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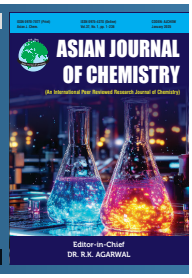

Kinetics, Pharmacokinetics, Drug-Likeness and Binding Affinity in Aqueous Iodinations of Regioisomers of Methyl Benzamine using Hydrodynamic Voltammetry, QSAR and Molecular Docking with Cytochrome P450

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Kinetics of equimolar concentrations of molecular iodine and *m*-methyl benzamine in aqueous medium has been investigated using hydrodynamic voltammetry. The study was also extended for *ortho* and *para* isomers of methyl benzamine. All the three reactions were found to be rapid and second order. Specific reaction rates, half-lives, frequency factors and energies of activation for these reactions have been determined from the kinetic data. The experimentally determined reactivity order of the three regio-isomers studied in these iodination reactions is found to be *m*-methyl benzamine > *o*-methyl benzamine > *p*-methyl benzamine. Drug-likeness and pharmacokinetics of the iodo products formed have been speculated from quantitative structure activity relationship (QSAR) models. Molecular docking simulations have been invoked to explore the binding affinities and interaction patterns of the iodo products formed with cytochrome P450 (CYP 450), a critical enzyme in drug metabolism. This experimental approach coupled with *in silico* data correlates the electrochemical propensities of the iodo products formed, of the regioisomers of methyl benzamine with their pharmacological potentials.

Keywords: Regioisomers of methylbenzamine, Molecular iodine, Rapid kinetics, Hydrodynamic voltammetry, Iodoproducts, QSAR.

INTRODUCTION

Halogenations, iodinations in particular are vital in the synthesis of bioactive compounds which enhance lipophilicity, metabolic stability and biological activities. Iodinations of aromatic substrates in aqueous solution devoid of iodide ions are rapid electrophilic aromatic substitution reactions [1,2]. The resulting organic iodo aromatic compounds are widely used in advanced organic synthesis [3,4], pharmaceutical indu-stry [5] and a variety of coupling reactions such as Kumada [6], Ullmann [7], Neigishi [8] and Suzuki [9]. Special methods are required to investigate the fast kinetics of these iodination reactions [10].

In this investigation, we have employed an inexpensive and a hands-on hydrodynamic voltammetry setup [11]. Recently, the regioisomers of nitroaniline have been iodinated using molecular iodine in aqueous solution [12]. More recently, the kinetics of *o*-methylbenzamine in aqueous medium were studied with pharmacokinetic insight from QSAR and molecular docking of its iodo product with CYP 450 [13]. Methylbenzamines, a class of aromatic amines, are known for their pharmacological relevances. The regioselective iodination of methylbenzamine regioisomers in aqueous medium offers an environmentally benign approach to generating potentially bioactive iodo derivatives. n extension to this study, herein we have studied the uncatalyzed iodinations of *m*-methylbenzamine and *p*-methylbenzamine at pH 7 at various temperatures using molecular iodine in aqueous solution devoid of iodide ions. This work focuses on the rapid iodination kinetics using hydrodynamic voltammetry, pharmacokinetics and drug-likeness of iodoproducts formed using QSAR as well as the binding affinity and the molecular interactions of the iodinated regioisomers with CYP 450.

EXPERIMENTAL

Chemicals having 99% purity were purchased from Sigma-Aldrich, USA and used as supplied. Stock solutions of 2.5×10^{-3} M potassium nitrate, 2.5×10^{-5} M *m*-methyl-benzamine and *p*-methylbenzamine and 2.5×10^{-5} M aqueous iodine were prepared in double-distilled water. In order to determine the

exact concentration of iodine solution, iodimetric titration was employed. The necessary concentrations of various solutions were prepared from these stock solutions, as indicated in Table-1. For the pH 7.0 buffer solution, stock solutions of 100 mM of monosodium phosphate (NaH_2PO_4) and disodium phosphate (Na_2HPO_4) were prepared. The pH of the solutions was measured using an Equiptronic Model EQ-610 digital pH meter. The reference electrode was the saturated calomel electrode (SCE) and the indication electrode was a rotating platinum electrode (RPE) in the hands-on hydrodynamic voltammetry setup [11].

