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RESEARCH PAPER

Synthesis, In Silico Study and Antiurease Potential of Imine Derivatives

Muhammad Sarfraz[1] · Shahbaz Ahmad[1] · Muhammad Ilyas Tariq[1] · Muhammad Naeem Qaisar[2]

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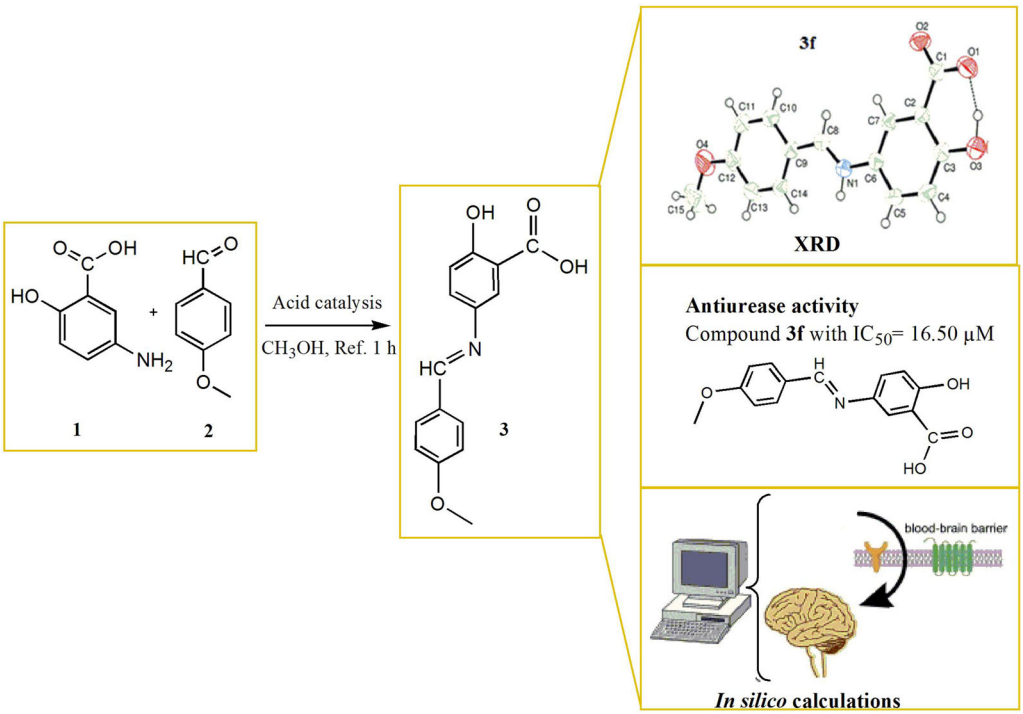
Abstract

In search of potent urease inhibitors, we have biologically evaluated our synthesized imine derivatives against jack bean urease. In vitro assay results showed that compound **3f** with IC_{50} value of 16.50 ± 0.20 μM can be considered as the most potent urease inhibitor, whereas compounds **3a** (IC_{50} = 23.10 ± 0.11 μM) and **3n** (IC_{50} = 23.34 ± 0.21 μM) were second and third most potent inhibitors, respectively. In silico study revealed that all compounds have good penetration across BBB and HIA; however, AMES toxicity and carcinogenic profiles of more than half of the compounds were not satisfactory. Leading compound **3f** was predicted to have very less penetration across BBB, whereas pharmacokinetic profile of compound **3l** was better than all other compounds with no toxicity and carcinogenicity. The synthesized compounds can be used as structural foundation for the preparation of new potent urease inhibitors.

Graphical Abstract



✉ Muhammad Sarfraz
sarfrazzed@gmail.com

[1] Department of Chemistry, University of Sargodha, Sargodha, Pakistan

[2] Department of Pharmacy, University of Sargodha, Sargodha, Pakistan

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1 Introduction

Enzyme inhibition has emerged as an important research area in the field of medicinal sciences since last couple of decades. Various biomedical scientists have discovered a variety of enzyme inhibitors which are reported to be effective for the control of different diseases and disorders (de Castro Barbosa et al. 2014; Sarfraz et al. 2017; Sultana et al. 2017; Jamil et al. 2017). These inhibitors bind to enzyme either by irreversible or by the reversible mechanism. Reversible inhibitors are further classified into two groups on the basis of binding interactions with enzyme, i.e., a competitive or a non-competitive binding. It has been observed that binding in reversible inhibitors occurs through a number of non-covalent interactions like hydrophobic interaction, hydrogen bonding and orientation of inhibitor and enzyme in an organized fashion (Amtul et al. 2002).

