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KINETIC AND MECHANISTIC STUDIES ON OXIDATION OF DONEPEZIL HYDRO CHLORIDE BY CHLORAMINE - T IN BASIC MEDIUM

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Donepezil hydrochloride, Oxidation, Kinetics, Chloramine - T, Alkaline medium

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ABSTRACT: Donepezil hydrochloride is United States Food and Drug Administration (USFDA) approved drug marketed under the trade name "Aricept" used for the treatment of mild to moderate alzheimer disease. The aim of the current investigation was Kinetic and mechanistic study of donepezil hydrochloride by sodium-N-chloro-p-tolunesulfonamide or chloramine-T (CAT) in NaOH medium was studied at 308 K. the reaction follows first order dependence on $[CAT]_0$, fractional order dependence on $[substrate]_0$, and $[OH^-]$ ion concentration. Variation of ionic strength and addition of toluene sulfonamide have no significant effect on the rate. The reaction was studied at five different temperatures; however, the thermodynamic parameters have been assessed from the Arrhenius plots. The stoichiometry of the reaction has been established to be 1:1 and oxidation product 2-(1-benzylpiperdin-4-yl) methyl)-5-6-dimethoxy 3*H*-inden-1-ol was predicted by Chromatographic and Spectroscopic analysis. The observed results were supported by probable mechanism and the related rate law has been deduced.

INTRODUCTION: Donepezil hydrochloride (DPZ) having molecular formula $C_{24}H_{29}NO_3HCl$ and its molecular weight is 415.96 (chemically 2,3 dihydro,5,6 dimethoxy-2[2(phenyl-methyl-4 piper dinyl)]1-*H*-inden-1-one hydrochloride) it is a white crystalline powder freely soluble in water, methanol, slightly soluble in ethanol, acetonitrile, insoluble in ethyl acetate and hexane [1].

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Donepezil is an oral medication used for the treatment of mild to moderate alzheimer disease. Act as centrally and selectively acetyl cholinesterase inhibitor developed (AChE) by Esai Company Limited Tokyo, Japan. It has recently approved for marketing in USA, Canada and several EU member states including the UK. *In-vitro* studies demonstrated that DPZ has a significantly greater degree of selectivity of AChE in the central nervous system [2, 3].

The most common adverse events that led to discontinuation, more often in patients treated with DPZ than placebo were diarrhea, nausea, vomiting, urinary tract infections, decreased appetite and aggression.

Each of these adverse events led to discontinuation of less than 2% of patients treated with DPZ [4]. The diverse nature of chemistry of *n*-halo-aryl sulfonamide generally known as *N*-haloamines is of interest due to the ability to act as haloniumcations, hypohalites and *N*-anions which act as bases, nucleophiles. As a result these compounds react with wide range of functional groups and affect variety of molecular changes [5, 6]. The prominent member of this class of compounds is sodium -*N*-chloro-*p*-tolunesulfonamide or Chloramine- T (*p*-$CH_3C_6S_4SO_2NClNa.3H_2O$ and abbreviated as (CAT) and other member is Chloramine-B sodium (*N*-chlorobenzenesulfonamide).

The *N-Cl* bond in CAT and CAB highly polar hence these two compounds are fairly strong electrophiles. CAT has been used for the variety of organic inorganic substances and oxidation their mechanism kinetically well studied [7, 12]. Donepezil is one of the important drug for alzheimer disease in Healthcare Industries. Review of literature support that there is no information available on oxidation kinetics of donepezil with Chloramine-T or any oxidants in alkaline media. So the present study was under taken to study the same.

Experimental: Chloramine - T ACS reagent (>98.0 % purity) obtained from Sigma Aldrich Company Limited India. Donepezil hydrochloride purity>99.0% checked by HPLC **Fig. 1** was received from Jubilant Bioscience, Limited freshly prepared desired strength whenever required. And analytical grade chemicals double distilled water were used throughout the experiment. All calculations was calculated using *fx*-991 MS scientific calculator, regression coefficient R was made using MS-Excel program Shimadzu LC-2010 used for HPLC analysis as per USP Monograph 2010 RP $C_{18,}$ 250 × 4.6 mm 5μcolumn used. Mass spectrometer Waters Synapt Q-TOF and FT-IR Perkin Elmer KBR pellet were used for analysis.

