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# Novel Schiff Bases: Green Synthesis *vs* Conventional Synthesis and *In-silico* SwissADME Toxicity Studies

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## ABSTRACT

Facile method under green reaction conditions *vs* conventional method has been developed for the synthesis of Schiff's bases. A green alternative approach with effective yield and high reaction rates was observed in comparison with conventional method. The conventional methods for the synthesis of Schiff‟s bases require long reaction times and use of organic solvents. A novel and eco-friendly condensation reaction method permitted the green synthesis of various Schiff‟s bases by stirring *o*-phenylenediamine with various heteroaromatic aldehydes in water as solvent in green route, ethanol as solvent in conventional synthesis. All the compounds synthesized were characterized by physically ($R_f$ values, Melting point, Molecular weight, Molecular formula) and the compounds were characterized for *in-silico* toxicity studies using SwissADME software. Among the synthesized compounds $N^1$,$N^2$- bis[(thiophen-2-yl)methylene]benzene-1,2-diamine **(2c)** gives high percentage yield (93.76%) in green route synthesis, $N^1$-[(pyridin-3-yl)methylene]benzene-1,2-diamine **(1b)** gives high percentage yield (75.24%) in conventional synthesis. In this present study we used SwissADME online software tool which is available free and it is used to evaluate the ADME properties of compounds **1a-1c** and **2a-2c**. All the compounds were analyzed for *in-silico* ADME properties and depicted in respected tables and boiled egg models were represented in figures. Further, the values can be used as monographs by researchers and scientists for development of potential semi-synthetic and synthetic drugs development.

**Keywords:** *o*-phenylenediamine, Schif's bases, green reaction conditions, conventional method, *in-silico* toxicity studies.

## INTRODUCTION

Schiff bases are the compounds carrying imine or azomethine (–C=N–) functional group. These are the condensation products of primary amines with carbonyl compounds and were first reported by Hugo Schiff [1–3]. Schiff bases form an important class of the most widely used organic

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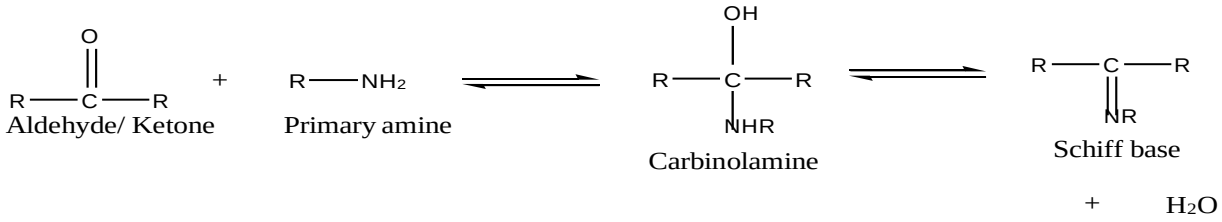
compounds and has a wide variety of applications in many fields including analytical, biological, and inorganic chemistry. Schiff bases have gained importance in medicinal and pharmaceutical fields due to a broad spectrum of biological activities like anti-inflammatory, analgesic, antimicrobial, anticonvulsant, antitubercular, anticancer, antioxidant, anthelmintic [4-8], and so forth. The nitrogen atom of azomethine may be involved in the formation of a hydrogen bond with the active centers of cell constituents and interferes in normal cell processes. Apart from biological activities, Schiff bases are also used as catalysts, intermediates in organic synthesis, dyes, pigments, polymer stabilizers, and corrosion inhibitors. Studies enlightened that metal complexes show greater biological activity than free organic compounds. Schiff bases have been utilized as synthons in the preparation of a number of industrial and biologically active compounds like formazans, 4-thiazolidinines, benzoxazines, and so forth, via ring closure, cycloaddition, and replacement reactions. Schiff base derivatives in various processes promoted the researchers for designing of novel heterocyclic/aryl Schiff bases for development of new environmental-friendly technology [9-12].

The chemistry of carbon-nitrogen double bond plays a vital role in the progresses of chemistry science. Schiff base ligands are essential in the field of coordination chemistry, especially in the development of complexes of Schiff bases because these compounds are potentially capable of forming stable complexes with metal ions. Such type of ligands represents vast utilized classes of new series of compounds in coordination chemistry [13].




In the present work, we report our results for the preparation of Schiff's bases in aqueous medium under the aspect of environmentally benign processes with high yields, which are superior to conventional methods. Our new method has the advantage that neither acid catalysts nor aromatic solvents for azeotropic water separation are needed. The product can be isolated simply by filtration, and it is noteworthy to mention that the condensation reactions occur very efficiently in the presence of water.

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## MATERIALS & METHODS

Chemicals and reagents used for the synthesis of a novel Schiff's base were bought from Merck, a commercial supplier, and they weren't purified before use. With the use of E.Merck grade silica gel 60GF-254 pre-coated plates, thin layer chromatography was used to monitor both the reaction's progress and completion. Uncorrected electrical melting point apparatus was used to determine melting points. Using the KBr pellet method, the compounds IR spectra were captured using the Bruker FT-IR spectrophotometer. On a Bruker-AMX spectrophotometer, chemical shifts in ppm of $^{1}$H-NMR and $^{13}$C-NMR spectra were noted in relation to tetramethylsilane (TMS) as internal standard. Using the *in-silico* SwissADME toxicity studies to find out the dug-likeliness, pharmacokinetic parameters, solubility, lipophilicity, physicochemical parameters etc.