Urease enzyme acts as virulence factor in the pathogens responsible for kidney stones, thus contributing toward the development of acute pyelonephritis along with other urinary tract infection which leads toward arthritis and gastric intestinal infections, and ultimately, this imbalance of urease is responsible for causing peptic ulcers (Mobley and Hausinger 1989). Due to involvement of urease in various physiological functions and associated health implications, urease inhibition has attracted attention of medicinal chemists now a day. These inhibitors are known to play a vital role in controlling the Helicobacter pylori which is responsible to cause an imbalance of ammonia levels in cirrhotic patients (Zullo et al. 1998). These inhibitors have capability of dissolving crystals and struvite kidney stones along with preventing the development of new crystals in the urine. A number of diversified natural and synthetic antiurease compounds have been reported in the literature which are of good pharmacological importance (Sarfraz et al. 2017; Upadhyay 2012; Shah and Soomro 2012). Urease inhibitors have been extensively studied due to their different potential uses including therapy against bacterial urease, to protect soil from pH elevation after use of urea fertilizers by controlling hydrolysis of urea in soil and as an analytical technique for determining substances acting as enzyme inhibitors (Mobley et al. 1995). The literature shows that biological significance and developed resistance for a large number of urease inhibitors (synthetic and natural origin) have attracted the attention of the scientists to design and study new versatile urease inhibitors (Amtul et al. 2002).

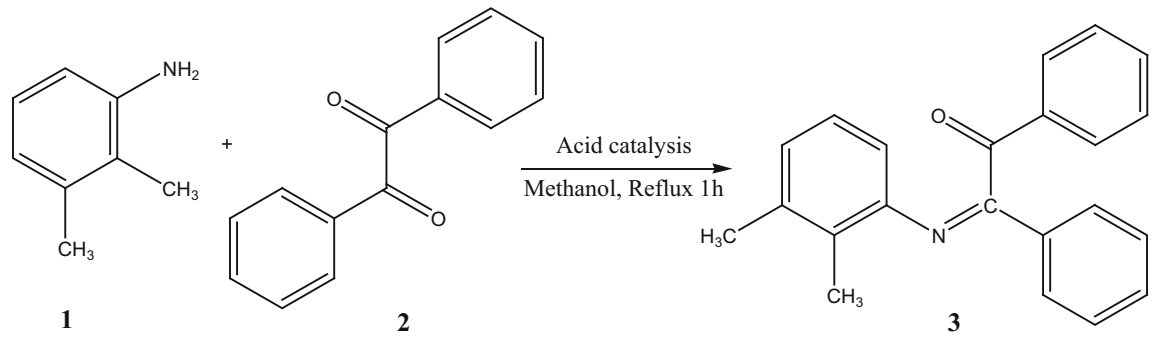
The chemistry of –C=N plays an important role in the progress of chemical sciences (Patai 1970). Imines or Schiff bases are the famous –C=N containing compounds named after Hugo Schiff, who discovered them in 1864, which have been extensively used in industry for the preparation of a large number of industrially important chemicals, compounds and medical substrates (Mahmud et al. 2010). Imines are capable of undergoing cycloaddition, ring closure and replacement reactions other than a number of versatile type of chemical transformations. Imine compounds have approved to be an important intermediate in a number of enzymatic reactions where interaction of the amino group of an enzyme with a carbonyl group of the substrate is involved (Lehlinger 1975). Imines are the unique ligands having structural similarities with those of natural biological substances, easy to prepare and possess flexible synthetic routes that enable researchers to design suitable structural properties (Jungreis and Thabet 1969). Many imine compounds have been synthesized from certain aromatic amines and derivatives of aromatic aldehydes, and the fluorescence properties have been studied in acidic as well as basic media (Ibrahim and Sharif 2007). Schiff bases have also been reported to display a wide range of biological activities, like antibacterial, antifungal, antimalarial, anti-inflammatory, antiproliferative, antiviral, antipyretic and cytotoxic (Tarafder et al. 2002; Vicini et al. 2003; Kahveci et al. 2005; Bekircan et al. 2006).

We have already reported potential of anthranilamide derivatives as urease inhibitor (Sarfraz et al. 2017). In order to extend our research for the discovery of potent urease inhibitors and due to overwhelming biological potential of imine compounds, we have chosen imine compounds for evaluation of their urease inhibition potential.

