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Sulphamic Acid: An Efficient and Green Synthesis of 2-[3-{4-(3-chlorophenyl)-1-piperazinyl} propyl]-1, 2, 4-triazolo [4, 3-a] pyridine-3- (2H)-one hydrochloride and its derivatives

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ABSTRACT

An efficient and green procedure has been developed for the synthesis of 2-[3-{4-(3-chlorophenyl)-1-piperazinyl}propyl]-1,2,4-triazolo[4,3-a]pyridine-3-(2H)-one hydrochloride and its derivatives using sulphamic acid (SA) as heterogeneous catalyst. The present methodology offers several advantages such as excellent yields, absence of side products and operational simplicity, recyclability and reusability of the catalyst are some of the salient features of this reaction.

Keywords: Green synthesis, Sulphamic acid, recyclability, Heterogeneous catalyst

INTRODUCTION

The lead compound 2-[3-{4-(3-chlorophenyl)-1-piperazinyl} propyl]-1, 2, 4-triazolo [4,3-a] pyridine-3- (2H)-one hydrochloride, known by the generic name "Trazodone hydrochloride" is a potential psychoactive drug of the piperazine and triazolopyridine chemical classes that has antidepressant, anxiolytic and hypnotic properties [1,2]. The hypothesis of pharmacological potential of Trazodone hydrochloride suggest that it inhibits the reuptake of serotonin, but possesses a far lower affinity for the serotonin transporter (SERT) than the drugs in the selective serotonin reuptake inhibitor (SSRI) class [3]. Its anxiolytic and antidepressant effects may be due to its antagonistic effects at the 5-HT_{2A} and 5-HT_{2C} receptors [4]. Its sedative-hypnotic effects may stem from its strong antagonistic activity at the 5-HT_{2A} and alpha-1 adrenergic receptor in addition to its moderate antagonistic activity at the H₁ receptors. Trazodone behaves as an antagonist at all of the receptors except 5-HT_{1A} where it acts as potential agonist [5]. Trazodone acts predominately as a 5-HT_{2A} receptor antagonist to mediate its therapeutic benefits against anxiety and depression. Its inhibitory effects on serotonin reuptake and 5-HT_{2C} receptors are relatively weak. Hence; Trazodone does not have similar properties to selective serotonin reuptake inhibitors (SSRIs) [6].

A new method for the synthesis of *2-[3-{4-(3-chlorophenyl)-1-piperazinyl} propyl]-1, 2, 4-triazolo [4,3-a] pyridine-3- (2H)-one hydrochloride* was developed in a greener way by using SA as heterogeneous and recyclable catalyst. Hence the drive is towards "Green chemistry" [7-10]. Unlike other catalysts, SA offers the potential for the superior performance & environmental integrity. Apart from easy to recover the reaction products SA catalysts can also allay concerns about safety and environmentally hazardous emissions made over solid catalyst [11-15] offer many advantages such as non-corrosiveness, safe and easy handling, and wide range of temperature and pressure that can be applied, easy separations of reactants and products from the catalyst, better selectivity, and possibility of working in a continuous mode [15].

The approach towards preparation of sodium salt of 1, 2, 4-triazolo [4, 3-a] pyridine-3-(2H)-one from mixture of 2-chloropyridine and semicarbazide hydrochloride also preparation of 2-[3-{4-(3-chlorophenyl)-1-piperazinyl} propyl]-1, 2, 4-triazolo [4,3-a] pyridine-3- (2H)-one hydrochloride and its derivatives from condensation of 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine and its derivatives and sodium salt of 1, 2, 4-triazolo [4, 3-a] pyridine-3-(2H)-one was described here with. The targets which are important class of biologically active organic compounds due to their broad spectrum of biological activities has made them heterocyclic structure in combinational drug discovery.

