-CH_2), 6.49-6.42 (m,2H, -ArH), 7.04-7.02 (m, 1H,-ArH), 9.99 (s, 1H, -NH)
Compound E	Conventional	IR	3368 (N-H stretching), 3109 (aromatic C-H stretching), 2944 (aliphatic C-H stretching), 1677 (C=O stretching), 1594-1445 (aromatic region), 1174 (C-N stretching), 779 (C-Cl stretching).
		NMR	ð 1.77-1.72 ppm (t, 2H, -CH_2), 1.83-1.79 (t, 2H, -CH_2), 2.50-2.45 (t, 2H, -CH_2), 2.63-2.58 (m, 6H, CO-CH_2-CH_2 of carbostyryl, CH_2 of piperazine), 2.91-2.86 (m, 2H, -CH_2 of piperazine), 3.06 (s, 4H, -CH_2 of piperazine), 6.30-6.29 (s, 1H, -ArH), 6.53-6.50 (d of d, 1H,-ArH), 6.98-6.93 (m, 1H, -ArH), 7.05-7.02 (d, 1H, -ArH), 7.16-7.10 (d, 2H, -ArH), 7.79 (s, 1H, -NH)

	Microwave	IR	3193 (N-H stretching), 3050 (aromatic C-H stretching), 2947 (aliphatic C-H sretching), 1674 (C=O stretching), 1519 (aromatic C=C stretching), 1380 (C-N stretching), 1195 (C-O stretching), 779 (C-Cl stretching)
		NMR	ð 1.62-1.52 ppm (t, 2H, -CH_2), 1.76-1.67 (t, 2H, -CH_2), 2.35-2.27 (m, 4H, CO-CH_2-CH_2 of carbostyryl), 2.70 (m, 3H, -CH_2, one H of piperazine), 2.85-2.74 (m, 5H,-CH_2 and -CH of piperazine), 3.93-3.89 (t, 2H, -CH_2), 6.55-6.42 (m, 2H, -ArH), 7.02 (d, 1H,-ArH), 7.10 (d, 1H, -ArH), 7.13 (t, 2H, -ArH), 10.00 (s, 1H, -NH)

CONCLUSION

The developed microwave method for the synthesis of Trazodone hydrochloride, Aripiprazole and their respective intermediates was found more efficient on overall performance compare to conventional method as desired.

The microwave irradiation technique led to improvement in the yield of all the target compounds with reduction in their reaction byproducts. This led to better impurity profile of compounds; especially for Trazodone hydrochloride and Aripiprazole drug molecules as desired. The microwave process also substantially reduced the overall process time as expected, by reduction in reaction time against the described conventional method.

The chemistry for the synthesis of target compounds using microwave irradiation is established in the lab by carrying out three successive experiments post initial optimization of key parameters; to ensure process robustness. The results of these validation experiments were found to be promising, indicating its wide use for researchers.

Using more advance instruments and infrastructure in Microwave assisted organic reaction enhancement (MORE); the process can be further evaluated for its scale up potential.

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