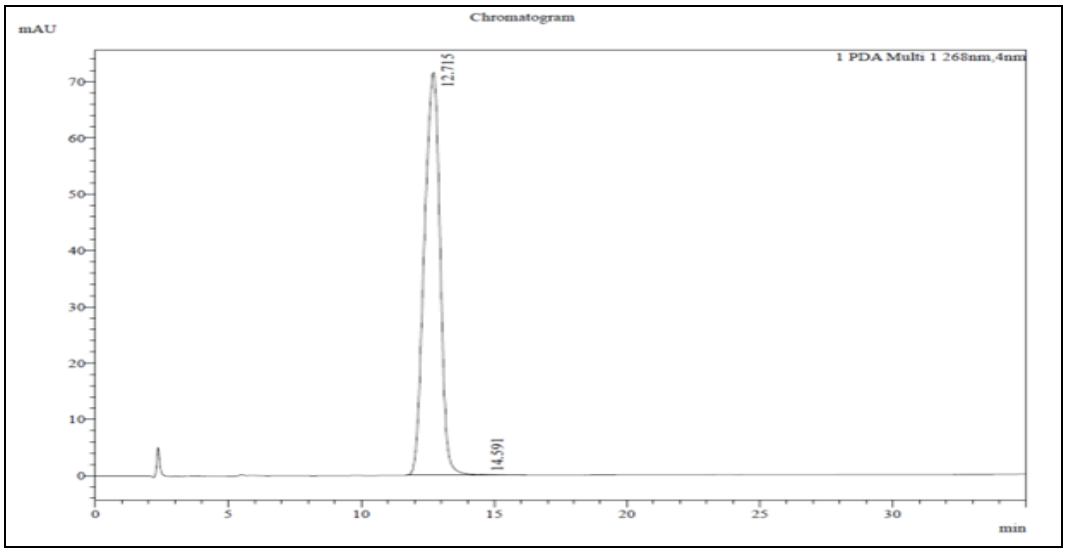


FIG. 1: HPLC CHROMATOGRAM OF DONEPEZIL HYDROCHLORIDE(RETENTION TIME 12.71)

Kinetic Procedure: The reactions were carried out pseudo first order conditions for kinetic runs. $[substrate]_0$ > $[Oxidant]_0$ required amount of donepezil, NaOH, were mixed in a stoppered brown colored bottle to prevent the photochemical reaction. Measured amount of water added to maintain a constant total volume, the tube thermo stated (Techno - ST - 405, India was used maintain the desired temperature) in a water bath at given temperature 308 K for 30 min. The reaction was initiated by adding a measured amount of pre equilibrated CAT to the mixture, the progress of reaction monitored by iodometric titration of unreacted CAT in measured aliquot 5.0 mL of mixture at different time intervals. The course of reaction was studied more than two half-lives, the rate constant ($k's^{-1}$) was calculated from the linear plots.

Stoichiometry and Product Analysis: Various ratios of CAT to DPZ were equilibrated at 308 K for 24 h. in the presence of alkali, the residual oxidant determined by iodometry and analysis shows that one mole of DPZ consumed by one mole of CAT.

$C_{24}H_{29}NO_3.HCl + TsNClNa \xrightarrow[H_2O]{NaOH}$ 2-(1-benzylpiperdin-4-yl)-5-6-dimethoxy 3*H*-inden -1- ol + $TsNH_2$ + NaCl

The reaction mixture in stoichiometric ratio in presence of base media under stirred condition was allowed to progress for 24 h. at 308 K. After completion, the reaction was monitored by thin layer chromatography [13] mobile phase chloroform: methanol 8:2. The reaction product neutralized by NaOH extracted with ether the organic product was identified by HPLC. **Fig. 2** Further confirmed by LC-MS it was molecular ion peak with m/z 380 amu **Fig. 3** and FT-IR analysis shows broad peak O-H stretching frequency at 3426 cm^{-1} C-O stretching at 1120 cm^{-1} that confirm the formation of secondary alcohol namely 2-(1-benzylpiperdin-4-yl) methyl)-5-6-dimethoxy 3*H*-inden-1-ol.