MATERIALS AND METHODS

All chemicals and reagents were purchased from Aldrich (*Sigma-Aldrich, St. Louis, MO, USA*), Lancaster (*Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA*) or Spectrochem Pvt. Ltd (*Mumbai, India*) and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 GF-254, and visualization on TLC was achieved by UV light or iodine indicator. Column chromatography was performed with Merck 60–120 mesh silica gel. ¹H spectra were recorded by Bruker UCNMR/XWIN-NMR (300 MHz) instruments. Chemical shifts (δ) were reported in ppm downfield from internal TMS standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined with an Electro thermal melting point apparatus, and were approximate.

Detailed Synthetic process:

Our new target compounds, 2-[3-{4-(3-chlorophenyl)-1-piperazinyl}propyl]-1,2,4-triazolo[4,3-a] pyridine-3-(2H)-one hydrochloride derivatives [5A-5J] listed in Table 1, were prepared using the process described in figure 1.

Step- 1: General procedure for the preparation of bis-(2-chloroethylamine) hydrochloride {1}

To the mixture of diethanolamine (100 gm, 0.9523 mol), para toluenesulphonic acid (PTSA) (3 gm, 3%) and Chloroform (250 mL) was added thionyl chloride (104.7 gm, 1.42 mol) at 25-30°C under stirring. After complete addition, the reaction mass is heated to 75-80°C when a mild reflux was observed. The reaction continued for 2 hours to ensure completion and cooled to 25°C when product crystallizes out of solution. The white crystalline product is isolated by filtration and dried under vacuum at 30°C.

Product Yield: 94.10 gm, 94.1 %.

Step-2: General procedure for the preparation of 1-(3-chlorophenyl)-piperazine hydrochloride and its derivatives {2}

The mixture of bis-(2-chloroethylamine) hydrochloride {1} (100 gm, 0.56 mol), 3-chloro-aniline (78.54 gm, 0.61 mol), para toluenesulphonic acid (PTSA) (3 gm, 3%) in xylene (300 mL) was heated to reflux (140-145°C) and progress of the reaction was monitored by TLC. On completion the reaction mass was cooled to 30°C and further chilled to 0-5°C when product crystallizes as off-white crystals. The product is isolated by filtration and washed with chilled xylene (5°C, 75 mL) followed by acetone (5°C, 75 mL) before drying in oven under reduced pressure (100 mm/Hg) at 40°C for 8 hours.

Product Yield: 110 gm, 84.6 %.

Step- 3: General procedure for preparation of 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine and its derivatives {3}

To the mixture of 1-(3-chlorophenyl)-piperazine hydrochloride {2} (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°C. The reaction was further stirred for 15 hours at same temperature and progress was monitored by TLC. On completion the stirring was stopped and reaction mass was settled when two layers were obtained. The lower organic layer was separated and evaporated to isolate product as pale yellow oily product.

Product Yield: 85.0 gm, 72.6 %.

