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Photocatalytic Solvent Free, Green Synthesis Of Schiff Bases In The Presence Of TiO_2-PANI At Room Temperature Under Visible Light – In Vitro Study And The ADME Properties Of TiO_2-PANI – In Silico Study

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Abstract

Mild and efficient photocatalytic synthesis of Schiff bases in the presence of photocatalyst TiO_2 - PANI under visible light. Compared to the conventional method of condensation utilizing acidic and basic medium, titanium dioxide with polyaniline (TiO_2-PANI), photocatalyst has the superior performance in the synthesis of Schiff base in a more environmentally friendly and solvent-free manner. In addition, TiO_2-PANI has rendered undesired polymerization and side reactions. When titanium dioxide is combined with polyaniline nanomaterial, the TiO_2-PANI photocatalyst exhibits good reusability and the medicinal properties. Swiss ADME web tool results the candidates under investigation possess high GI absorption, good BBB and skin penetration. It is inferred that TiO_2-PANI fastens an upright bioavailability score and worthy synthetic accessibility.

Keywords: Titanium dioxide, Polyaniline, Nano-catalyst, Schiff Base, Swiss ADME and bio-availability radar

I. INTRODUCTION

Schiff bases are commonly employed as anticancer, antiviral, antifungal, and antibacterial active ingredients. They are formed by the condensation reactions of primary amines with ketones or aldehydes under conditions that are ideal (Hamed, A. A. 2020). Their use is widespread in stabilizing metal cations, which improves their industrial, biological, and catalytic uses (Reshma, R. et.al., 2019). Lewis acids, inorganic bases, and organic bases are examples of homogeneous catalysts that must be disposed of carefully to prevent environmental risks because they cannot be recovered. Consequently, there was a lot of interest in using recoverable catalysts. Because of their great effectiveness and easy nature of recovery, heterogeneous catalysts have recently drawn interest in the field of organic synthesis. (Aqeel Ashraf, M. et.al., 2021). Without significantly lowering the yield of synthesized chemical compounds, the use of these recoverable heterogeneous catalysts lowers the hazards to the environment that can result from the use of nonrecoverable homogeneous catalysts (Appaturi, J. N. et.al., 2021). In the presence of UV light, FeCu@N-doped carbon is an effective catalyst that can be applied for converting amines with alcohols into Schiff bases (Wang, K. et.al., 2019). The unusual features of titanium dioxide (TiO_2) have made it a substance of great interest in materials science and chemistry. (Yang, Y. et.al., 2022). In the process of photocatalysis, a catalyst is activated by light energy, starting chemical processes. When exposed to visible and ultraviolet light, nanocomposites like ZnO/Polyaniline (ZnO/PANI) and TiO_2/Polyaniline (TiO_2/PANI) have shown excellent photocatalytic efficiency (Mirzaei, A. et.al., 2016). Polyanaline's (PANI's) strong conductivity and semiconductor characteristics enable effective charge transfer. Additionally, PANI has better redox characteristics and can increase photocatalytic performance by adding additional active sites to the photocatalyst's surface.(Zarrin, S. et.al., 2018). In our Previous work we have synthesized TiO_2-PANI composite (Urkude, K. et.al., 2014) by simple sol–gel method reported by H. Zhang et al. The solution of 0.008 g L 1 concentration was obtained by dissolving about 0.005 g PANI in 100 ml tetrahydrofuran (THF); to this solution a 5 g of TiO_2 was added. The suspension was ultrasonicated for 1 h, and stirred for 6 h, and then filtered. The prepared precipitate was washed with water several times and then dried at 60 8C for 6 h. . Prepared catalyst found to be highly efficient in the reduction of 4-NP under visible light irradiation.