## EXPERIMENTAL

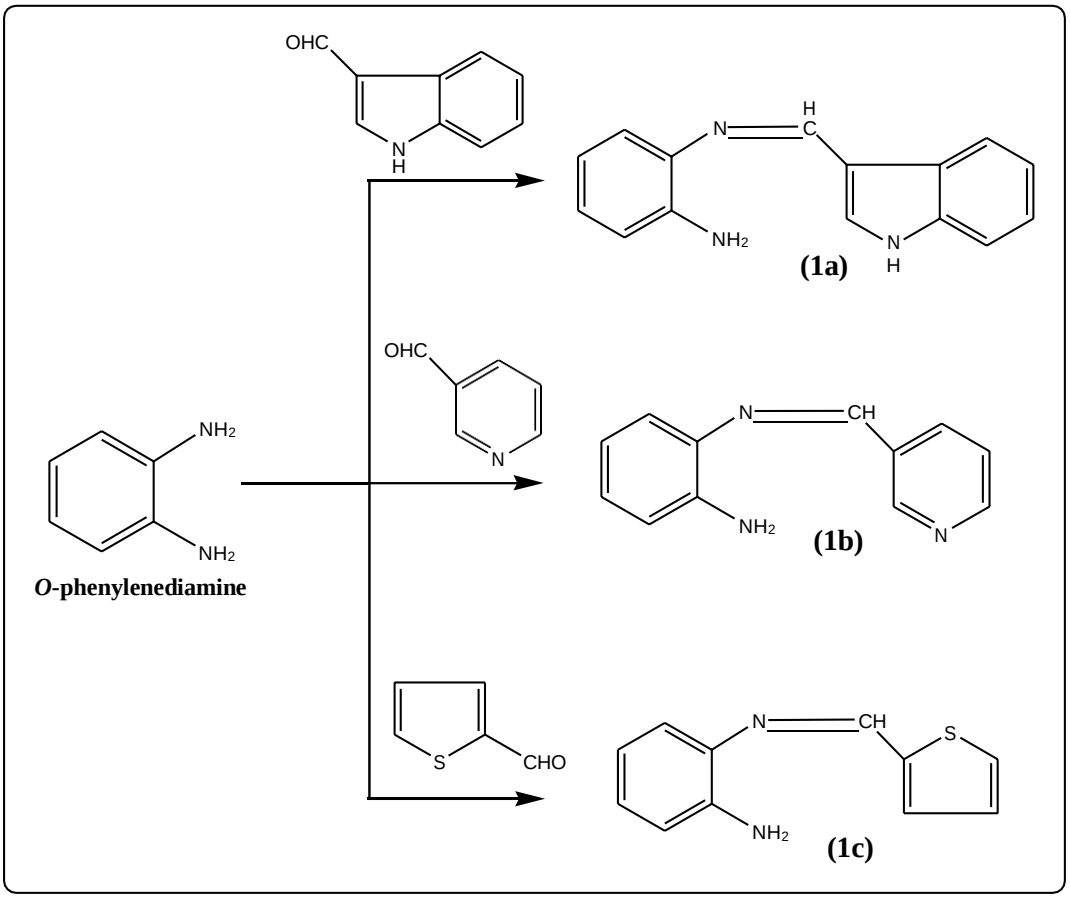


**Fig-1: Synthesis of Schiff bases 1a-1c**

***Conventional route:*** Solvent - ethanol; Reflux - 2 hrs

***Green route:*** Solvent - water; stirring at room temperature – 10 to 15 mins

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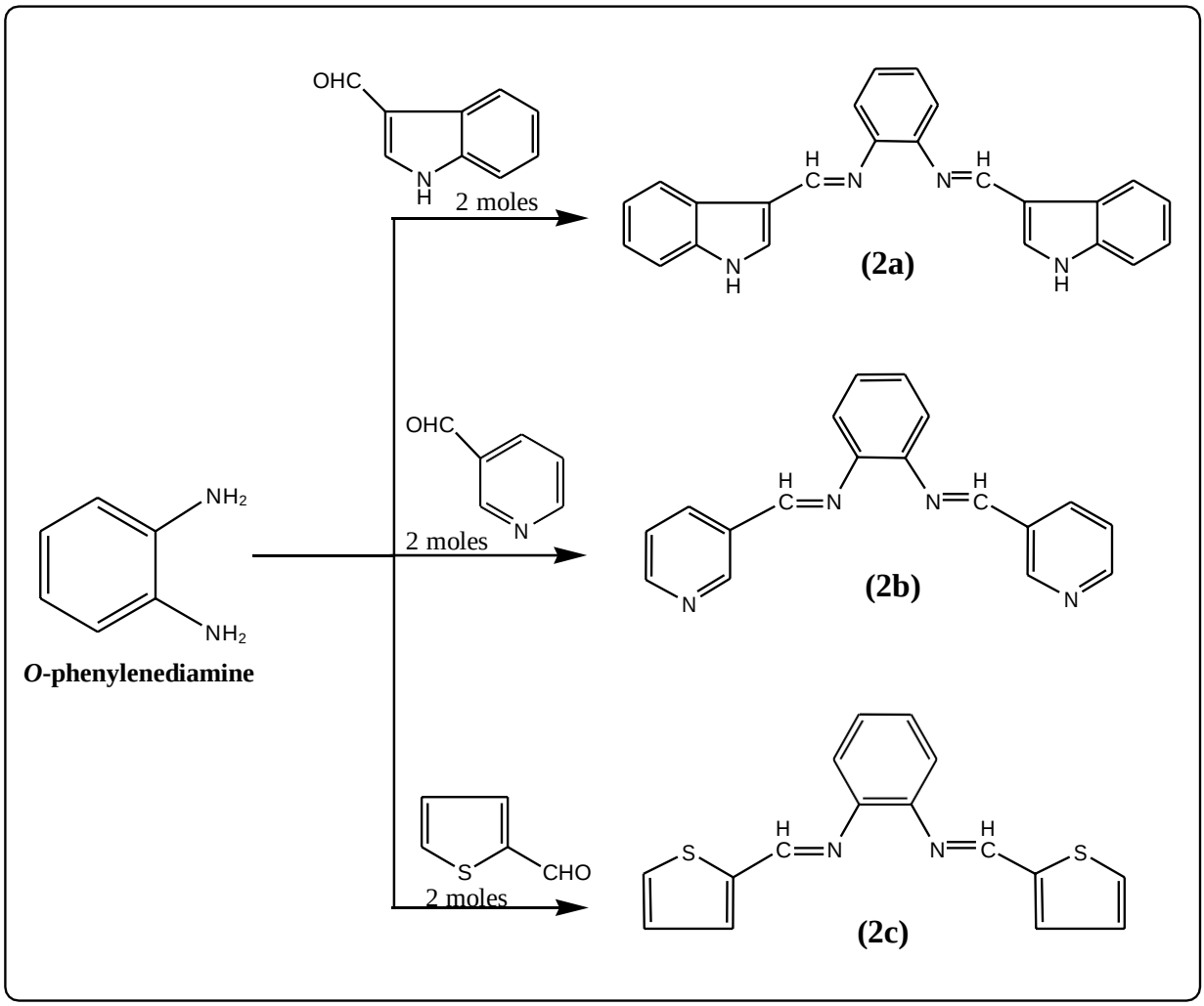


**Fig-2: Synthesis of Schiff bases 2a-2c**

***Conventional route:*** Solvent - ethanol; Reflux - 2 hrs

***Green route:*** Solvent - water; stirring at room temperature – 10 to 15 mins

**General procedure for synthesis of Schiff bases (1a-1c) & (2a-2c)** [14-17]

***Conventional method***

To a solution of 0.01 mole of *o*-phenylenediamine in 30 ml of ethanol, a solution of 0.01 mole of aldehyde in 20 ml of ethanol was added. A few drops of 10% NaOH were added to adjust the pH and the reaction mixture then refluxed with stirring for two hours and the obtained precipitate was collected by filtration through Buchnner funnel, recrystallized from methanol, and dried at room temperature to afford desired Schiff bases (**1a-1c**).

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***Green route method***

To a solution of 0.01 mole of *o*-phenylenediamine in 10 ml of water, 0.01 mole of aldehyde was added. The resulting mixture was then stirred for 10-15 min at room temperature. The yellow precipitate formed was filtered, washed with water, and dried to afford desired Schiff bases (**1a-1c**).