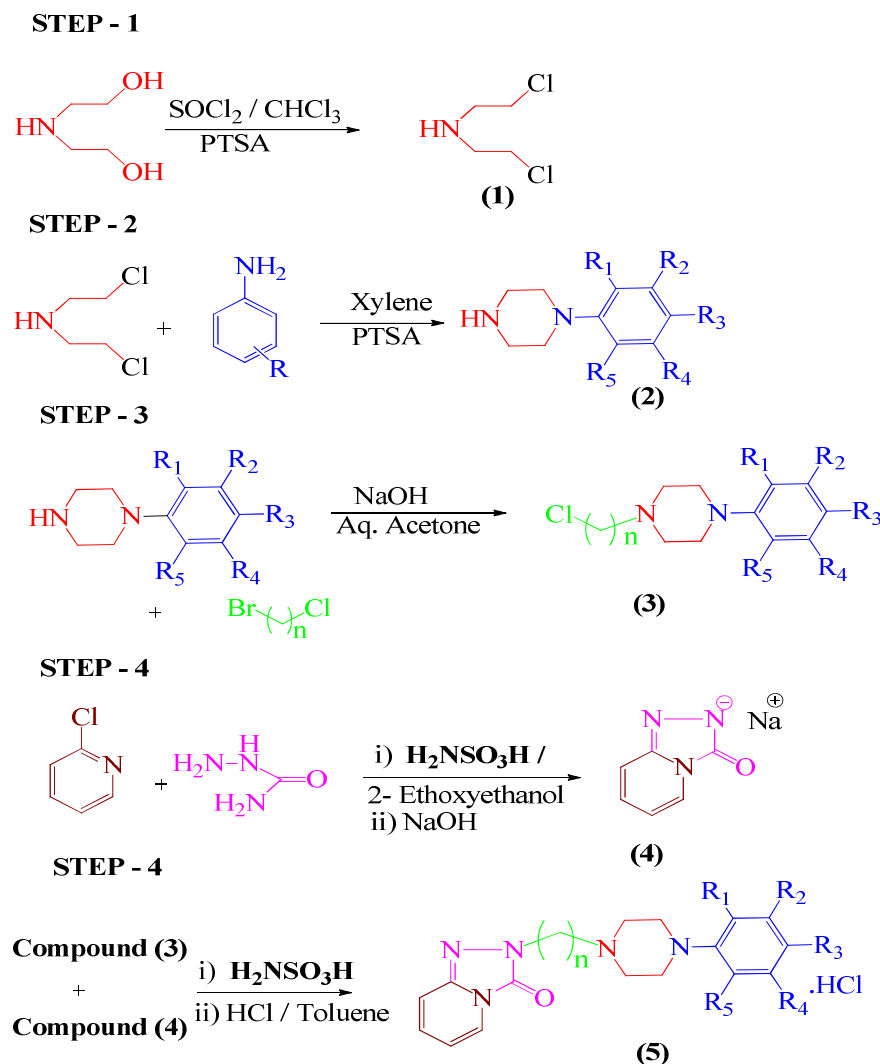


Figure- 1

Step- 4: General procedure for preparation of sodium salt of 1, 2, 4-triazolo [4, 3-a] pyridine-3-(2H)-one {4}

A mixture of 2-chloropyridine (0.88 mol) and semicarbazide hydrochloride (1.79 mol) in 2-ethoxyethanol (200 mL) and Sulphamic acid (0.2 mol) was heated to 110-120°C for 7.5 hours. Progress of the reaction was monitored by TLC. On completion the reaction mass was cooled to 60°C and water (400 mL) was added. The solution further cooled to 0°C and stirred for 0.5 hours. The precipitated product was isolated by filtration. The filtrates contain Sulphamic acid mixed with water which was later recovered.

Product Yield: 112.83 gm, 95%.

The above solid was then dissolved in 30 % sodium hydroxide solution (100 mL) and warmed to 40°C when a clear solution was obtained. The solution was then slowly cooled to 0°C when product crystallizes as sodium salt and thick slurry was obtained. The sodium salt of the product was isolated by filtration and washed with chilled water (0°C, 200 mL) prior to drying at 70°C under reduced pressure (10 mm/Hg) for 12 hours.

Product Yield: 127.2 gm, 97.0 %.

Step- 5: General procedure for preparation of 2-[3-{4-(3-chlorophenyl)-1-piperazinyl} propyl]-1, 2, 4-triazolo [4, 3-a] pyridine-3- (2H)-one hydrochloride and its derivatives {5A- 5J}

The mixture of 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine {3} (100 gm, 0.36 mol), 1, 2, 4-triazolo [4, 3-a] pyridine-3- (2H)-one {4} (66.1 gm, 1.15 mol) and Sulphamic acid (6 gm, 6%) in acetonitrile (300 mL) was refluxed

at 65-75°C for 14 hours. Progress of the reaction was monitored by TLC to ensure formation of product and complete conversion of starting 2-[3-{4-(3-chlorophenyl)-1-piperazinyl} propyl]-1. On completion the reaction mass was cooled to 50°C and filtered. The acetonitrile was recovered by atmospheric distillation (~80 %) and toluene (300 mL) was added to residual reaction mass and filtered. After filtration the Sulphamic acid was recovered as residue which was later recovered. Filtrate solution was further washed twice with 20% sodium hydroxide solution (2x 50 mL) followed by 2% brine solution (2x 50 mL) at 50°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 recrystallized from methanol (200 mL) to achieve white crystalline compound.
Product Yield: 136.37 gm, 92.0 %.