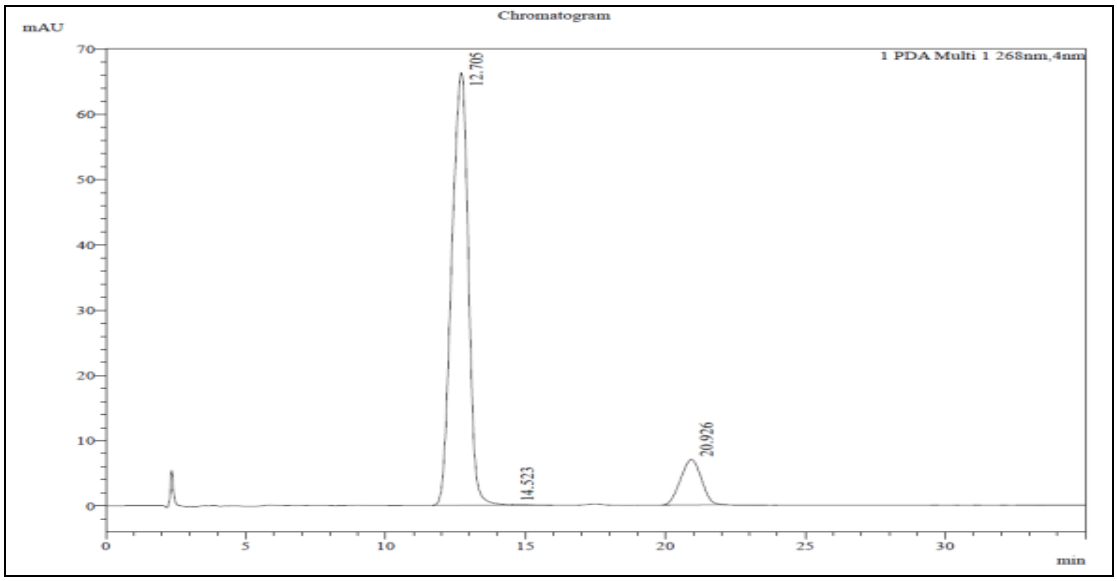


FIG. 2: OXIDATION OF DONEPEZIL HYDROCHLORIDE IDENTIFY BY HPLC RETENTION TIME 12.70 MIN DONEPEZIL AND 20.92 DONEPEZIL OXIDATION PRODUCT

Chromatographic Conditions as per USP Monograph 2010: Solutions should be prepared freshly.

Column : C18, 4.6 mm X 25cm 5µ
Wavelength : 268 nm
Flow rate : 1.2 mL/min
Mobile phase : Methanol: Buffer (2:3)
Column temp : 40 °C
Injection volume : 20µL