The same experimental procedure was adopted for the preparation of the compounds **(2a-2c)** by taking 0.02 moles of aldehyde with 0.01 mole of *o*-phenylenediamine. The Schiff‟s bases obtained by both conventional and green route methods are subjected to melting point determination. The yields are highly varying, in conventional method and in the green route method.

$N^1$,$N^2$-bis[(1H-indol-3-yl)-methylene]-benzene1,2-diamine（**2a**)75.84% (yield from conventional synthesis), 92.10% (yield from green synthesis), yellow crystalline solid, melting point 184-186°C, Rf value 0.65 from using ethylacetate and hexane (3:7 v/v). IR [KBr ν cm-1 ]: 3324.50 (-NH-), 3024.23 (=C-H), 1310.52 (C-N), 1655.30 (C=C). 1H-NMR [400 MHz, δ, ppm, DMSO-d6]: 8.421 (2H, s, -N=CH-), 12.040 (2H, s, indole-NH-), 6.982-7.258 (2H, d, phenyl C3-H & C4-H), 6.982-7.258 (2H, t, phenyl C2-H & C5-H), 7.587- 8.674 (10H, d & t, indole). 13C-NMR [100 MHz, δ, ppm, DMSO-d6]: 102.45, 111.15, 118.24, 120.12, 122.33, 124.03, 126.48, 129.66, 131.86, 136.74, 141.92, 161.16. ESI-MS: (M+ ) m/z 362.15.

Melting points were determined by open ended capillary tube and are uncorrected. Purity of the compounds was identified by the TLC by using silica gel-G as stationary phase.