RESULTS AND DISCUSSION

In continuation of our interest to develop new methodologies in organic reaction, herein we would like to report a simple, efficient and rapid method for the synthesis of *1,2,4-triazolo[4,3-a]pyridine-3(2H)-one*. The previous co-workers reported methods for the aforesaid synthesis [1] but there is certain limitations regarding the yield and reaction time. In search, the Sulphamic acid used for the synthesis of *1,2,4-triazolo[4,3-a]pyridine-3(2H)-one* and the desired product was obtained in excellent yields. Considering the reaction time and yield of product, Sulphamic acid was selected as optimum catalyst to promote this synthesis.

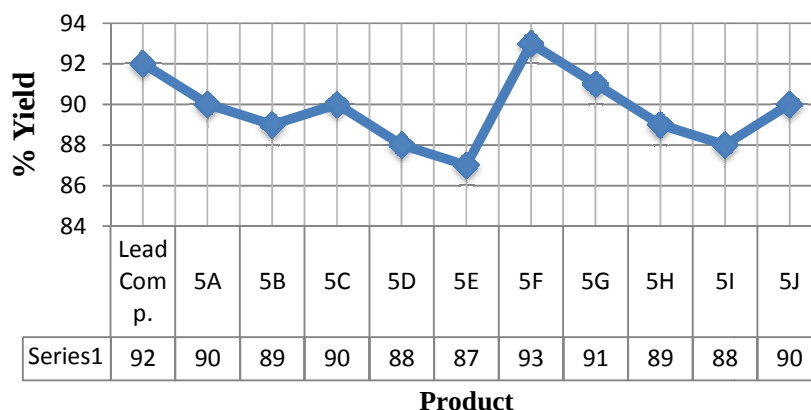
In first part of the synthetic process bis-(2-chloroethylamine) hydrochloride is prepared by chlorination of diethanolamine with thionyl chloride in CHCl_3 , which is then condensed with various substituted anilines to get different derivatives of 1-(3-chlorophenyl)-piperazine hydrochloride intermediate. Alkylation of these using 1-bromo-3-chloropropane in alkaline aqueous acetone (50 %) gave various analogs of 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine intermediate [1].

We have developed a novel Green chemistry route for both step-{4} and step-{5}. In step-{4}, the synthesis of 1, 2, 4-triazolo [4, 3-a] pyridine-3(2H)-one is based on the condensation and subsequent cyclization reactions of 2-chloropyridine, semicarbazide in 2-ethoxyethanol and Sulphamic acid at 110-120°C for 7.5 hours the reaction does not require any additional catalyst because Sulphamic acid itself acts as an efficient catalyst, and hence the reaction proceeds well. In this methodology, one pot synthesis of 1, 2, 4-triazolo [4, 3-a] pyridine-3(2H)-one were completed in a shorter time and with excellent yields (95%).

Similarly in the step-{5}, 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine and its derivatives {3}, 1, 2, 4-triazolo [4, 3-a] pyridine-3(2H)-one and Sulphamic acid in acetonitrile was refluxed at 65-75°C for 14 hours the reactions undergo condensation to get *1,2,4-triazolo[4,3-a]pyridine-3(2H)-one*. The reactions were compatible with various substituents such as chloro, fluoro, bromo, methoxy and ethoxy there was slightly significant substituents effect was observed in compound 5F (graph-1) regarding the yield of product, this is due to the presence of two electron donating methoxy group present on R_1 and R_4 on the {3} which makes the aromatic ring more electron rich. During the condensation the chloro group present on the side chain of {3} was removed via SN^2 displacement process and hence inversion products were to be expected in the aforesaid synthesis. (Table 1)