Gas-phase degradation of benzene has been performed with the assistance of carbon nanotubes (CNT)/TiO_2 nanocomposite photocatalyst which was prepared by a simple impregnation method. A reasonable model was proposed for explaining the role of CNT in CNT/TiO_2 composites as a photocatalyst for degradation of organic pollutants (Yanhui, Z. et.al., 2010). Experimental studies showed that Transition metal (Fe, V and W)-doped TiO_2 which was synthesized via the solvothermal technique and immobilized onto fiberglass cloth (FGC) for uses in photocatalytic decomposition of gaseous volatile organic compounds—benzene, toluene, ethylbenzene and xylene (BTEX)—under visible light and the results were compared to that of the standard commercial pure TiO_2 (P25) coated FGC. All doped samples exhibited higher visible light catalytic activity than the pure TiO_2 (Laksana, L. et.al., 2012). It has been documented that thin films of titanium dioxide dispersed in poly(vinylidenefluoride) are sensitive to benzene at room temperature with possible applications in benzene monitors. The films are sensitive to benzene only at the higher voltages (Mohammed, M. et.al., 2002). Many researches are going on due to the photocatalytic properties, low cost, good biocompatibility, and high chemical stability of nanoscale TiO_2. There are results showing the properties, modifications, and applications of versatile material of titanium dioxide (TiO_2), especially at the nanometer scale, have been investigated extensively and intensively in applications from energy and environment to health (Xiaodong, Y. et.al., 2015). The results of a computational and experimental study have been reported on the reaction of hydrazoic acid, HN_3, adsorbed on 15−20 nm TiO_2 particle films. Experimentally, FTIR spectra of HN_3(a) have been measured by varying HN_3 dosage, UV irradiation time and surface annealing temperature (Jeng H, W. et.al., 2005).

In this work, TiO_2 PANI was utilized as a base-free catalyst in the synthesis of Schiff bases. The developed catalyst was characterized by X-ray diffraction analysis (XRD), infrared spectroscopy (IR), transmission electron microscopy (TEM). The synthesized Schiff bases were characterized by different spectral analyses such as IR, 1 H NMR, UV−Vis absorption and mass spectrometry. The recovery and reusability of the catalyst were investigated for four cycles. It is intriguing to do research on ADME properties of TiO_2 with polyaniline since it has been reported to have various applications as nanomaterial in distinct fields. To the best of our knowledge no work was performed on ADME properties of TiO_2 with polyaniline. Therefore, this work has focused on finding physicochemical, pharmacokinetics, druglikeness and medicinal properties of TiO_2, polyaniline and TiO_2 with polyaniline using SWISSADME web tool (Daina, A. et.al., 2017).

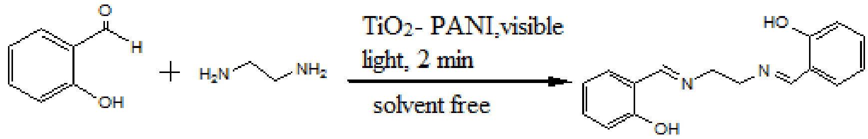
II. EXPERIMENTAL WORK

All chemicals used in our experiments were reagent grade and used without further purification.

Typical experiment set-up

The reaction mixture of salicylaldehyde (0.244g, 2 mmol), ethylenediamine (0.060g, 1 mmol) in 2:1 mole ratio and 20 mg of TiO_2 -PANI was taken in round bottom flask. The reaction mixture was stirred under visible light by using Philips xenon lamp at room temperature. The lamp was placed 10 cm away from the round bottom flask, which was used to provide a full-spectrum emission without any filter to simulate sunlight. Within 2 minutes bright yellow colour crystals were obtained (monitored by TLC). It was then filtered, dried and transferred into 50mL water, and neutralized with dilute HCl. The yield was separated by filtering it, washed thoroughly with water and dried. The crude product was then purified by crystallization from ethanol and the pure Schiff base was obtained. Similarly, various other substituted salicylaldehyde and amines were carried out by the same method. However, small amount of ethanol is required to dissolve and provide reaction medium to different amines as they are in solid form.