TABLE-1
CONSTANT PARAMETERS IN THE KINETICS OF IODINATION OF *m*-METHYLBENZAMINE AND *p*-METHYLBENZAMINE IN AQUEOUS MEDIUM AT VARIOUS TEMPERATURES AT pH 7.0

Parameters	Values	Units
Potential applied at the RPE *vs.* SCE	0.10	V
Initial concentration of molecular iodine	1.25×10^{-5}	M
Initial concentration of *m*-methylbenzamine	1.25×10^{-5}	M
Initial concentration of *p*-methylbenzamine	1.25×10^{-5}	M
Concentration of KNO_3	1.25×10^{-3}	M
Total volume of the reaction mixture	100	cm^3

Calibration and kinetics: At pH 7.0, using hydrodynamic voltammetry, the rapid uncatalyzed iodination kinetics of *m*-methylbenzamine and *p*-methylbenzamine by aqueous molecular iodine were investigated. The only electro-reducible species among the reactants and products in the reaction under investigation at the applied potential of 0.10 V was iodine and the diffusion current (I_D) at the RPE showed that its concentration was declining over the duration of the reaction at different time intervals. Before beginning the kinetic analysis, the diffusion current was calibrated. Fig. 1 present the $[I_2]$ calibration at pH 7.0 and at 12.0 ºC, 17.2 ºC, 22.1 ºC, 27.5 ºC and 32.2 ºC. The necessary supporting electrolyte and buffers were kept in a thermostat along with aqueous iodine and *m*-methylbenzamine and *p*-methylbenzamine solutions one after another that were 50 mL and 2.5×10^{-5} M, respectively. Both reactants were added simultaneously to the reaction vessel with the two electrodes once the temperature was reached. After mixing, the initial concentration of both reactants decreased to 1.25×10^{-5} M after being diluted twice. At 10 sec intervals, the diffusion current at the RPE was used to record the decrease in iodine concentration over the course of the reaction. The process was done at pH 7.0 and at various temperatures. Tables 2 and 3 presents a typical set of observations about the kinetics of iodination of *m*-methylbenzamine and *p*-methylbenzamine respectively in an aqueous medium at pH 7.0. In order to determine the precise reaction rates at various temperatures, $[I_2]^{-1}$ *versus* time were plotted, as seen in Fig. 2.

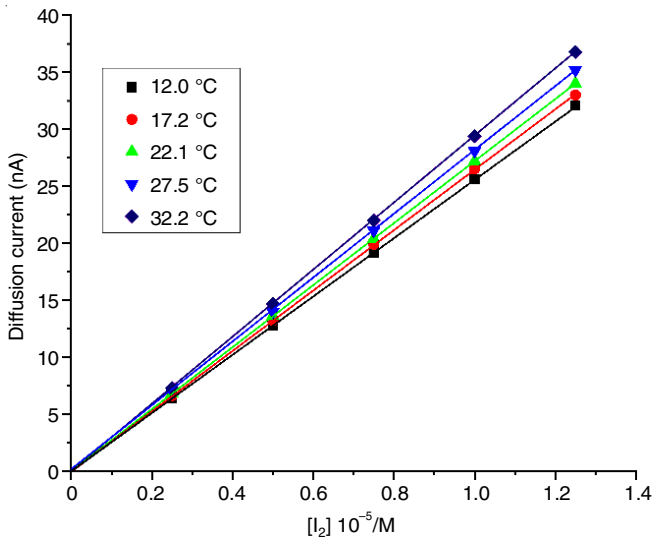


Fig. 1. Calibration of iodine solutions in aqueous medium at pH 7.0

QSAR analysis: The physico-chemical properties, lipophilicity, water solubility, pharmacokinetics, drug likeness, medi-

TABLE-2
KINETICS OF IODINATION OF *m*-METHYLBENZAMINE BY I_2 IN AQUEOUS MEDIUM AT pH 7 (± 0.2 nA error)

Time (s)	Diffusion current (nA)					$[I_2]/10^{-5}$ M					$[I_2]^{-1}/10^4$ M^{-1}				
	12.0 ºC	17.2 ºC	22.1 ºC	27.5 ºC	32.2 ºC	12.0 ºC	17.2 ºC	22.1 ºC	27.5 ºC	32.2 ºC	12.0 ºC	17.2 ºC	22.1 ºC	27.5 ºC	32.2 ºC
0	34.2	34.2	34.2	34.2	34.2	1.25	1.25	1.25	1.25	1.25	8.00	8.00	8.00	8.00	8.00
10	24.4	22.4	18.6	18.2	16.4	0.98	0.86	0.66	0.66	0.57	10.2	11.6	15.0	15.0	17.4
20	20.2	17.4	15.6	12.6	10.2	0.78	0.65	0.56	0.44	0.34	12.8	15.2	17.6	22.4	29.4
30	17.0	13.2	12.4	9.80	8.40	0.65	0.52	0.44	0.33	0.26	15.2	19.0	22.4	29.6	37.4
40	14.4	11.6	10.0	8.40	6.40	0.56	0.43	0.36	0.27	0.20	17.6	23.0	27.4	36.8	48.0
50	12.0	10.0	8.80	7.20	4.20	0.49	0.37	0.31	0.17	0.15	20.2	26.8	32.0	42.0	54.0