Table 1:- Synthesis of 2-[3-{4-(3-chlorophenyl)-1-piperazinyl} propyl]-1,2,4-triazolo[4,3-a]pyridine-3(2H)-one hydrochloride and its derivatives {5A-5J}

Entry	Product	R_1	R_2	R_3	R_4	R_5	n	% Yield	Melting Point(°C)	
									Observed	Reported
1	Lead (5)	-H	-Cl	-H	-H	-H	3	92	222	223
2	5A	-Cl	-Cl	-H	-H	-H	3	90	253	>250
3	5B	-H	-Cl	-Cl	-H	-H	3	89	251	>250
4	5C	-H	-Br	-H	-H	-H	3	90	211	211-213
5	5D	-H	-H	-F	-H	-H	3	88	243	240-242
6	5E	-Cl	-H	-Cl	-Cl	-H	3	87	252	>250
7	5F	-CH ₃	-H	-H	-CH ₃	-H	3	93	232	230-232
8	5G	-C ₂ H ₅	-H	-H	-H	-H	3	91	207	204-206
9	5H	-H	-Cl	-H	-H	-H	2	89	219	218-220
10	5I	-H	-Cl	-H	-H	-H	4	88	227	227-230
11	5J	Naphthyl	-H	-H	-H	-H	3	90	226	225-227

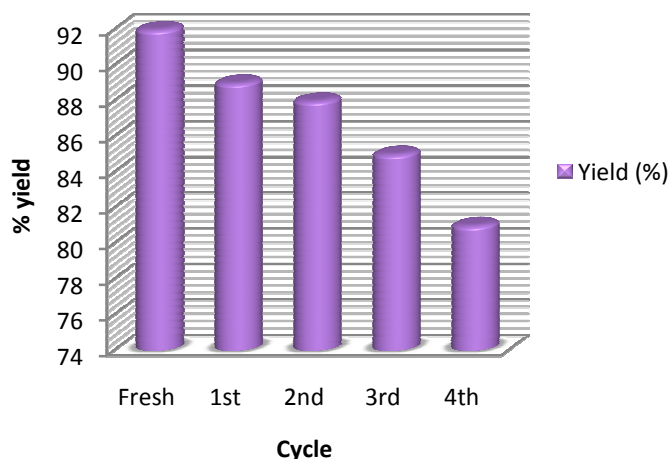


Graph 1:- Comparison between various substituents of product against % Yields of the reaction

We have examined the catalytic activity of recovered Sulphamic acid for the (Lead Compound- 5) and these results clearly indicate that the recovered Sulphamic acid can be recycled successfully without significant loss of its activity upto 4th cycle. In order to show the merits of our present method in comparisons with other reported Methods for the similar reactions (Table 2).

Table 2:- Recycling of Sulphamic acid for the synthesis of 2-[3-{4-(3-chlorophenyl)-1-piperazinyl} propyl]-1, 2, 4-triazolo [4, 3-a] pyridine-3- (2H)-one hydrochloride (Lead Compound- 5)

Sr. no.	Cycle	Yield (%)
1	Fresh	92
2	1 st	89
3	2 nd	88
4	3 rd	85
5	4 th	81



The IUPAC name and the spectral characteristics (FT-IR, ¹H-NMR, and EIMS) of the products obtained and their analytical data (by elemental analysis) are given. Condensation reaction is an excellent tool for the synthesis of several biologically important organic compounds. In this present investigation, aforesaid condensation reactions were carried out with {4} & {5} in the presence of Sulphamic acid as under thermal condition to afford the corresponding products i.e. <i><ii>. The reagent Sulphamic acid is recoverable and reusable for several times without potential loss in its catalytic activity.