2 Result and Discussion

Aromatic imine compounds constitute an important class of organic compounds having extensive extended conjugation due to mobile л electron system. This conjugation is responsible for stability of these compounds as well as attitude toward a number of chemical transformations. Since the discovery of Schiff bases in 19th century, a variety of methods for the synthesis of imines have been described (Zheng et al. 2009). Condensation reaction of different carbonyl compounds with primary amines/phenyl hydrazine was carried out to afford corresponding imine compounds **3a**–**p** under acid catalysis (HCl/HNO_3 = 1:1). Synthetic scheme for representative compound **3a** shows that 2,3-dimethyl aniline **1** reacts with benzil **2** to form (2Z)-2-[(2,3-dimethylphenyl)imino]-1,2-diphenylethanone **3** under reflux conditions.

It was noted that substitution at only one carbonyl group of the benzil has been observed even after using two equivalents of corresponding aniline as shown in Scheme 1. By varying amino **1** and carbonyl compound **2**,



Scheme 1 Synthesis of (2Z)-2-[(2,3-dimethylphenyl)imino]-1,2-diphenylethanone **3**

we were able to synthesize different imine compounds as shown in Table 1.

Reaction time and yield of the synthesized imine compounds **3a**–**p** varied depending upon the steric hindrance and reactivity of amino **1** and carbonyl **2** compounds. Among all, highest yield (87%) was obtained for compound **3d**, whereas lowest yield (56%) was reported for compound **3h**. Melting point of all synthesized compounds ranged from 161 to 229 °C, and highest m.p. was noted for compound **3a**. Reaction time for reported synthesis was also variable, and lowest reaction time (25 min) was reported for compound **3e** with phenyl hydrazine and 2-nitro benzaldehyde as reactants, whereas highest reactions time 2.5 h was noted for compound **3c** having 4-(dimethylamino)benzaldehyde as reactant. FTIR spectra showed that C=N peak varied from 1620 to 1664 cm^{-1} in all compounds. Assignment of peaks in ^{1}H NMR spectra of all synthesized compounds was carried out on the basis of their chemical shift values, ^{1}H signals position in aromatic or aliphatic regions and coupling constants. Disappearance of peaks for NH_2 and appearance of singlet ranging from 8.18 to 8.46 ppm corresponding to –CH in all synthesized compounds except **3a** confirmed the formation of imine compounds. All other resonances were assigned on the basis of comparison with the literature of structural related compounds and additive rules for the ^{1}H-NMR shifts.

Suitable crystals of desired product **3a**–**p** were grown in ethanol/diethyl ether (64:40) and single-beam X-rays crystallographic analysis of the synthesized compounds was carried out for confirmation of the structure. ORTEP diagrams of few representative compounds are shown in Fig. 1.

2.1 In Vitro Antiurease Activity

The urease enzyme hydrolyses urea to carbamic acid and ammonia and carbamic acid on further decomposition produces carbon dioxide and ammonia which ultimately elevate *p*H. Inhibition of urease enzyme is of vital importance to suppress the negative role of urease in living organisms which will reduce infections including gastric and peptic ulcers, proteus-related species in the urinary tract, hepatic encephalopathy, hepatic coma urolithiasis and pyelonephritis resulted due to the production of excess ammonia urease activity of *Helicobacter pylori*. Therefore, inhibitors of urease activity may have potential of being used as antiulcer drugs (Mobley et al. 1995; Li and Mobley 2002). All the synthesized compounds were screened against *jack bean urease* (JBU), and IC_{50} values are summarized in Table 1.

The IC_{50} value of all these compounds ranged from 16.50 ± 0.20 to 96.40 ± 0.5 μM, and only one compound **3f** showed IC_{50} value better than standard drug thiourea. Compound **3a** which is the derivative of benzil has IC_{50} value of 23.10 ± 0.11 μM and can be considered the second most active urease inhibitor, whereas compound **3n** with IC_{50} = 23.34 ± 0.21 μM is the third most active urease inhibitor compound. Generally, all compounds possessing chloro, methoxy or nitro substituents at *meta* and *para* position of the benzaldehyde or amino compound possessed better activity than other compounds. Antiurease activity of compounds synthesized by using aliphatic aldehydes revealed that these compounds are good enzyme inhibitor. However, among all, compound **3f** with a number of hydrogen binding sites along with having balanced hydrophilic and lipophilic sites can be considered the most potent urease inhibitor (IC_{50} = 16.50 ± 0.20 μM).