TABLE-3
KINETICS OF IODINATION OF *p*-METHYLBENZAMINE BY I_2 IN AQUEOUS MEDIUM AT pH 7 (± 0.2 nA error)

Time (s)	Diffusion current (nA)					$[I_2]/10^{-5}$ M					$[I_2]^{-1}/10^4$ M^{-1}				
	12.0 ºC	17.2 ºC	22.1 ºC	27.5 ºC	32.2 ºC	12.0 ºC	17.2 ºC	22.1 ºC	27.5 ºC	32.2 ºC	12.0 ºC	17.2 ºC	22.1 ºC	27.5 ºC	32.2 ºC
0	32.1	33.0	34.0	35.2	36.8	1.25	1.25	1.25	1.25	1.25	8.00	8.00	8.00	8.00	8.00
10	31.8	31.6	32.0	33.4	32.6	1.23	1.20	1.17	1.19	1.16	8.10	8.30	8.50	8.40	8.60
20	31.2	31.0	31.0	31.6	32.0	1.21	1.17	1.13	1.12	1.08	8.20	8.50	8.84	8.90	9.20
30	30.6	29.6	30.5	29.8	30.0	1.19	1.14	1.12	1.06	1.02	8.40	8.70	8.90	9.40	9.80
40	29.8	28.6	30.0	28.4	28.2	1.16	1.12	1.10	1.01	0.96	8.60	8.90	9.00	9.90	10.4
50	29.2	28.4	29.5	27.4	26.4	1.14	1.08	1.08	0.97	0.90	8.70	9.20	9.20	10.3	11.0

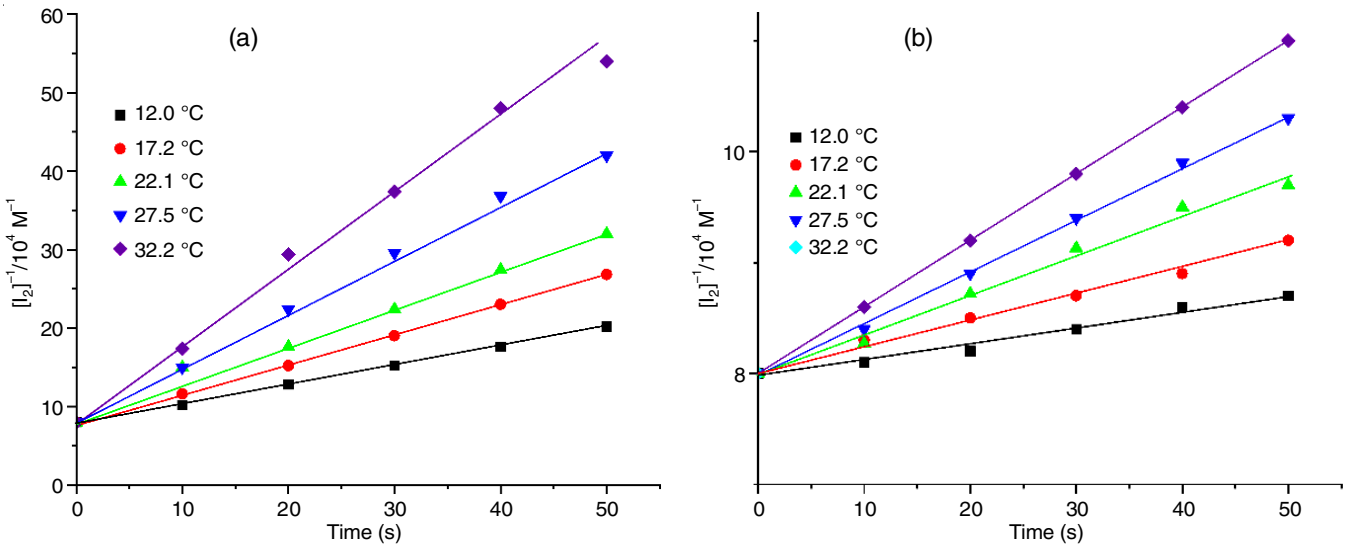


Fig. 2. Kinetics of uncatalyzed iodination of (a) *m*-methylbenzamine and (b) *p*-methylbenzamine in aqueous medium at pH 7.0

cinal chemistry of the iodo-product of regioisomers of methyl benzamine were obtained from online QSAR model Swiss-ADME [14]. Lipinski's rule of five, bioavailability scores and ADMET properties were also evaluated [15].