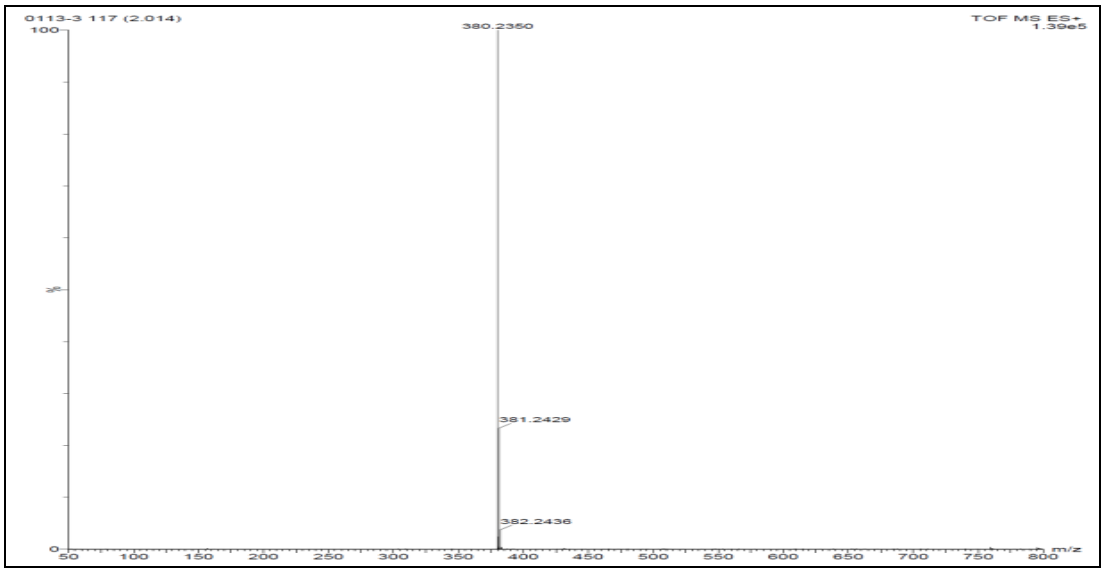


FIG. 3: LC-MS SPECTRUM OF 2-(1-BENZYLPIPERDIN-4-YL) METHYL)-5-6-DIMETHOXY 3*H*-INDEN-1-OL WITH ITS MOLECULAR ION PEAK AT 380 AMU

RESULTS AND DISCUSSION:

TABLE 1: EFFECT OF VARYING OXIDANT, SUBSTRATE AND NaOH CONCENTRATIONS ON THE RATE OF REACTION AT 308 K

10^4 [CAT] (mol dm^{-3})	10^3 [Substrate] (mol dm^{-3})	10^2 [NaOH] (mol dm^{-3})	10^4 k' (s^{-1})
2.0	9.0	2.0	3.15
4.0	9.0	2.0	3.19
6.0	9.0	2.0	3.21
8.0	9.0	2.0	3.32
4.0	5.0	2.0	2.43
4.0	7.0	2.0	2.68
4.0	11.0	2.0	3.45
4.0	13.0	2.0	3.83
4.0	9.0	0.7	2.32
4.0	9.0	0.9	2.74
4.0	9.0	4.0	3.55
4.0	9.0	6.0	3.84
4.0*	9.0	2.0	3.20
4.0**	9.0	2.0	3.31

* In presence of tolunesulfonamide; ** At ionic strength 0.2 mol/dm^{-3}

Effect of Chloramine -T Concentration on the Rate: The reaction carried out in the presence of alkaline media under pseudo first order conditions $[DPZ]_0 > [CAT]_0$ gave linear plot of log CAT versus time (R^2=0.9940) indicating pseudo first order dependence of the rate on $[CAT]_0$ rate constants($k's^{-1}$) obtained reported in **Table 1**.

Effect of Substrate Concentration on the Rate: Rate of reaction was studied at different concentrations of substrate kept all other experimental conditions constant, an increase the $[DPZ]_0$ increase the rate constants plot log k' versus log $[DPZ]_0$ was linear (R^2=0.9722) with slope 0.61; its shows fractional order dependence on $[DPZ]_0$ **Table 1**, **Fig. 4**.

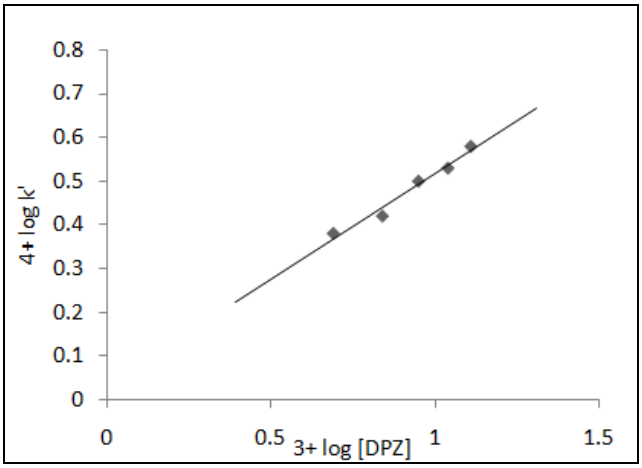


FIG. 4: PLOT 4+LOG K' *vs* 3+LOG [DPZ]

Effect of Alkali Concentration on the Rate: The rate increases with increase of the [NaOH] However, plot log k' versus log NaOH was linear with slope 0.22. This is appearance of fractional order dependence on Alkali. **Table 1**, **Fig. 5**