**Table 1:** Reaction times, percentage yields and melting points of synthesized Schiff‟s bases

| Compound | Reaction time | | Yield (%) | | Melting point |
|---|---|---|---|---|---|
| | Conventional route | Green route | Conventional route | Green route | |
| **1a** | 90 min | 10 min | 72.18 | 89.64 | 180-182 ˚C |
| **1b** | 85 min | 12 min | 75.24 | 90.32 | 160-162 ˚C |
| **1c** | 100 min | 10 min | 69.12 | 88.36 | 168-170 ˚C |
| **2a** | 95 min | 14 min | 72.10 | 91.58 | 220-222 ˚C |
| **2b** | 90 min | 8 min | 62.64 | 87.48 | 172-174 ˚C |
| **2c** | 100 min | 12 min | 73.55 | 93.76 | 194-196 ˚C |

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## SwissADME TOXICITY STUDIES

To be effective as a drug, a potent molecule must reach its target in the body in sufficient concentration, and stay there in a bioactive form long enough for the expected biologic events to occur. Drug development involves assessment of absorption, distribution, metabolism and excretion (ADME) increasingly earlier in the discovery process, at a stage when considered compounds are numerous but access to the physical samples is limited. In that context, computer models constitute valid alternatives to experiments. Here, we present the new SwissADME web tool that gives free access to a pool of fast yet robust predictive models for physicochemical properties, pharmacokinetics, drug-likeness and medicinal chemistry friendliness, among which in-house proficient methods such as the BOILED Egg, iLOGP and Bioavailability Radar. Easy efficient input and interpretation are ensured thanks to a user-friendly interface through the login-free website http://www.swissadme.ch. It has been demonstrated that early estimation of ADME in the discovery phase reduces drastically the fraction of pharmacokinetics-related failure in the clinical phases. A large variety of *in-silico*methods share the objective of predicting ADME parameters from molecular structure. Noteworthy, the pioneer work of Lipinski *et al.* examined orally active compounds to define physicochemical ranges for high probability to be an oral drug (i.e. the drug-likeness). This so-called *Rule-of-five* delineated the relationship between pharmacokinetic and physicochemical parameters [18-20]. In SwissADME, it is possible to have a chemical description of the problematic fragments found in a given molecule by flying over the "question mark" icon appearing after the fragment list. This is implemented for both PAINS and Brenk filters. By applying these and other physicochemical filters to design screening libraries, observed that most of the remaining compounds satisfy criteria for "leadlikeness". This concept is similar to drug-likeness, yet focusing on physicochemical boundaries defining a good lead, i.e. a molecular entity suitable for optimization. Drug candidates should possess favorable ADME properties and ideally non-toxic. Therefore, the designed compounds were evaluated of their ADME profile, including drug-likeness, partition coefficient, solubility, and several other parameters using SwissADME module provided in SIB (Swiss Institute of Bioinformatics) [21-23].

## RESULTS AND DISCUSSION

Indole, pyridine, thiophene moiety containing various schiff"s bases were designed and prepared by green route synthesis as well as conventional synthesis. Diverse schiff"s bases **1a-1c** and **2a-**

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**2c**were synthesized using the appropriate synthetic procedure by green route synthesis as well as conventional synthesis i.e. reaction of *o*-phenylenediamine with various hetero aromatic aldehydes according to the scheme mentioned in the experimental part.Melting points were determined in open capillaries and are uncorrected. Thin layer chromatography was performed on silica gel G (Merck). All the synthesized compounds charachterized physically for their molecular weight, molecular formula, melting point, recrystallization, $R_f$ values. All the synthesized compounds studied for i*n-silico*SwissADME toxicity studies to find out the dug-likeliness, pharmacokinetic parameters, solubility, lipophilicity, physicochemical parameters, medicinal chemistry properties, etc. In the present study we used SwissADME online software tool which is available free and it is used to evaluate the ADME properties of compounds **1a-1c** and **2a-2c**. All the compounds were analyzed for in-silico ADME properties and depicted in respected tables and boiled egg models were represented in figures. Further, the values can be used as monographs by researchers and scientists for development of potential semi-synthetic and synthetic drugs development.

**Table 2:** Canonical SMILES notations of compounds **1a-1c** & **2a-2c**

| Compound | Formula | Canonical SMILES notation |
|---|---|---|
| **1a** | $C_{15}H_{13}N_3$ | NC1=CC=CC=C1\N=C/C1=CNC2=CC=CC=C12 |
| **1b** | $C_{12}H_{11}N_3$ | NC1=CC=CC=C1\N=C/C1=CC=CN=C1 |
| **1c** | $C_{11}H_{10}N_2S$ | NC1=CC=CC=C1\N=C/C1=CC=CS1 |
| **2a** | $C_{24}H_{18}N_4$ | N1C=C(\C=N\C2=CC=CC=C2\N=C\C2=CNC3=CC=CC=C23)C2=CC=CC=C12 |
| **2b** | $C_{18}H_{14}N_4$ | C(=N/C1=CC=CC=C1\N=C\C1=CN=CC=C1)\C1=CC=CN=C1 |
| **2c** | $C_{16}H_{12}N_2S_2$ | S1C=CC=C1\C=N\C1=C(C=CC=C1)/N=C/C1=CC=CS1 |

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**Table 2:** Canonical SMILES notations of compounds **1a-1c** & **2a-2c**

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| **1b** | $C_{12}H_{11}N_3$ | NC1=CC=CC=C1\N=C/C1=CC=CN=C1 |
| **1c** | $C_{11}H_{10}N_2S$ | NC1=CC=CC=C1\N=C/C1=CC=CS1 |
| **2a** | $C_{24}H_{18}N_4$ | N1C=C(\C=N\C2=CC=CC=C2\N=C\C2=CNC3=CC=CC=C23)C2=CC=CC=C12 |
| **2b** | $C_{18}H_{14}N_4$ | C(=N/C1=CC=CC=C1\N=C\C1=CN=CC=C1)\C1=CC=CN=C1 |
| **2c** | $C_{16}H_{12}N_2S_2$ | S1C=CC=C1\C=N\C1=C(C=CC=C1)/N=C/C1=CC=CS1 |