Spectral and elemental analysis data:

(Lead Compound):

IR (KBr) cm⁻¹: 3000 (aromatic C-H stretching), 2954 (aliphatic C-H stretching), 1704 (>C=O stretching), 1650 (C=N stretching), 1600 (aromatic C=C stretching), 1350.80 (C=N stretching), 750 (C-Cl stretching); **¹H NMR δ ppm**: -2.16-2.12 ppm (t, 2H, N-CH₂-CH₂-CH₂-N), 2.64-2.60 (t, 2H, N-CH₂), 2.73 (s, 4H, -CH₂-N-CH₂), 3.09 (s, 4H, CH₂-N-CH₂), 4.12-4.07 (t, 2H, -CH₂-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); **MS m/z**: -372 (M^+); **Physical data**: - MF: - $C_{19}H_{22}ClN_5O$; MW: - 372

(5A):IR (KBr) cm^{-1} : 3000 (aromatic C-H stretching), 2850 (aliphatic C-H stretching), 1700 (C=O stretching), 1650 (C-N stretching), 1600 (aromatic C-H stretching), 1350 (C-N stretching), 750 (C-Cl stretching); **1H NMR δ ppm**: - 2.50-2.49 (m, 2H, -CH₂), 3.21-3.15 (m, 8H, CH₂- piperazine), 3.60 (t, 2H -CH₂), 4.01(t, 2H, -CH₂) ,6.65-6.63 (m,1H, -ArH), 7.25-7.21(m, 3H, -ArH), 7.36-7.34 (t, 2H, -ArH), 7.88-7.86 (d,1H, -Ar H); **MS m/z**: - 406 (M^+)

Physical data: - MF: - $C_{19}H_{21}Cl_2N_5O$, MW: - 406

(5B): IR (KBr) cm^{-1} : 3050, 3100 (aromatic C-H stretching), 2862, 2947(aliphatic C-H stretching), 1704.96 (C=O stretching), 1643.24 (C-N stretching), 1635.23 (aromatic C-H stretching), 1350.08 (C-N stretching), 750 (C-Cl stretching); **1H NMR δ ppm**: -2.26-2.19 (m, 2H, CH₂) , 3.23-3.01(m, 6H, CH₂- piperazine), 3.40-3.50 (d, 2H, CH₂- piperazine), 3.90-3.86 (d, 2H, CH₂), 4.01-3.97 (t, 2H, CH₂), 6.67-6.60 (m,1H,Ar H), 7.01-6.97 (m, 1H, -Ar H), 7.21-7.20 (m, 3H, -Ar H), 7.40 (d,1H, -Ar H), 7.88-7.859 (d,1H, -Ar H); **MS m/z**: - 406.3 (M^+); **Physical data**: - MF: - $C_{19}H_{21}Cl_2N_5O$, MW:- 406

(5C): IR (KBr) cm^{-1} : 3000 (aromatic C-H stretching), 2870 (aliphatic C-H stretching), 1710 (C=O stretching), 1635 (C=N stretching), 1610 (aromatic C=C stretching), 1350 (C=N stretching), 575 (C-Br stretching); **1H NMR δ ppm**: -2.28-2.26 (t, 2H, CH₂), 3.09 (t, 2H, CH₂-piperazine), 3.23-3.20 (d, 4H, CH₂- piperazine), 3.53-3.51 (t,2H,CH₂-Piperazine), 3.87-3.84 (d, 2H, CH₂), 4.02-3.98 (t, 2H, CH₂), 6.64-6.63 (t,1H, -ArH), 6.86-6.84 (m,1H, -Ar H), 6.96-6.95 (d,1H, -Ar H), 7.04-7.03 (t,1H, -Ar H), 7.26-7.22 (m, 3H, -Ar H), 7.87-7.85 (d,1H, -ArH); **MS m/z**: - 415 (M^+); **Physical data**: - MF: - $C_{19}H_{22}BrN_5O$; MW: - 415