2.2 Preliminary In Silico Pharmacokinetic

The purpose of this study is to predict the synthesized compounds for penetration across blood–brain barrier (BBB), human intestinal absorption (HIA), AMES toxicity (AT) and their carcinogenicity. *In silico* pharmacokinetic studies of all synthesized compounds were carried out using online ADMET SAR server, and predicted properties were compared with the standard drug donepezil as shown in Table 2. All compounds were having good HIA and penetration across BBB. However, more than 50% compounds were predicted to have AT and carcinogenic

Table 1 In vitro urease inhibitory activity of the synthesized compounds **3a–p**

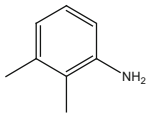
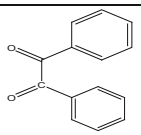
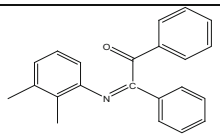
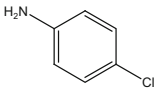
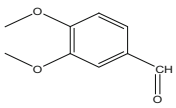
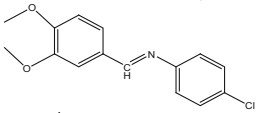
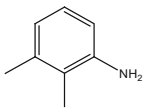
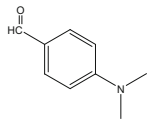
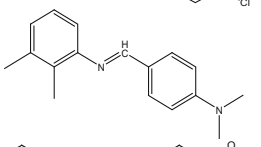
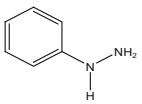
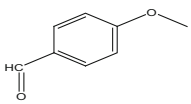
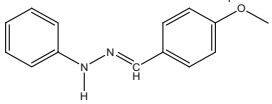
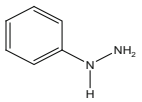
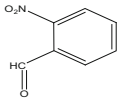
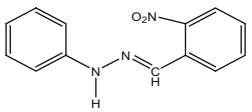
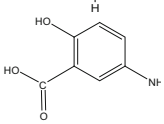
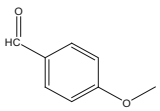
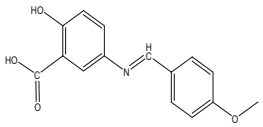
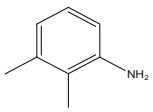
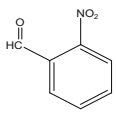
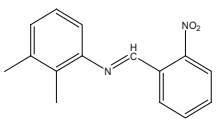
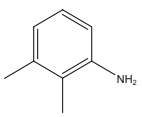
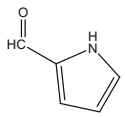
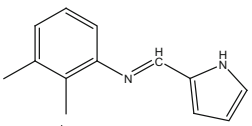
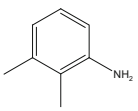
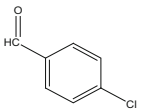
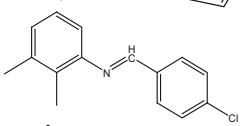
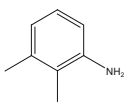
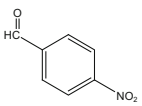
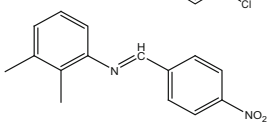
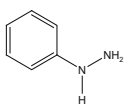
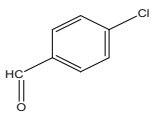
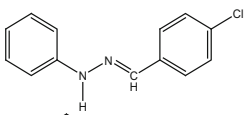
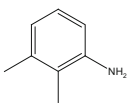
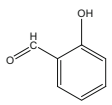
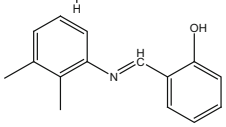
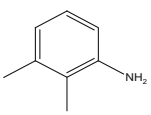
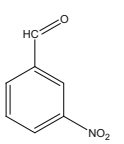
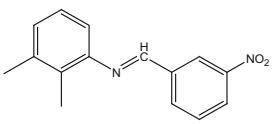
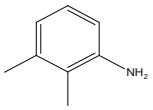
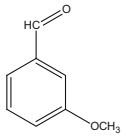
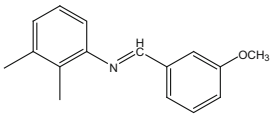
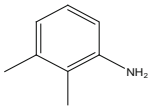
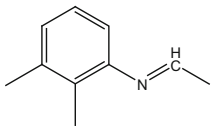
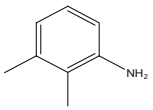
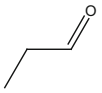
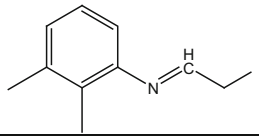
Compound	1	2	3	Yield (%)	IC50 (μM ±SEM)a	Refs.
3a				69	23.10 ± 0.11	Tariq et al. (2010a)
3b				72	32.32 ± 0.05	Tahir et al. (2010a)
3c				83	86.20 ± 0.10	Sarfraz et al. (2010)
3d				87	96.40 ± 0.05	Mufakkar et al. (2010)
3e				85	71.30 ± 0.15	Shad et al. (2010)
3f				81	**[b]16.50 ± 0.20**	Tahir et al. (2010b)
3g				68	65.00 ± 0.10	Tahir et al. (2010c)
3h				56	28.80 ± 0.15	Tahir et al. (2010d)
3i				84	41.81 ± 0.19	Tahir et al. (2010e)
3j				72	42.70 ± 0.19	Tariq et al. (2010b)
3k				71	39.37 ± 0.08	Tahir et al. (2011)
3l				70	26.85 ± 0.12	Tahir et al. (2010f)
3m				78	34.55 ± 0.14	