**Table 3:** Physicochemical Propertiesof compounds **1a-1c** & **2a-2c**

| Compound | Formula | MW | No. of Heavy atoms | No. of Aromatic heavy atoms | Fraction Csp3 | No. of Rotatable bonds | No. of H-bond acceptors | No. of H-bond donors | Molar Refractivity | TPSA |
|---|---|---|---|---|---|---|---|---|---|---|
| **1a** | $C_{15}H_{13}N_3$ | 235.28 | 18 | 15 | 0 | 2 | 1 | 2 | 76.4 | 54.17 |
| **1b** | $C_{12}H_{11}N_3$ | 197.24 | 15 | 12 | 0 | 2 | 2 | 1 | 62.34 | 51.27 |
| **1c** | $C_{11}H_{10}N_2S$ | 202.28 | 14 | 11 | 0 | 2 | 1 | 1 | 62.42 | 66.62 |
| **2a** | $C_{24}H_{18}N_4$ | 362.43 | 28 | 24 | 0 | 4 | 2 | 2 | 117.55 | 56.3 |
| **2b** | $C_{18}H_{14}N_4$ | 286.33 | 22 | 18 | 0 | 4 | 4 | 0 | 89.42 | 50.5 |
| **2c** | $C_{16}H_{12}N_2S_2$ | 296.41 | 20 | 16 | 0 | 4 | 2 | 0 | 89.59 | 81.2 |

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**Table 4:** Lipophilicityof the compounds **1a-1c** & **2a-2c**

| Compound | Formula | iLOGP | XLOGP3 | WLOGP | MLOGP | Silicos-IT Log P | Consensus Log P |
|---|---|---|---|---|---|---|---|
| **1a** | $C_{15}H_{13}N_3$ | 1.92 | 2.67 | 3.51 | 1.97 | 3.7 | 2.75 |
| **1b** | $C_{12}H_{11}N_3$ | 1.66 | 1.47 | 2.42 | 1.06 | 2.6 | 1.84 |
| **1c** | $C_{11}H_{10}N_2S$ | 2.26 | 2.55 | 3.09 | 1.7 | 3.79 | 2.68 |
| **2a** | $C_{24}H_{18}N_4$ | 2.99 | 4.78 | 6.15 | 3.02 | 6.89 | 4.77 |
| **2b** | $C_{18}H_{14}N_4$ | 2.01 | 2.38 | 3.98 | 1.43 | 4.7 | 2.9 |
| **2c** | $C_{16}H_{12}N_2S_2$ | 3.19 | 4.55 | 5.31 | 2.76 | 7.09 | 4.58 |

**Table 5:** Water Solubility of the compounds **1a-1c** & **2a-2c**

| Compound | ESOL Log S | ESOL Solubility (mg/ml) | ESOL Solubility (mol/l) | ESOL Class | Ali Log S | Ali Solubility (mg/ml) | Ali Solubility (mol/l) | Ali Class | Silicos-IT LogSw | Silicos-IT Solubility (mg/ml) | Silicos-IT Solubility (mol/l) | Silicos-IT class |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1a** | -3.47 | 8.06E-02 | 3.42E-04 | Soluble | -3.46 | 8.17E-02 | 3.47E-04 | Soluble | -5.54 | 6.75E-04 | 2.87E-06 | Moderately soluble |
| **1b** | -2.45 | 7.01E-01 | 3.56E-03 | Soluble | -2.15 | 1.39E+00 | 7.03E-03 | Soluble | -4.28 | 1.04E-02 | 5.25E-05 | Moderately soluble |
| **1c** | -3.15 | 1.43E-01 | 7.08E-04 | Soluble | -3.6 | 5.12E-02 | 2.53E-04 | Soluble | -3.92 | 2.42E-02 | 1.19E-04 | Soluble |
| **2a** | -5.47 | 1.23E-03 | 3.40E-06 | Moderately soluble | -5.69 | 7.34E-04 | 2.02E-06 | Moderately soluble | -9.34 | 1.65E-07 | 4.56E-10 | Poorly soluble |

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| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **2b** | -3.46 | 1.00E-01 | 3.50E-04 | Soluble | -3.08 | 2.37E-01 | 8.29E-04 | Soluble | -6.87 | 3.88E-05 | 1.36E-07 | Poorly soluble |
| **2c** | -4.87 | 3.98E-03 | 1.34E-05 | Moderately soluble | -5.98 | 3.12E-04 | 1.05E-06 | Moderately soluble | -6.15 | 2.11E-04 | 7.13E-07 | Poorly soluble |

**Table 6:** Pharmacokinetic parameters of the compounds **1a-1c** & **2a-2c**

| Compound | GI absorption | BBB permeant | Pgp substrate | CYP1A2 inhibitor | CYP2C19 inhibitor | CYP2C9 inhibitor | CYP2D6 inhibitor | CYP3A4 inhibitor | log Kp (cm/s) |
|---|---|---|---|---|---|---|---|---|---|
| **1a** | High | Yes | Yes | Yes | Yes | No | Yes | Yes | -5.84 |
| **1b** | High | Yes | No | Yes | No | No | No | No | -6.46 |
| **1c** | High | Yes | No | Yes | Yes | No | No | No | -5.72 |
| **2a** | High | No | Yes | Yes | Yes | No | No | Yes | -5.12 |
| **2b** | High | Yes | No | Yes | Yes | Yes | No | Yes | -6.36 |
| **2c** | High | No | No | Yes | Yes | Yes | No | No | -4.88 |