Molecular docking: Molecular docking was performed using MGL Tools 1.5.6 software with the Auto Grid 4.2.6 and Auto Dock 4.2.6 packages [16,17]. The 'Swiss Target Prediction' web server (http://www.swisstargetprediction.ch) was used to predict the target molecule of the product ligand, *i.e.* the iodo product of *m*-methylbenzamine and *p*-methylbenzamine. CYP was the best target suggested. 6cir, a stable, high-expression variant of human CYP, was downloaded from PDB (www.rcsb.org). The downloaded structure was processed in Discovery Studio to remove water, heteroatoms and ligands. The processed protein structure was saved as a protein PDB file. In the MarvinSkech software, 3D structures of 4-iodo-3-methylbenzamine and 2-iodo-4-methylbenzamine were drawn and saved separately as ligand PDB files. The optimized PDBQT structure of enzyme CYP and ligands 4-iodo-3-methylbenzamine and 2-iodo-4-methylbenzamine were used in the molecular docking study. Lamarckian genetic algorithm (GA) 4.2 was used in this docking study. Polar hydrogen and Kollman charges were added before starting molecular docking. Auto grid was used to set the grid point. All other parameters were set to the default setting and 10 docking runs were carried out.

RESULTS AND DISCUSSION

Reaction conditions leading to product formation: In aqueous solution, halogenations of aromatic substrates are pH-dependent processes [18]. In order to iodinate *m*-methylbenzamine and *p*-methylbenzamine by molecular iodine in an aqueous solution free of iodide ions, pH 7 has been employed. Hydrolysis of molecular iodine in an aqueous medium produces iodide ions, hydrogen ions and hypoiodous acid.

$$I_2 + H_2O \rightleftharpoons HOI + H^{\oplus}_{aq.} + I^{\ominus}_{aq.}$$

Taking into account the magnitude of the equilibrium constant (5.4×10^{-13} M^2) for iodine hydrolysis, diluted aqueous solutions employed in this investigation. The concentration of iodide ions in these solutions is insignificant since the equilibrium is moved much to the left [19]. Electrophilic substitution reactions occur during the iodination of these aromatic substrates. The -NH_2 and -Me groups in the aromatic substrate methylbenzamine isomers are *ortho*-, *para* directing, in *m*-methylbenzamine, the combined effect of these groups results in the formation of 4-iodo-3-methyl aniline (*p*-iodo *m*-methylbenzamine). While in *p*-methylbenzamine, the combined effect of -NH_2 and -CH_3 results in 2-iodo-4-methyl aniline (*o*-iodo *m*-methylbenzamine). This was determined using stoichiometric analysis and chromatography.

Calculation of specific reaction rate k: A plot of $[I_2]^{-1}$ *vs.* time was found to be linear, confirming that the reaction is of the second order. The slope of this plot is the specific reaction rate. The second-order velocity constant for iodination of *m*-methylbenzamine was found to be 9778 Ms^{-1} at 22.10 ºC and the second-order velocity constant for iodination of *p*-methylbenzamine was found to be 55.55 M s^{-1} at pH 7.0.

Energy of activation (E_a): The activation energy (E_a) of iodination of *m*-methylbenzamine and *p*-methylbenzamine in aqueous solution was obtained from the Arrhenius plot of the reaction, which was studied at five different temperatures. The variation of specific reaction rates with temperatures at pH 7.0 is reported in Table-4. The E_a was calculated by using eqn. 1. Iodination of *m*-methylbenzamine and *p*-methylbenzamine was found to be was 18.96 and 51.05 kJ mol^{-1}, respectively.

$$E_a = -2.303 \times R \times \text{Slope of the plot log k } vs.\ T^{-1} \quad (1)$$

Pre-exponential or frequency factor (A): The values of E_a and k were used to calculate the frequency factor A using the Arrhenius equation. Using eqns. 2 and 3, the value of A was calculated. Iodination of *m*-methylbenzamine and *p*-methylbenzamine was found to be 2.2×10^7 M^{-1} s^{-1} and 1.087×10^9 M^{-1} s^{-1}, respectively.

$$k = A.\exp\left(-\frac{E_a}{RT}\right) \quad (2)$$

TABLE-4
VARIATION OF SPECIFIC REACTION RATES OF IODINATION OF *m*-METHYLBENZAMINE AND *p*-METHYLBENZAMINE BY I_2 IN AQUEOUS MEDIUM WITH TEMPERATURE AT pH 7.0 (± 0.2 nA error)