Table 1 continued

3n				79	23.34 ± 0.21
3o				85	88.37 ± 0.18
3p				81	82.68 ± 0.19
		Thiourea			**21.0 ± 0.01**

[a]Values are expressed as mean (standard error of the mean of at least three experiments)

[b]Bold values are for highly active compounds

behavior. Most active compound **3f** was having good probabilities for non-AT and non-carcinogenicity along with HIA except having very less possibility to cross BBB. On the other hand, second more potent compound **3a** was predicted to have very good BBB and HIA probabilities, but it was AMES toxic and carcinogenic as well. Among all, only one compound **3l** was have been predicted to have good penetration across BBB and HIA probabilities along with having non-AT and non-carcinogenic behavior. So compound **3l** with IC_{50} = 26.85 ± 0.12 μM can be considered to have good pharmacokinetic properties and better safety profile.

3 Materials and Methods

Chemicals and reagents employed for the synthesis of all compounds were of analytical grade and 2, 3 dimethylaniline was procured from E-Merck (1668), Germany; 4-chloroaniline from E-Merck (1668), Germany; 2-nitrobenzaldehyde from Tianjin Pharmacn Medical Technology Co., Ltd (2006), China; 2-hydroxybenzaldehyde from E-Merck (1668), Germany; 4-anisaldehyde from E-Merck (1668), Germany; phenylhydrazine from E-Merck (1668), Germany; benzal from Tianjin Pharmacn Medical Technology Co., Ltd (2006), China; 3,4-dimethoxybenzaldehyde from *CAPOT* Chemical Co., Ltd (1996), China; 4-(dimethylamino)benzaldehyde from *CAPOT* Chemical Co., Ltd (1996), China; and 5-aminosalicylic acid from E-Merck (1668), Germany. Commercial grade solvents available in local market were utilized for synthetic medium, purification and recrystallization purpose after double distillation in the laboratory. For measurement of melting point, SMP30 Stuart Scientific melting point apparatus was used and ^{1}HNMR spectra were recorded on Bruker DRX 400 MHz NMR spectrometer at University of Science and Technology, Hefei, China. ^{1}H chemical shifts are reported Vs SiMe4 and were determined by reference to the residual ^{1}H solvent peaks and coupling constants (*J*) were reported in Hz. Single-beam X-rays crystallographic analysis was carried out by using Bruker KAPPA Apex II diffractometer at University of Sargodha, Pakistan.

3.1 General Procedure for the Synthesis of Imines (3a–l)

Equimolar quantities of substituted aniline/hydrazine (0.01 mol) and carbonyl compound/benzaldehyde (0.01 mol) were dissolved in methanol and refluxed for 15 min to 2.5 h under acid catalysis (1:1 = HCl/HNO_3). However, compounds **3c**, **3e**, **3g** and **3k** were synthesized without using acid as catalysts. Reaction completion was monitored by TLC, and after completion of the reaction, product was concentrated by rotary evaporator. Crude product was washed with plenty of water and dried in oven to afford crystalline product which was recrystallized in ethanol/diethyl ether (64:40) to obtain yellowish/colorless crystals. Finally, product was characterized by using X-rays crystallographic, elemental analysis and NMR techniques.