(5D): IR (KBr) cm^{-1} : 3050 (aromatic C-H stretching), 2850, 2950 (aliphatic C-H stretching), 1720 (C=O stretching), 1650 (C=N stretching), 1500 (aromatic C=C stretching), 1325 (C-N stretching), 1164.92 (C-F stretching); **1H NMR δ ppm**: - 2.31-2.24 (m, 2H, CH₂), 3.20-3.12 (m, 6H, CH₂-piperazine), 3.56-3.53 (d, 2H,CH₂- piperazine), 3.72-3.69 (d, 2H, CH₂), 4.03-3.99 (t, 2H, CH₂), 6.66- 6.61(m,1H, -Ar H), 7.13-7.00 (m, 4H, -Ar H), 7.25-7.24 (d, 2H, -Ar H), 7.88-7.86 (d,1H, -Ar H); **MS m/z**: - 356 (M^+); **Physical data**: - MF: - $C_{19}H_{22}FN_5O$; MW: - 356

(5E):IR (KBr) cm^{-1} : 3010 (aromatic C-H stretching), 2875 (aliphatic C-H stretching), 1715 (C=O stretching), 1650 (C-N stretching), 1550 (aromatic C-H stretching), 1350.45 (C-N stretching), 775 (C-Cl stretching); **1H NMR δ ppm**: - 1.94-1.88 (m, 2H, CH₂), 2.38-2.28 (m, 2H, CH₂), 2.44-2.40 (s, 4H, CH₂-piperazine), 3.07-3.04 (t, 4H, CH₂- piperazine), 3.97-3.93 (t, 2H, CH₂), 6.61-6.65(m,1H, -Ar H), 6.90-6.97 (m, 2H, -Ar H), 7.12-7.09 (s,1H, -Ar H), 7.25-7.15 (m,1H, -Ar H), 7.84-7.82; (d,1H, -Ar H); **MS m/z**: - 441 (M^+); **Physical data**: - MF: - $C_{19}H_{20}Cl_3N_5O$; MW: - 440.5

(5F):IR (KBr) cm^{-1} : 3000 (aromatic C-H stretching), 2947.03 (aliphatic C-H stretching), 1710 (C=O stretching), 1650 (C=N stretching), 1500 (aromatic C=C stretching), 1350 (C-N stretching); **1H NMR δ ppm**: - 1.92-1.87 (t, 2H, CH₂), 2.09-2.03 (d, 6H, -Ar-CH₃), 2.50-2.36 (m, 6H, CH₂ piperazine), 2.66 (s, 4H, CH₂-piperazine), 3.98-3.94 (t, 2H, CH₂), 6.62-6.58 (t,1H, -Ar H), 6.82-6.80 (d,1H, -Ar H), 6.93-6.90 (d, 2H, -Ar H), 7.25-7.10 (m, 2H,-Ar H), 7.86-7.84 (d,1H, -Ar H); **MS m/z**: - 366 (M^+); **Physical data**: - MF: - $C_{21}H_{27}N_5O$; MW: - 366

(5G):IR (KBr) cm^{-1} : 3050 (aromatic C-H stretching), 2850 (aliphatic C-H stretching), 1700 (C=O stretching), 1650 (C=N stretching), 1600 (aromatic C=C stretching), 1347 (C-N stretching) ; **1H NMR δ ppm**: - 1.16-1.13 (t, 3H, CH₃), 1.93-1.89 (m, 2H, CH₂), 2.29 (t, 2H, CH₂), 2.99-2.77 (m, 6H, CH₂, CH₂-piperazine), 3.17 (t, 2H, CH₂), 4.12-3.93 (m, 4H, CH₂- piperazine), 5.20 (m, 1H, -ArH), 5.77 (m, 1H, -ArH), 6.59-6.57 (m, 2H, ArH), 6.8 (d,1H, -ArH), 7.07 (d,1H, -ArH), 7.27-7.17 (d, 2H, -ArH); **MS m/z**: - 366.53 (M^+); **Physical data**: - MF: - $C_{21}H_{27}N_5O$; MW: - 366