Temp. (ºC)	Temp. (K)	$[T]^{-1}/10^{-3}$ K^{-1}	*p*-Methylbenzamine		*m*-Methylbenzamine	
			k_2/M^{-1} s^{-1}	log k_2	k_2/M^{-1} s^{-1}	log k_2
32.2	305.2	3.276	102.27	2.0097	18000	4.225
27.1	300.5	3.327	77.16	1.8873	13330	4.124
22.1	295.2	3.387	55.55	1.7446	9777.7	3.990
17.2	290.2	3.445	39.47	1.5962	7789.7	3.890
12.0	285.0	3.508	25.64	1.4089	5000.0	3.690

$$\log A = \log k + \frac{E_a}{2.303RT} \quad (3)$$

Entropy of activation ($\Delta S^{\ddagger}$): All the reactions are in aqueous solution, hence, eqn. 4 was used to calculate $\Delta S^{\ddagger}$.

$$\Delta S^{\ddagger} = 2.303R \log k - 2.303R \log\left(\frac{ekBT}{h}\right) + \frac{E_a}{T} \quad (4)$$

In eqn. 4, R is the molar gas constant (8.314 JK^{-1} mol^{-1}), k is the specific reaction rate at temperature T in Kelvin, e = Euler's number = 2.718, kB is Boltzmann's constant (1.38×10^{23} JK^{-1}) and h is Planck's constant (6.67×10^{-34} Js).

The $\Delta S^{\ddagger}$ for the iodination of *m*-methylbenzamine was found to be -112.16 M^{-1} s^{-1} and -243.51 M^{-1} s^{-1}, respectively. Entropy of activation is negative for the reaction studied, indicating an associative mechanism and gives evidence of the formation of a stable arenium ion intermediate in the iodination reaction studied. The reactions studied and plausible mechanisms for iodination of *m*-methylbenzamine and *p*-methylbenzamine in aqueous medium are suggested in **Schemes I** and **II**.

In present study, the aqueous iodination reaction of *m*-methylbenzamine had a half-life of 8 s and that of *p*-methylbenzamine 1441 s at 22.10 ºC. From the previously published work, the aqueous iodination of *o*-methylbenzamine reaction had a half-life of 90 s at 22.10 ºC [13]. This indicates that *m*-methylbenzamine has the highest reactivity among the three regioisomers. The reactivity order for rapid iodination of two methylbenzamine isomers is as follows:

m-methylbenzamine > *o*-methylbenzamine > *p*-methylbenzamine

Out of the three methylbenzamine regioisomers, the relative reactivity of iodination had only been speculated qualitatively using stereochemical principles and direct kinetic measurement for a quantitative evaluation was *hitherto* lacking, probably due to the rapidity these reactions. The reactivity is dependent upon the nucleophilicity of the aromatic ring, influenced by the donating characteristics of nitrogen, the induced electrophilicity of iodine and the associated stereochemical constraints. *m*-Methylbenzamine is the fastest among all the regioisomers of methylbenzamine due to less steric compulsion and the donating effect of the *ortho* directing methyl group and *para* directing $-NH_2$ group operative in unison.

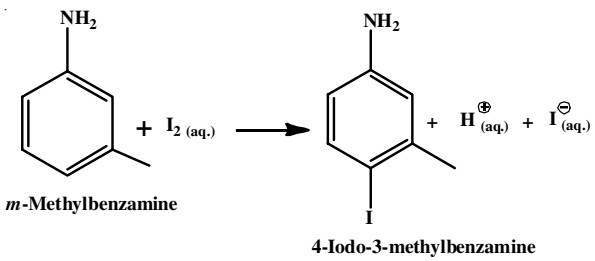
QSAR predictions: The physico-chemical descriptors, druglikeness and pharmacokinetic properties were predicted using the QSAR models and are reported in Tables 5-7, respectively. The results indicated that the iodinated regioisomers are adhered to the Lipinski's rule, with improved lipophilicity and bioavailability compared to their parent compounds. All the iodo-derivatives exhibited the Druglikeness score.

Molecular docking: To ensure the biological activity of the iodoproducts formed, their binding with CYP 450 has been computed by the *in silico* method of molecular docking . The minimum binding energies of molecular docking were found to be -4.23 kcal, -5.78 kcal and -5.70 kcal for the iodo-products of iodinations of 2-methylbenzamine, 3-methylbenzamine and 4-methylbenzamine, respectively. The 2D interactions and 3D interactions of molecular docking of regioisomers of methyl benzamine are shown in Fig. 3.