Synthesis of (2Z)-2-[(2,3-Dimethylphenyl)imino]-1,2-Diphenylethanone (3a) Synthesis of compound (**3a**) was carried out by refluxing 2,3-dimethylaniline (1.3 ml, about 0.01 mol) and benzal (2.10 g, 0.01 mol) for 1 h as yellow

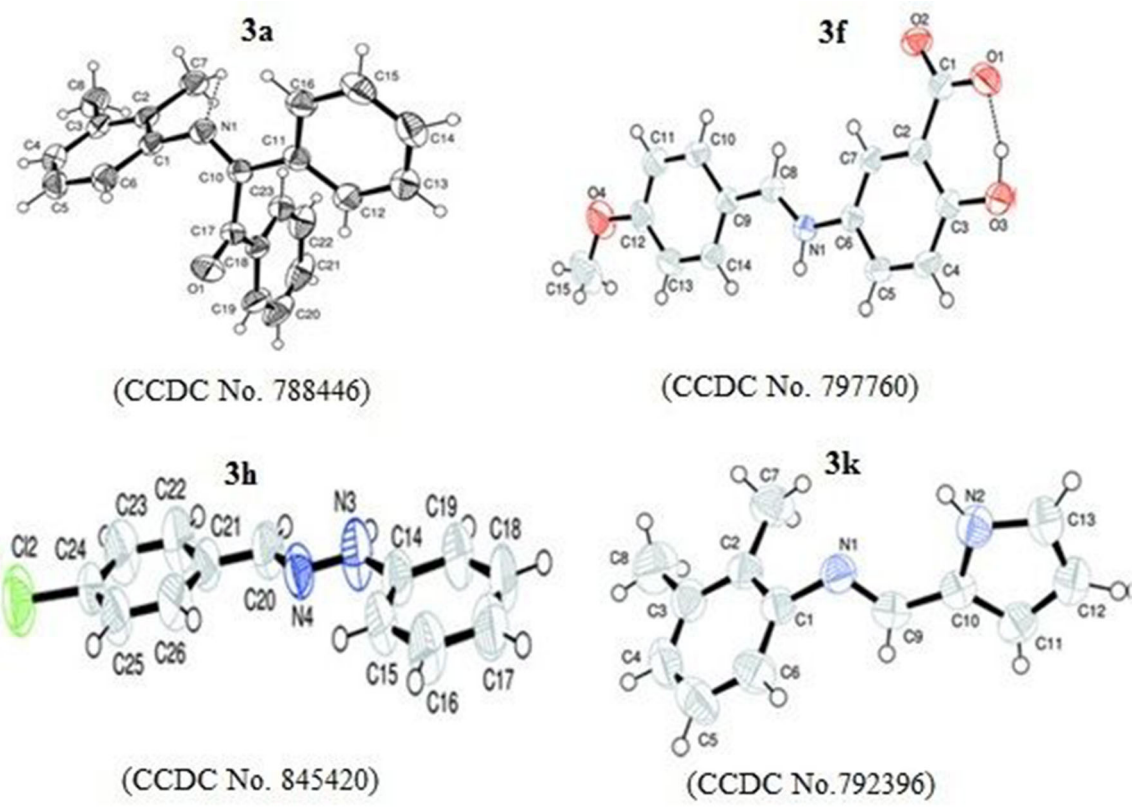


Fig. 1 ORTEP diagrams of synthesized compounds **3a**, **3f**, **3h** and **3k**

Table 2 Calculated in silico probabilities of synthesized imine compounds

Sample code	Penetration across BBB		Human intestinal absorption		AMES toxicity		Carcinogenicity	
	Results	Probability	Results	Probability	Results	Probability	Results	Probability
Donepezil	BBB+	0.9953	HIA+	0.9966	Non-AT	0.6441	Non-carcinogens	0.9528
3a	BBB+	0.961	HIA+	0.9877	AT	0.5644	Carcinogens	0.5943
3b	BBB+	0.9577	HIA+	0.983	AT	0.6635	Non-carcinogens	0.6016
3c	BBB+	0.9319	HIA+	0.9031	Non-AT	0.6976	Carcinogens	0.7602
3d	BBB+	0.9698	HIA+	0.9827	AT	0.9371	Carcinogens	0.544
3e	BBB+	0.9407	HIA+	0.9229	Non-AT	0.6997	Carcinogens	0.5971
3f	BBB-	0.529	HIA+	0.5555	Non-AT	0.7277	Non-carcinogens	0.7382
3g	BBB+	0.9325	HIA+	0.9618	AT	0.6227	Carcinogens	0.6596
3h	BBB+	0.9501	HIA+	0.9704	AT	0.6091	Non-carcinogens	0.7178
3i	BBB+	0.9812	HIA+	0.9683	Non-AT	0.6074	Carcinogens	0.704
3j	BBB+	0.9394	HIA+	0.9478	AT	0.8293	Carcinogens	0.6888
3k	BBB+	0.981	HIA+	0.9786	AT	0.5218	Carcinogens	0.8106
3l	BBB+	0.9104	HIA+	0.9572	Non-AT	0.507	Non-carcinogens	0.5789
3m	BBB+	0.9394	HIA+	0.9478	AT	0.8293	Carcinogens	0.6888
3n	BBB+	0.9509	HIA+	0.9715	AT	0.6417	Non-carcinogens	0.5762
3o	BBB+	0.9591	HIA+	0.9562	AT	0.5753	Carcinogens	0.6670
3p	BBB+	0.9551	HIA+	0.9733	Non-AT	0.7194	Carcinogens	0.7299