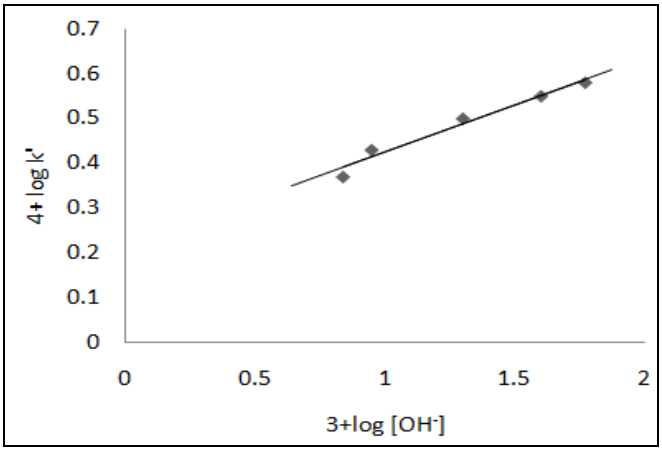


FIG. 5: PLOT 4+LOG K' *vs* 3+LOG [OH^-]

Effect of P-tolunesulfonamide Concentration on Rate: Addition of (2.0×10^{-4} - 8.0×10^{-4}mol dm^{-3}) to the reaction mixture did not alter the rate of reaction it indicates that p-tolunesulfonamide does not involved in any step prior to rate determine step.

Effect of varying Temperature on the rate: The reaction was studied at different temperature (298-318K) by keeping all other experimental conditions constant. From the linear Arrhenius plot of log k' versus 1/T **Fig. 6** values of activation parameters namely energy of activation Ea, enthalpy of formation $\Delta H^{\#}$, Gibbs free energy $\Delta G^{\#}$ and entropy $\Delta S^{\#}$, log A, were computed. **Table 2**

TABLE 2: EFFECT OF VARYING TEMPERATURE ON THE RATE OF REACTION AND ACTIVATION PARAMETERS FOR OXIDATION OF DPZ BY CAT IN ALKALINE MEDIUM

Temp (K)	10^4 k'(s^{-1})
298	2.06
303	2.45
308	3.19
313	3.69
318	4.41
E_a kJ/mol^{-1}	29.67
$\Delta H^{\#}$ kJ/mol^{-1}	27.11
$\Delta G^{\#}$ kJ/mol^{-1}	93.76
$\Delta S^{\#}$ Jk^{-1}/mol^{-1}	-216.49
Log A	3.50

$[CAT]_0 = 4.0\times10^{-4}$mol dm^{-3} $[DPZ]_0 = 9.0\times10^{-3}$mol dm^{-3} $[NaOH]_0 = 2.0\times10^{-2}$ mol dm^{-3}

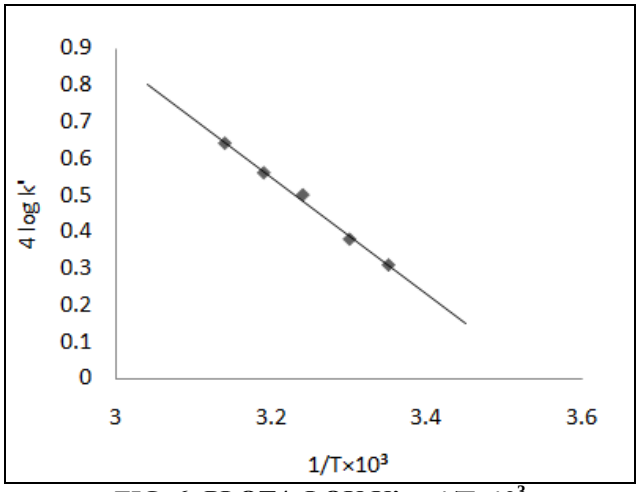


FIG. 6: PLOT4+LOK K' *vs* 1/T×10^3

Effect of Ionic Strength and Solvent Effect on the Rate of Reaction: The reaction rate remains unaffected by varying the ionic strength of the medium through an addition of sodium perchlorate (0.1 - 0.2 mol dm^{-3}), indicates nonionic species involved in the rate determining step, the dielectric permittivity of the medium was varied at different proportions of acetonitrile (0-20 %) but there is no significant change in the rate observed. **Table 3**