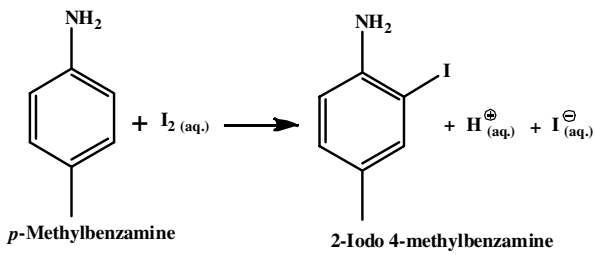
Molecular docking studies revealed that the iodinated products exhibited favourable binding interactions with CYP 450. The *m*-iodo derivative displayed the strongest binding affinity, with hydrogen bonding and hydrophobic interactions playing critical roles. The quantitative parameters of regioisomers of methyl benzamine are summarized in Table-8.

Conclusion

This study provides the quantitative evidences for rapid aqueous iodination of equimolar concentrations of iodine and methylbenzamine regioisomers. The QSAR and molecular docking studies of the iodoproducts of the regioisomers of methylbenzamine exhibits their druglikeness, pharmacokinetic

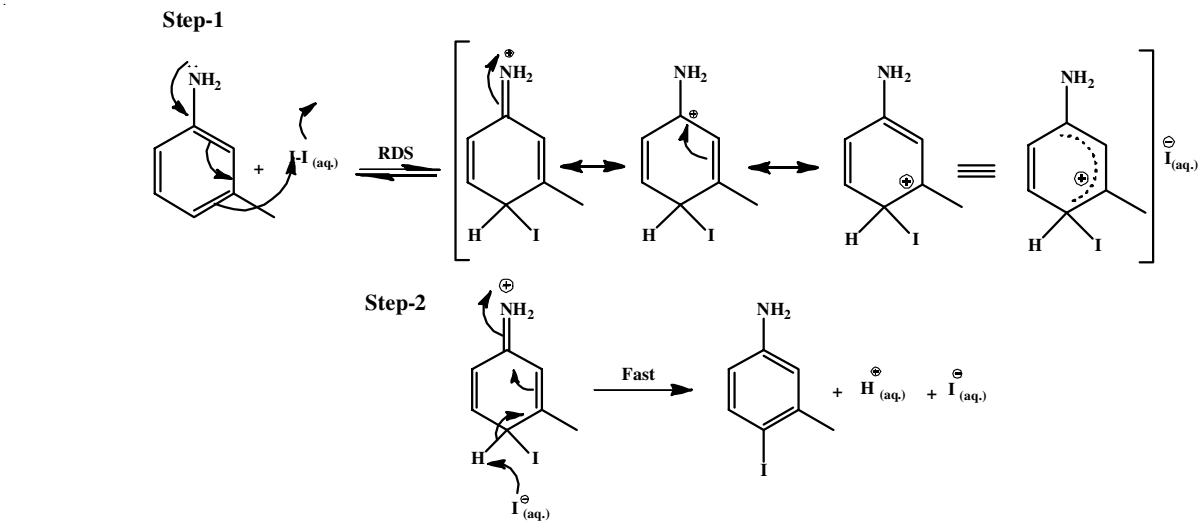


(a) Iodination of *m*-methyl benzamine

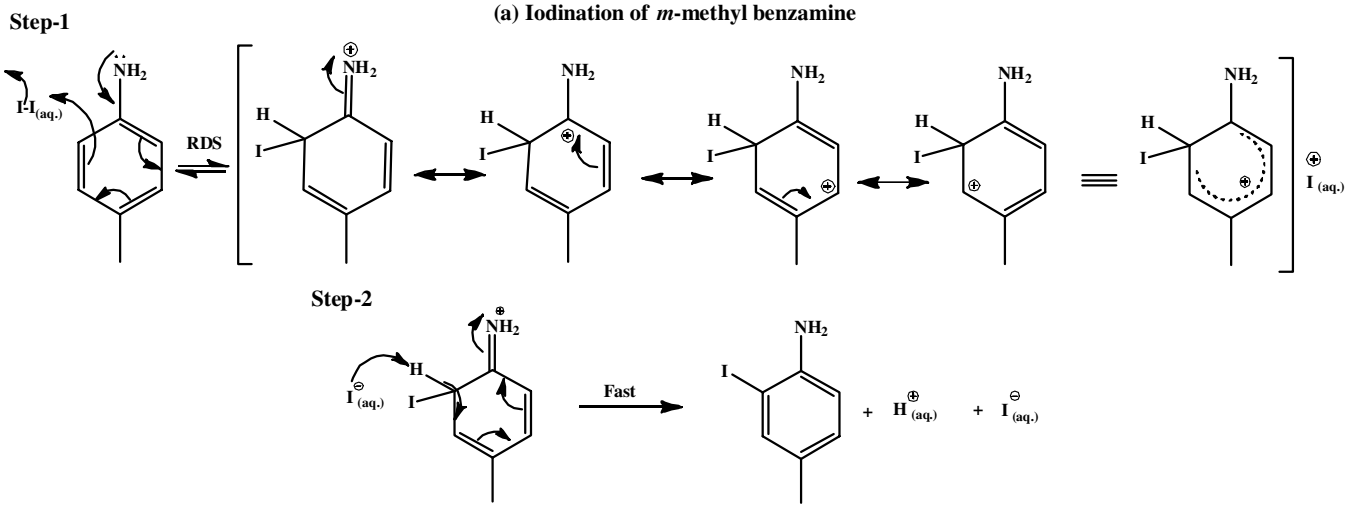


(b) Iodination of *p*-methyl benzamine

Scheme-I: Iodination of *meta*- and *para*-methyl benzamine



(a) Iodination of *m*-methyl benzamine



(b) Iodination of *p*-methyl benzamine

Scheme-II: Plausible mechanisms of iodination of *meta*- and *para*-methyl benzamine

TABLE-5
PHYSICO-CHEMICAL DESCRIPTORS OF IODOPRODUCTS OF REGIOISOMERS OF METHYLBENZAMINE

Physico-chemical descriptors	4-Iodo-2-methylbenzamine	4-Iodo-3-methylbenzamine	2-Iodo-4-methylbenzamine