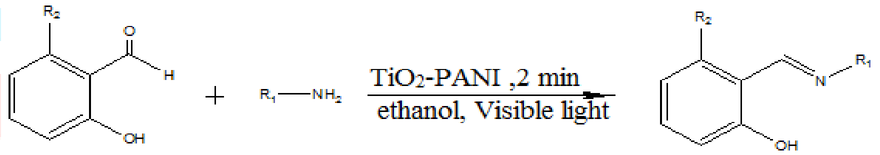
Scheme of Reaction



Scheme 1. Reaction scheme of formation of Schiff base

Table 1. Comparative study of catalysts for synthesis of Schiff base in various solvents

Entry	Catalyst	Solvent	Time/min	%yield	Ref.
1	Conventional method (refluxing)	Ethanol	120	99	*Ir. J Sc.& Tech A3 (2011) 235*
2	K_2CO_3	Water	45	93	*Ir. J Sc.& Tech A3 (2011) 235*
3	TiO_2	CH_3CN	720	2	*Jn. Am. Soc. 105 (1983) 7180*
4	Pt-TiO_2	CH_3CN	720	97	*Chem. Soc. Jap.58 (1985) 1075*
5*	TiO_2-PANI	_	20	>99	
Reaction condition*: equimolar quantities 1 mol of salicylaldehyde and 2 mol of ethylenediamine were dissolved in ethanol (10 ml), visible light.					



Scheme 2. Reaction of substituted salicylaldehyde with amine in the presence of catalyst to give imine. (R_2 is H and R_1 is $CH_2CH_2NH_2$)