TABLE 3: EFFECT OF VARYING DIELECTRIC CONSTANT OF THE MEDIUM

% of CH_3CN	10^{-4} K ($k's^{-1}$)	D
0	3.19	70.08
5	2.58	69.0
10	2.63	67.3
15	2.77	65.7
20	2.87	64.2

$[CAT]_0$ = 4.0×10^{-4} mol dm^{-3} $[DPZ]_0$ = 9.0×10^{-3} mol dm^{-3} $[NaOH]_0 = 2.0\times10^{-2}$ mol dm^{-3}

Reactive Species of Chloramine - T: CAT (TsNClNa) act as oxidizing agent in both acidic and alkaline solutions CAT behaves as a strong electrolytes in aqueous solution forming different species [14, 17] equations 1, 6, 8.

$TsNClNa \rightleftharpoons TsNCl^- + Na^+$ ..…1
$TsNCl^- + H^+ \rightleftharpoons TsNHCl$ ….. 2
$TsNHCl + H_2O \rightleftharpoons TsNH_2 + HOCl$ ….. 3
$2TsNHCl \rightleftharpoons TsNH_2 + TsNCl_2$ 4
$HOCl + H^+ \rightleftharpoons H_2OCl^+$ ..… 5
$HOCl^+ \rightleftharpoons H^+ + OCl^-$ ..…6

In acidic solution of CAT probable oxidizing species were free acids (TsNHCl) dichloramine T ($TsNHCl_2$), HOCl and H_2OCl^+, in alkaline solution of CAT $TsNCl_2$ and H_2OCl^+ do not exist. Therefore the expected reactive species in basic medium are HOCl, TsNHCl and $TsNCl^-$. The possible species $TsNCl^-$, OCl^- could be transformed into more oxidizing species TsNHCl and HOCl through reaction 7 - 9.

$TsNCl^- + H_2O \rightleftharpoons TsNHCl + OH^-$ ..…7
$TsNCl^- + H_2O \rightleftharpoons TsNH_2 + OCl^-$ ….. 8
$OCl^- + H_2O \rightleftharpoons HOCl + OH^-$ …..9

If TsNHCl and HOCl are consider to be reactive oxidizing species then the retardation of rate by add $TsNH_2$ (*p*-tolunesulfonamide) and OH^- would be expected, However no such effect were observed in present case. Hence can these species can ruled out as reactive oxidizing species $TsNCl^-$ is most likely to oxidizing species in alkali accelerating the reaction with substrate.

Reaction Scheme 1:

$TsNHCl + OH^- \overset{k_1}{\rightleftharpoons} TsNCl^- + H_2O$ fast
$TsNCl^- + DPZ \xrightarrow{k_2} X_{(complex)}$ slow/rds
$X + H_2O \xrightarrow{k_3} Products$ fast

In Reaction scheme 1 DPZ represents the substrate, and X is the intermediate species. With an initial equilibrium in involves the formation of active oxidizing species of the oxidant, in the next step $TsNCl^-$ attack to substrate to form intermediate Complex (X). This step is rate determining step. Finally the intermediate complex hydrolysis to give end product where detailed plausible mechanism of oxidation of DPZ with CAT in basic medium. (**Scheme 2**)

Kinetic rate law: The total effective concentration of CAT is $[CAT]_t$ then

$[CAT]_t = [TsNHCl] + [TsNCl^-] + [X]$ …..10

By substituting [TsNHCl] and $[TsNCl^-]$ from equilibrium steps of scheme 1 in equation 10 gets.

$$[X] = \frac{K_1K_2[CAT]_t[DPZ][OH^-]}{[H_2O] + K_1[OH^-] + K_1K_2[DPZ][OH^-]} \quad .....11$$