Formula	C_7H_8IN	C_7H_8IN	C_7H_8IN
Molecular weight	233.05 g/mol	233.05 g/mol	233.05 g/mol
Num. heavy atoms	9	9	9
Num. arom. heavy atoms	6	6	6
Fraction Csp3	0.14	0.14	0.14
Num. rotatable bonds	0	0	0
Num. H-bond acceptors	0	0	0
Num. H-bond donors	1	1	1
Molar refractivity	48.53	48.53	48.53
TPSA	26.02 Å^2	26.02 Å^2	26.02 Å^2

TABLE-6
DRUGLIKENESS OF IODO PRODUCTS OF REGIOISOMERS OF METHYLBENZAMINE

Druglikeness	4-Iodo-2-methylbenzamine	4-Iodo-3-methylbenzamine	2-Iodo-4-methylbenzamine
Lipinski	Yes, 0 violation	Yes, 0 violation	Yes, 0 violation
Ghose	No, 1 violation: #atoms < 20	No, 1 violation: #atoms < 20	No, 1 violation: #atoms < 20
Veber	Yes	Yes	Yes
Egan	Yes	Yes	Yes
Muegge	No, 1 violation: Heteroatoms < 2	No, 1 violation: Heteroatoms < 2	No, 1 violation: Heteroatoms < 2
Bioavailability score	0.55	0.55	0.55

TABLE-7
PHARMACOKINETICS OF IODOPRODUCTS OF REGIOISOMERS OF METHYLBENZAMINE

Pharmacokinetics	4-Iodo-2-methylbenzamine	4-Iodo-3-methylbenzamine	2-Iodo-4-methylbenzamine
GI absorption	High	High	High
BBB permeant	Yes	Yes	Yes
P-gp substrate	No	No	No
CYP1A2 inhibitor	Yes	Yes	Yes
CYP2C19 inhibitor	No	No	No
CYP2C9 inhibitor	No	No	No
CYP2D6 inhibitor	No	No	No
CYP3A4 inhibitor	No	No	No
log K_p (skin permeation)	-6.32 cm/s	-6.21 cm/s	-6.32 cm/s