**Table 7:** Drug-likeness properties of the compounds **1a-1c** & **2a-2c**

| Compound | Formula | Lipinski violations | Ghose violations | Veber violations | Egan violations | Muegge violations | Bioavailability Score |
|---|---|---|---|---|---|---|---|
| **1a** | $C_{15}H_{13}N_3$ | 0 | 0 | 0 | 0 | 0 | 0.55 |
| **1b** | $C_{12}H_{11}N_3$ | 0 | 0 | 0 | 0 | 1 | 0.55 |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **1c** | $C_{11}H_{10}N_2S$ | 0 | 0 | 0 | 0 | 0 | 0.55 |
| **2a** | $C_{24}H_{18}N_4$ | 0 | 1 | 0 | 1 | 0 | 0.55 |
| **2b** | $C_{18}H_{14}N_4$ | 0 | 0 | 0 | 0 | 0 | 0.55 |
| **2c** | $C_{16}H_{12}N_2S_2$ | 0 | 0 | 0 | 0 | 0 | 0.55 |

 

**Table 8:** Medicinal Chemistry properties of the compounds **1a-1c** & **2a-2c**

| Compound | Formula | PAINS alerts | Brenk alerts | Lead-likeness violations | Synthetic Accessibility |
|---|---|---|---|---|---|
| **1a** | $C_{15}H_{13}N_3$ | 0 | 2 | 1 | 2.48 |
| **1b** | $C_{12}H_{11}N_3$ | 0 | 2 | 1 | 2.35 |
| **1c** | $C_{11}H_{10}N_2S$ | 0 | 2 | 1 | 2.61 |
| **2a** | $C_{24}H_{18}N_4$ | 0 | 1 | 2 | 3.02 |
| **2b** | $C_{18}H_{14}N_4$ | 0 | 1 | 0 | 2.69 |
| **2c** | $C_{16}H_{12}N_2S_2$ | 0 | 1 | 1 | 2.87 |

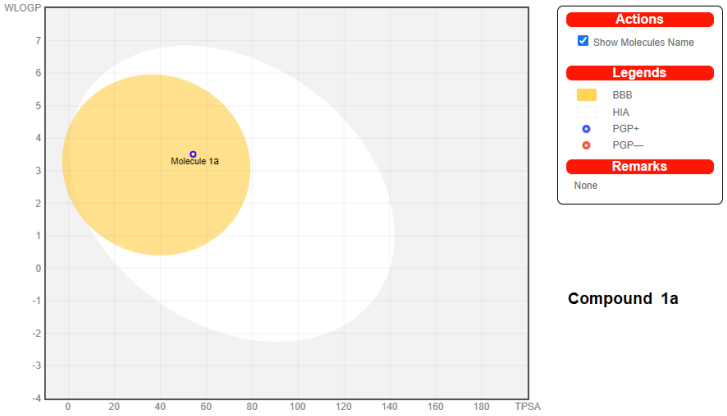


**Fig. 3:** Boiled Egg Model of Compound **1a**

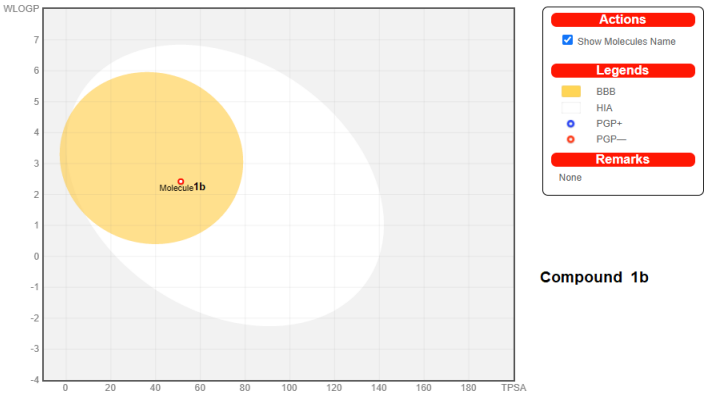

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**Fig. 4:** Boiled Egg Model of Compound **1b**