(5H): IR (KBr) cm^{-1} : 3132 (N-H stretching), 3050 (aromatic C-H stretching), 2862 (aliphatic C-H stretching), 1710 (C=O stretching), 1650 (C=N stretching), 1500 (aromatic C-H stretching), 1430 (C-N symmetric stretching), 1350 (C-N stretching), 750 (C-Cl stretching); **1H NMR δ ppm**: - 1.16-1.13 (t, 3H, CH₃), 1.93-1.89 (m, 2H, CH₂), 4.02-3.97 (t, 2H, CH₂), 3.19-3.02 (m, 6H, CH₂-piperazine), 3.80-3.76 (t, 2H, CH₂), 3.54-3.50 (d, 2H, CH₂- piperazine), 6.65-6.60 (m, 1H, -ArH), 7.01-6.95 (m, 1H, -ArH), 7.18-7.17 (m, 1H, ArH), 7.25-7.19(t,2H, -ArH), 7.31-7.25(m,1H, -ArH), 7.88-7.85 (d, 2H, -ArH),11.08(broad s, 1H, -NH); **MS m/z**: - 358(M^+); **Physical data**: - MF: - $C_{18}H_{20}N_5OCl$; MW: - 358

(5I):IR (KBr) cm^{-1} : 3105 (N-H stretching), 3000 (aromatic C-H stretching), 2850 (aliphatic C-H stretching), 1700 (C=O stretching), 1650 (C-N stretching), 1600 (aromatic C-H stretching), 1431 (C=N symmetric stretching), 1350 (C-N stretching), 750 (C-Cl stretching); **$^1\text{H NMR } \delta \text{ ppm}$:** 1.40-1.20 (m, 2H, CH_2), 1.60-1.41 (m, 2H, CH_2), 2.30-2.15 (t, 2H, CH_2), 3.02-2.74 (m, 4H, CH_2 -piperazine), 3.26-3.08 (t, 2H, CH_2), 4.17-4.05 (m, 4H, CH_2 -piperazine), 6.26-6.12 (d, 1H, -ArH), 7.05-6.74 (t, 1H, -ArH), 7.11-7.05 (d, 1H, ArH), 7.26-7.11 (m, 1H, -ArH), 8.02-7.74 (m, 2H, -ArH), 8.25-8.12 (d, 1H, -ArH), 8.52-8.30 (t, 1H, -ArH); **MS m/z:** - 386(M^+); **Physical data:** - MF: - $\text{C}_{20}\text{H}_{24}\text{N}_5\text{OCl}$; MW: - 386

(5J): IR (KBr) cm^{-1} : 3152 (N-H stretching), 3050 (aromatic C-H stretching), 2850, 2925 (aliphatic C-H stretching), 1700 (C=O stretching), 1650 (C=N stretching), 1535 (aromatic C=C stretching), 1416 (C=N symmetric stretching), 1325 (C-N stretching); **$^1\text{H NMR } \delta \text{ ppm}$:** 2.65-2.63 (t, 2H, CH_2), 3.24-3.22 (m, 4H, CH_2 -piperazine), 3.41-3.38 (t, 2H, CH_2), 3.77-3.68 (m, 4H, CH_2 -piperazine), 4.21-4.18 (t, 2H, CH_2), 6.55 (t, 1H, -ArH), 7.21-7.11 (m, 6H, -ArH), 7.42 (s, 1H, ArH), 7.49-7.47 (m, 1H, -ArH), 7.63-7.62 (d, 1H, -ArH), 7.78-7.76 (d, 1H, -ArH); **MS m/z:** - 388 (M^+)
Physical data: - MF: - $\text{C}_{23}\text{H}_{25}\text{N}_5\text{O}$; MW: - 388

CONCLUSION

In summary, an efficient protocol for the preparation of 2-[3-{4-(3-chlorophenyl)-1-piperazinyl} propyl]-1,2,4-triazolo [4,3-a] pyridine-3-(2H)-one hydrochloride and its derivatives was described. The reactions were carried out under thermal conditions with short reaction time and produce the corresponding products in good to excellent yields. The methodology is safer than those using conventional catalysts like H_2SO_4 , H_3PO_4 and PPA with respect to the amount, hazard and reaction conditions. Also the catalyst could be successfully recovered and recycled at least for four runs without significant loss in activity.

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