crystalline solid by adopting the general procedure. Yield 69%; m.p. 229 °C; FTIR (KBr): 1620 cm^{-1} (C=N); ^{1}H NMR (400 MHz, CDCl3, 25 °C): δ = 7.88 (dd, ^3J = 8 Hz, ^4J = 1 Hz, 2H, Ar*H*), 7.67 (dd, ^3J = 8 Hz, ^4J = 1 Hz, 2H, Ar*H*), 7.58–7.54 (m, 1H, Ar*H*), 7.44 (t, ^3J = 7 Hz, 2H, Ar*H*), 7.32–7.27 (m, 3H, Ar*H*), 7.13–7.08 (m, 3H, Ar*H*), 2.39 (s, 6H, 2 × CH_3).

Synthesis of 4-Chloro-N-[(E)-(3,4-Dimethoxyphenyl)-Methylidene]aniline (3b) (Chakraborti et al. 2004) The above-mentioned general procedure was followed to synthesize the compound (**3b**) by refluxing 4-chloroaniline (1.09 g, 0.01 molar) and 3,4-dimethoxybenzaldehyde (1.66 g, 0.01 molar) for 30 min as light yellow crystalline solid. Yield 72%; m.p. 193–194 °C; IR (KBr): 1644 cm^{-1} (C=N); ^{1}H NMR (400 MHz, CDCl3, 25 °C): δ = 8.46 (s, 1H, CH), 7.58 (d, ^3J = 8 Hz, 2H, Ar*H*), 7.37 (d, ^3J = 8 Hz, 2H, Ar*H*), 7.14 (d, ^3J = 7 Hz, 1H, Ar*H*), 7.09 (s, 1H, Ar*H*), 6.72 (d, ^3J = 7 Hz, 1H, Ar*H*), 3.82 (s, 6H, 2 × CH_3).

Synthesis of N-{(E)-[4-(Dimethylamino)phenyl]-Methylidene}-2,3-Dimethylaniline (3c) Compound (**3c**) was obtained by refluxing 2,3-dimethylaniline (1.3 ml, about 0.01 mol) and 4-(dimethylamino)benzaldehyde (1.5 g, 0.01 mol) for 2.5 h as colorless crystalline solid. Yield 83%; m.p. 187–188 °C; IR (Kbr): 1664 cm^{-1} (C=N); ^{1}H NMR (400 MHz, CDCl3, 25 °C): δ = 8.44 (s, 1H, CH), 7.51 (d, ^3J = 8 Hz, 2H, Ar*H*), 7.21–7.16 (m, 3H, Ar*H*), 6.65 (d, ^3J = 7 Hz, 2H, Ar*H*), 2.91 (s, 6H, 2 × CH_3), 2.42 (s, 3H,CH_3).

Synthesis of (E)-1-(4-Methoxybenzylidene)-2-Phenylhydrazine (3d) Synthesis of compound (**3d**) was done by following general procedure from phenylhydrazine (1.08 g, 0.01 molar) and 4-methoxybenzaldehyde (1.36 g, 0.01 molar) under reflux conditions for 45 min as yellow crystalline solid. Yield 87%; m.p. 161–162 °C; IR (Kbr): 1647 cm^{-1} (C=N); ^{1}H NMR (400 MHz, CDCl3, 25 °C): δ = 8.18 (s, 1H, CH), 7.86 (d, ^3J = 8 Hz, 2H, Ar*H*), 7.14 (d, ^3J = 8 Hz, 2H, Ar*H*), 7.05–7.01(m, 2H, Ar*H*), 6.64–6.59(m, 1H, Ar*H*), 6.48 (dd, ^3J = 8 Hz, ^4J = 1 Hz, 2H, Ar*H*), 5.12 (s, 1H, N*H*), 3.81 (s, 3H,CH_3).