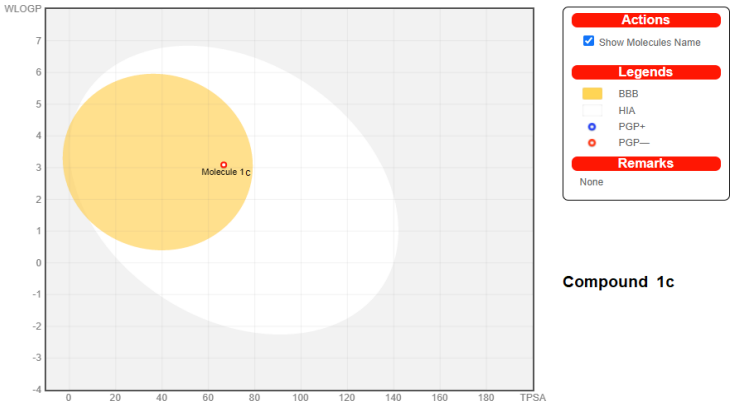


**Fig. 5:** Boiled Egg Model of Compound **1c**

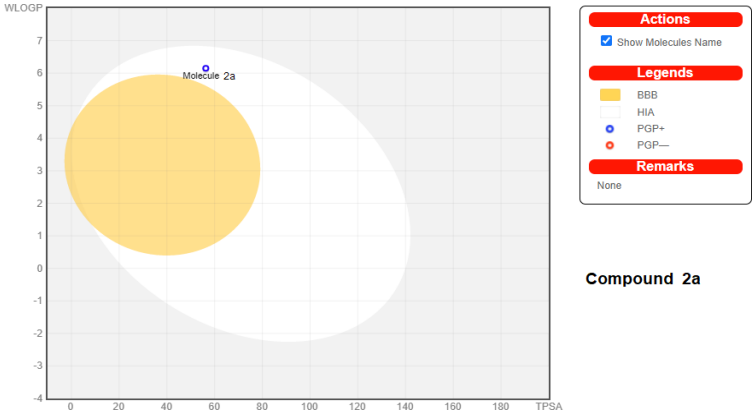


**Fig. 6:** Boiled Egg Model of Compound **2a**

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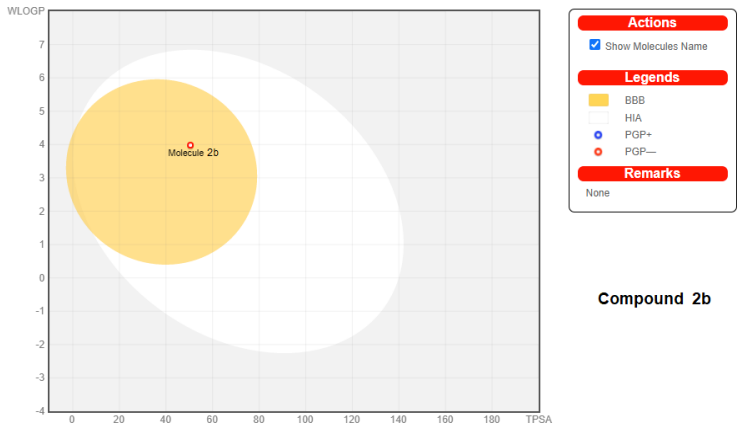


**Fig. 7:** Boiled Egg Model of Compound **2b**

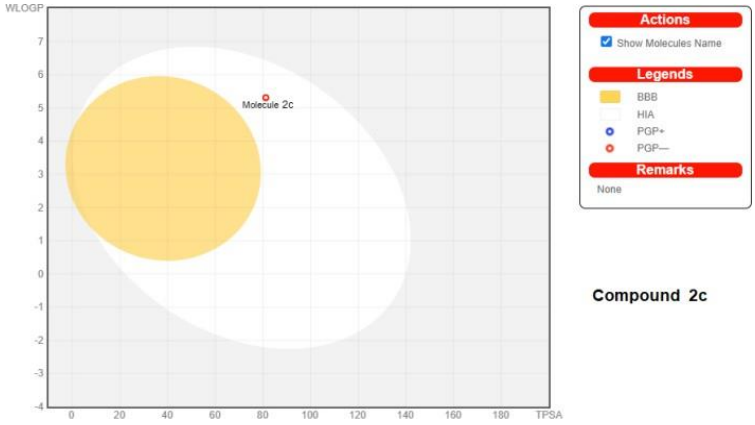


**Fig. 8:** Boiled Egg Model of Compound **2c**

## CONCLUSION

In the present work, facile method under green reaction conditions *vs* conventional method has been developed for the synthesisofSchiff‟sbases. Agreenalternativeapproachwitheffectiveyieldandhighreactionrates was observed in comparison with conventional method. Theconventionalmethods for the synthesis of Schiff‟s bases require long reaction times and use of organic solvents. Anovel and eco-

 

friendly condensation reaction method permitted the „„green synthesis"" of various Schiff"s basesbystirringo-phenylenediaminewithvarious hetero aromaticaldehydesinwaterassolvent in green route, ethanol as solvent in conventional synthesis. All the compounds synthesized were characterized by physically ($R_f$ values, Melting point, Molecular weight, Molecular formula) and the compounds were characterized for *in-silico* toxicity studies using SwissADME software. Among the synthesized compounds $N^1$,$N^2$-bis[(thiophen-2-yl)methylene]benzene-1,2-diamine **(2c)** gives high percentage yield (93.76%) in green route synthesis, $N^1$-[(pyridin-3-yl)methylene]benzene-1,2-diamine **(1b)** gives high percentage yield (75.24%) in conventional synthesis. In this present study we used SwissADME online software tool which is available free and it is used to evaluate the ADME properties of compounds **1a-1c** and **2a-2c**. All the compounds were analyzed for *in-silico* ADME properties and depicted in respected tables and boiled egg models were represented in figures. Further, the values can be used as monographs by researchers and scientists for development of potential semi-synthetic and synthetic drugs development.

## REFERENCES

1. Z. Cimerman, S. Miljanic, and N. Galic, "Schiff bases derived from aminopyridines as spectrofluorimetric analytical reagents," *CroaticaChemicaActa*, vol. 73, no. 1, pp. 81–95, 2000.