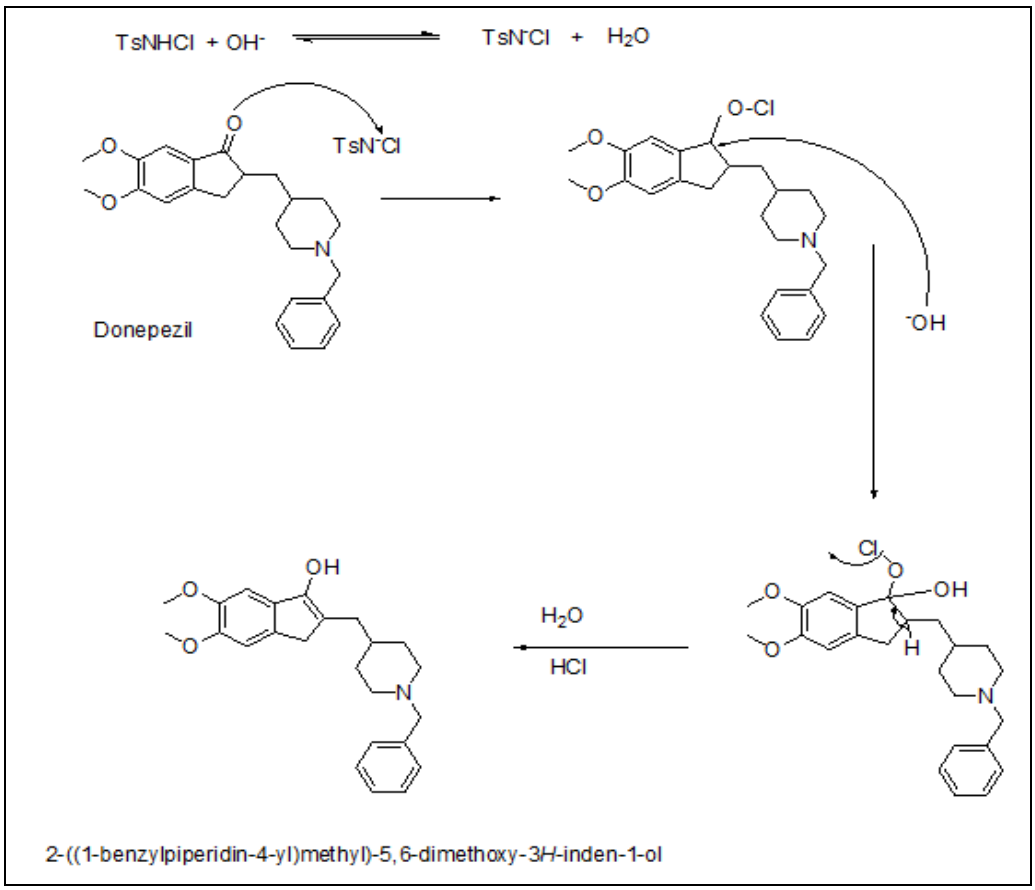
from the slow step of **Scheme 1**

Rate = $k_3[X]$…..12 by substituting [X] from 11 in to equation 12

$$\text{Rate} = \frac{K_1 K_2 K_3 [CAT]_t [\text{DPZ}] [\text{OH}^-]}{[H20 + K1\ [OH^-] + K1\ K2\ [DPZ]} \quad .....13$$

The above rate law expression (equation 13) is good agreement with experimental results, the detailed mode of oxidation of DPZ by Chloramine-T in **Scheme 2**. The proposed mechanism is supported by observed activation parameters. Further the high positive energy values of Gibbs free energy of activation and enthalpy of activation shows transition state with highly solvated while high negative value of entropy indicates for the formation of compact transition state in which several degree of freedom were lost [18].

Mechanism:



SCHEME 2: DETAILED MECHANISTIC ELUCIDATION FOR OXIDATION OF DPZ BY CAT IN BASIC MEDIUM

CONCLUSION: Donepezil hydrochloride oxidation by CAT in alkaline medium has been studied at 308 K. The stoichiometry of the reaction was found to be 1:1 oxidation products were characterized and thermodynamic parameters were computed by Arrhenius plot. The observed results have been supported by plausible mechanism. However, related rate law has been deduced.

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CONFLICT OF INTEREST: Authors do not have any conflict of interest.

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