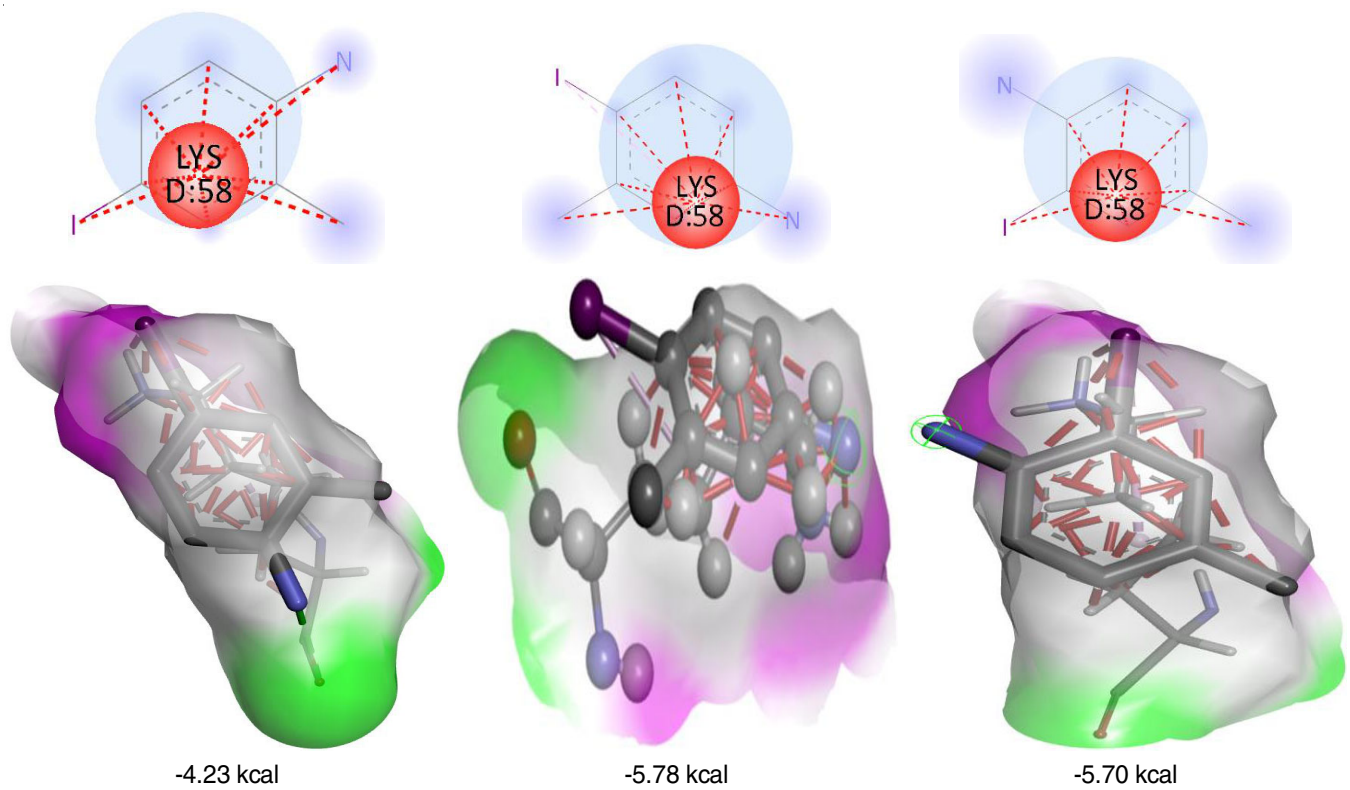


Fig. 3. 2D and 3D interaction of molecular docking of regioisomers of methyl benzamine with CYP 450

TABLE-8
QUANTITATIVE PARAMETERS OF REGIOISOMERS ARE SUMMARIZED AS FOLLOWS

	o-Methylbenzamine	*m*-Methylbenzamine	*p*-Methylbenzamine
Half life ($t_{1/2}$)	90 s	8 s	1441 s
Reaction rate (k_2)	893 M^{-1} s^{-1}	9778 M s^{-1}	56 M s^{-1}
Energy of activation (E_a)	24.07 kJ mol^{-1}	18.96 kJ mol^{-1}	51.05 kJ mol^{-1}
Frequency factor (A)	1.62×10^7 M^{-1} s^{-1}	2.200×10^7 M^{-1} s^{-1}	1.087×10^9 M^{-1} s^{-1}
Entropy of activation ($\Delta S^{\ddagger}$)	-114.61 JK^{-1} mol^{-1}	-112.16 JK^{-1} mol^{-1}	–243.51 JK^{-1} mol^{-1}
Binding energy	-4.23 kcal	-5.78 kcal	-5.7 kcal

behaviour and binding affinities towards CYP 450. The combined experimental and computational approach provides valuable insights into the design of iodinated bioactive molecules with potential therapeutic applications. The regioisomeric nature of methylbenzamine significantly influences their iodination kinetics, drug-likeness, pharmacokinetics and interactions with CYP 450 enzyme. *m*-Methylbenzamine exhibits the most favourable combination of rapid iodination, druglikeness and binding affinity with CYP 450, making it a promising scaffold for further drug development. Future studies will explore *in vitro* and *in vivo* pharmacological evaluations of these iodinated derivatives.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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