2. H. Schiff, "MittheilungenausdemUniversitätslaboratorium in Pisa: eineneuereiheorganischerBasen," *Justus LiebigsAnnalen der Chemie*, vol. 131, no. 1, pp. 118–119, 1864.

3. D. N. Dhar and C. L. Taploo, "Schiff bases and their applications," *Journal of Scientific and Industrial Research*, vol. 41, no. 8, pp. 501–506, 1982.

4. B. S. Sathe, E. Jaychandran, V. A. Jagtap, and G. M. Sreenivasa, "Synthesis characterization and anti-inflammatory evaluation of new fluorobenzothiazoleschiff's bases," *International Journal of Pharmaceutical Research and Development*, vol. 3, no. 3, pp. 164–169, 2011.

 

5. S. M. Sondhi, N. Singh, A. Kumar, O. Lozach, and L. Meijer, "Synthesis, anti-inflammatory, analgesic and kinase (CDK-1, CDK-5 and GSK-3) inhibition activity evaluation of benzimidazole/benzoxazole derivatives and some Schiff's bases," *Bioorganic and Medicinal Chemistry*, vol. 14, no. 11, pp. 3758–3765, 2006.

6. A. Pandey, D. Dewangan, S. Verma, A. Mishra, and R. D. Dubey, "Synthesis of schiff bases of 2-amino-5-aryl-1,3,4-thiadiazole and its analgesic, anti-inflammatory, anti-bacterial and anti-tubercular activity," *International Journal of ChemTech Research*, vol. 3, no. 1, pp. 178–184, 2011.

7. C. Chandramouli, M. R. Shivanand, T. B. Nayanbhai, B. Bheemachari, and R. H. Udupi, "Synthesis and biological screening of certain new triazole schiff bases and their derivatives bearing substituted benzothiazole moiety," *Journal of Chemical and Pharmaceutical Research*, vol. 4, no. 2, pp. 1151–1159, 2012.

8. R. Miri, N. Razzaghi-asl, and M. K. Mohammadi, "QM study and conformational analysis of an isatin Schiff base as a potential cytotoxic agent," *Journal of Molecular Modeling*, vol. 19, no. 2, pp. 727–735, 2013.

9. S. M. M. Ali, M. AbulKalam Azad, M. Jesmin et al., "In vivo anticancer activity of Vanillin semicarbazone," *Asian Pacific Journal of Tropical Biomedicine*, vol. 2, no. 6, pp. 438–442, 2012.

10. P. G. Avaji, C. H. Vinod Kumar, S. A. Patil, K. N. Shivananda, and C. Nagaraju, "Synthesis, spectral characterization, in-vitro microbiological evaluation and cytotoxic activities of novel macrocyclicbishydrazone," *European Journal of Medicinal Chemistry*, vol. 44, no. 9, pp. 3552–3559, 2009.

11. S. Ershad, L. Sagathforoush, G. Karim-Nezhad, and S. Kangari, "Electrochemical behavior of $N_2SO$ Schiff-base Co(II) complexes in non-aqueous media at the surface of solid electrodes," *International Journal of Electrochemical Science*, vol. 4, no. 6, pp. 846–854, 2009.

12. F. Tisato, F. Refosco, and G. Bandoli, "Structural survey of technetium complexes," *Coordination Chemistry Reviews*, vol. 135-136, pp. 325–397, 1994.

13. A. Jarrahpour, D. Khalili, E. De Clercq, C. Salmi, and J. M. Brunel, "Synthesis, antibacterial, antifungal and antiviral activity evaluation of some new bis-Schiff bases of isatin and their derivatives," *Molecules*, vol. 12, no. 8, pp. 1720–1730, 2007.

 

14. Mirkhani,V.;Moghadam,M.;Tangestaninejad,S.;Bahramian,B.;Mallekpoor-Shalamzari,A.*Appl.Catal.A.Gen.*2007,*321*(1),49−57.

15. KoteswaraRao, V.; SubbaReddy, S.;SatheeshKrishna, B.;ReddiMohanNaidu,K.;NagaRaju, C.;and Ghosh, S.K. *GreenChemistryLettersandReviews.*2010,3 (3),217−223.

16. Basim M. AL-Shimary, National Journal of Chemistry, 2008, *31*, 428-438.

17. M. Zarei, and A. Jarrahpour, *Iranian Journal of Science & Technology*, (2011) A3: 235-242.

18. S. Bala, G. Uppal, S. Kamboj, V. Saini, and D. N. Prasad, *Medicinal Chemistry Research*, 2012, 21(11), 1–13.

19. RN Patel, PV Patel, KR Desai, PY Purohit, KS Nimavat, KB Vyas, Heterocyclic Letters, 2012, 2(1), 99–105.

20. S Ganguli, M Firdous, TS Maity, RK Bera, M Panigrahi, *International Journal of Pharmacy and Pharmaceutical Sciences*, 2012, 4(2), 175– 178.

21. KM Khan, M Khan, M Ali, Bioorganic and Medicinal Chemistry, 2009, 17(22), 7795–7801.

22. Daina, A. *et al.* SwissADME: a free web tool to evaluate pharmacokinetics, druglikeness and medicinal chemistry friendliness of small molecules. *Sci. Rep.* **7**, 42717; (2017), 1-13.

23. Mahanthesh MT, Ranjith D, RaghavendraYaligar, Jyothi R, Narappa G and Ravi MV. Journal of Pharmacognosy and Phytochemistry 2020; 9(3): 1799-1809.