Synthesis of (E)-1-(2-Nitrobenzylidene)-2-Phenylhydrazine (3e) Synthesis of compound (**3e**) was achieved by refluxing phenylhydrazine (1.08 g, 0.01 molar) and 2-nitrobenzaldehyde (1.51 g, 0.01 molar) for 25 min as violet crystalline solid. Yield 85%; m.p. 187–188 °C; IR (Kbr): 1663 cm^{-1} (C=N); ^{1}H NMR (400 MHz, CDCl3, 25 °C): δ = 8.18 (s, 1H, CH), 8.28 (dd, ^3J = 8 Hz, ^4J = 8 Hz, 1H, Ar*H*), 7.91–7.86 (m, 3H, Ar*H*), 7.05–7.01(m, 2H, Ar*H*), 6.64–6.59 (m, 1H, Ar*H*), 6.46 (dd, ^3J = 8 Hz, ^4J = 1 Hz, 2H, Ar*H*), 5.10 (s, 1H, N*H*).

Synthesis of 2-Hydroxy-5-{[(E)-4-Methoxybenzylidene]azaniumyl}Benzoate (3f) Compound (**3f**) was obtained by the reaction of 5-aminosalicylic acid (1.54 g, 0.01 molar) and 4-anisaldehyde (1.36 g, 0.01 molar) under reflux conditions for 30 min by following general procedure to afford light brown crystalline solid. Yield 81%; m.p. 207–208 °C; IR (Kbr): 1657 cm^{-1} (C=N); ^{1}H NMR (400 MHz, CDCl3, 25 °C): δ = 10.8 (s, 1H, OH), 8.42 (s, 1H, CH), 8.02 (s, 1H, Ar*H*), 7.56 (d, ^3J = 8 Hz, 2H, Ar*H*), 7.48 (d, ^3J = 8 Hz, 1H, Ar*H*), 6.59 (d, ^3J = 8 Hz, 1H, Ar*H*), 6.86 (d, ^3J = 8 Hz, 2H, Ar*H*), 5.22 (s, 1H, O*H*), 3.79 (s, 3H, CH_3).

3.2 Urease Inhibition Assay

Jack bean urease (JBU) enzyme (25 µL), mixed with phosphate buffer solution (55 µL, 3 mM, 4.5 pH) and synthesized compound (5 µL), was incubated at 30 °C for 15 min in 96-well plates. Urease activity was determined by measuring the ammonia released during the reaction by using indophenol method (Weatherburn 1967). More specifically, in each well phenol reagent (40 µL) containing a mixture of 0.005% of sodium nitroprusside and 1% phenol in addition to the appropriate amount of sodium hydroxide (NaOH) was added. After reaction time of 50 min, the increase in absorbance of the reaction mixture was measured at 630 nm using a microplate reader and results were computed on the microplate reader machine. All reactions were carried out in triplicate, and all assays were done at pH of 6.8 to measure percentage inhibition. Thiourea was used as control, and IC50 values were computed by using EZFit kinetic database (Perrella Scientific Inc., Amherst, NH, USA).

3.3 Determination of In Silico Pharmacokinetic Properties

The ADMET structure–activity relationship server, known as *admet*SAR, is a comprehensive knowledge and tool used to predict ADMET properties of various drug candidates and other chemicals (Cheng et al. 2012). Online ADMET SAR server was used to carry out in silico predictions of all synthesized compounds including penetration across blood–brain barrier (BBB), human intestinal absorption (HIA), AMES toxicity (AT) and carcinogenicity. SMILES files were used to predict ADMET properties of all synthesized compounds in comparison with standard drug donepezil.

4 Conclusion

We have synthesized various imine compounds and biologically evaluated our small molecules as inhibitor of urease enzyme. In vitro results showed that compounds **3f**

with IC_{50} value of 16.50 ± 0.20 μM can be considered the most potent urease inhibitor as compared to standard drug thiourea, whereas compounds **3a** (IC_{50} = 23.10 ± 0.11 μM) and **3n** (IC_{50} = 23.34 ± 0.21 μM) are reported to be the second and third most potent inhibitor. In silico predictions showed that all synthesized compounds have good penetration across BBB and HIA, except **3f** which have very less possibility to cross BBB. In silico pharmacokinetic profile of compound **3l** (IC_{50} = 26.85 ± 0.12 μM) was better than all other compounds with no toxicity and carcinogenic behavior.

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Compliance with Ethical Standards

Conflict of interest Authors of this research paper declare no conflicts of interest.

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