Proposed mechanism

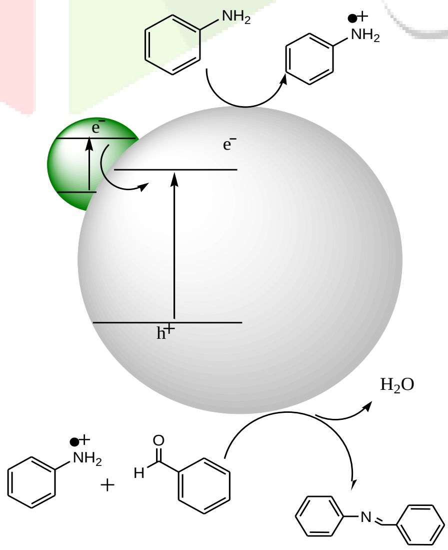


Figure 1. Proposed mechanism for synthesis of Schiff base

III. RESULTS AND DISCUSSION

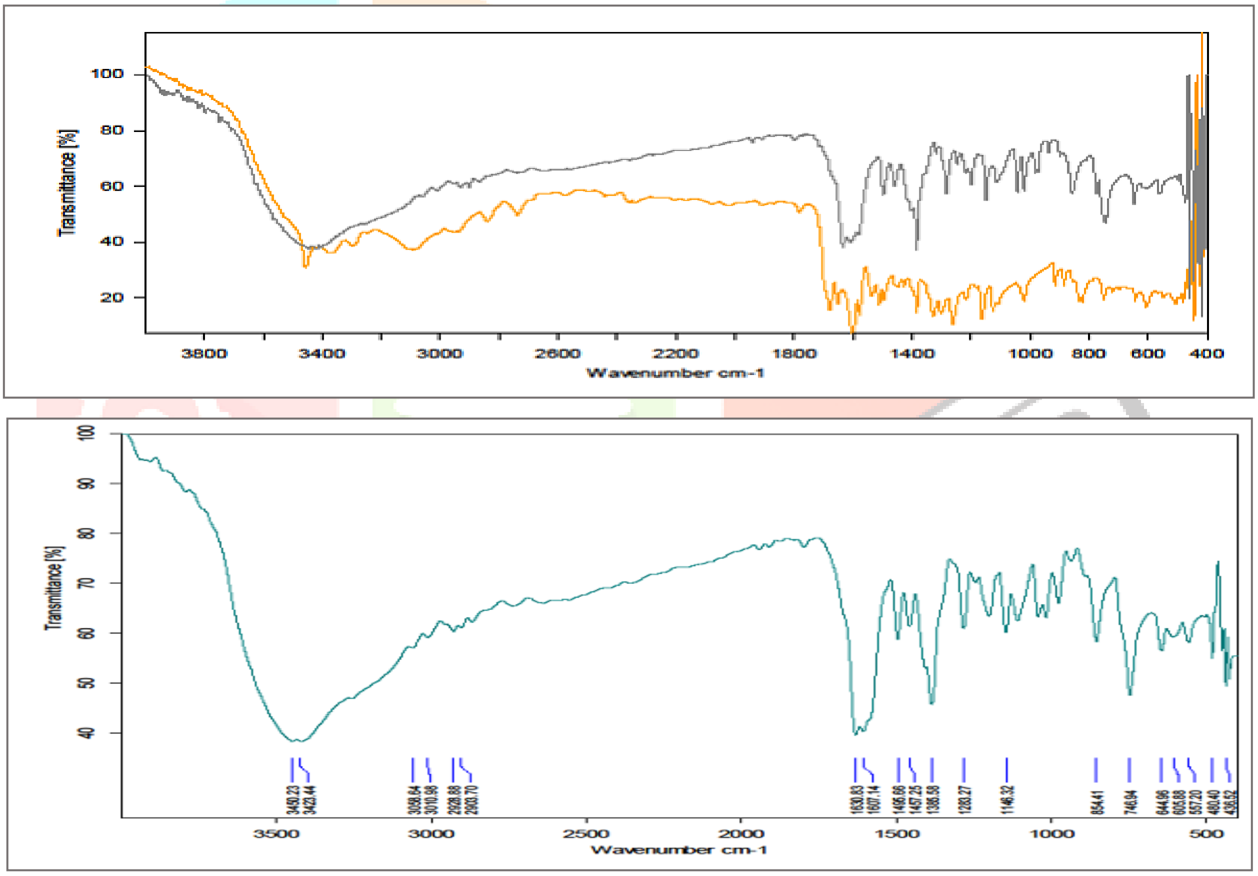
The product TiO_2-PANI composite synthesize by H. Zhang et al. method was verified by XRD, TEM, DRS spectroscopic methods and results are comparable to the reports (ESI). The Figure 1. shows the TiO_2 can be activated by UV radiation, which excites the electrons in the TiO_2 lattice, forming electron-hole pairs (e^-/h^+) as shown in eq.1.

$$\mathbf{TiO_2 + hv \rightarrow TiO_2 + (hole) + TiO_2 - (electron)}\text{………eq. 1}$$

Reactive oxygen species (ROS), including hydroxyl radicals (OH.) and superoxide anions ($O_2^{\cdot}$-), can now be generated when these excited electrons (TiO_2-) and holes (TiO_2+) react with water, oxygen, or other molecules adsorbed onto the catalyst's surface.

The carbonyl group in benzaldehyde may be reduced or the aniline may be activated in some other way as a result of the electron-hole pairs produced in the TiO_2 particles encouraging Electron migration to the reactants. For instance, the electrophilic benzaldehyde may be attacked by the superoxide anion ($O_2^{\cdot}$-) or hydroxyl radical (OH-) that forms on the surface of TiO_2, potentially resulting in reduction or coupling reactions.

Aniline and benzaldehyde react to generate Schiff bases when TiO_2 nanocatalysts have been added, and TiO_2 catalyses this reaction through surface adsorption or photocatalysis. Even in mild circumstances, TiO_2 facilitates the reaction by encouraging the activation of both reactants under UV light.



C=O-1700cm-1, HC=N-1630-1607 cm-1, OH- 3450 cm-1

Figure 2. IR analysis of the N, N'- disalicylethelyenediamine and scheme 2 product.

The above comparative IR analysis (Figure 2.) shows the formation of Schiff base by the appearance of the **C=N stretching band** and the disappearance or shift of the **C=O band** (from the aldehyde or ketone).

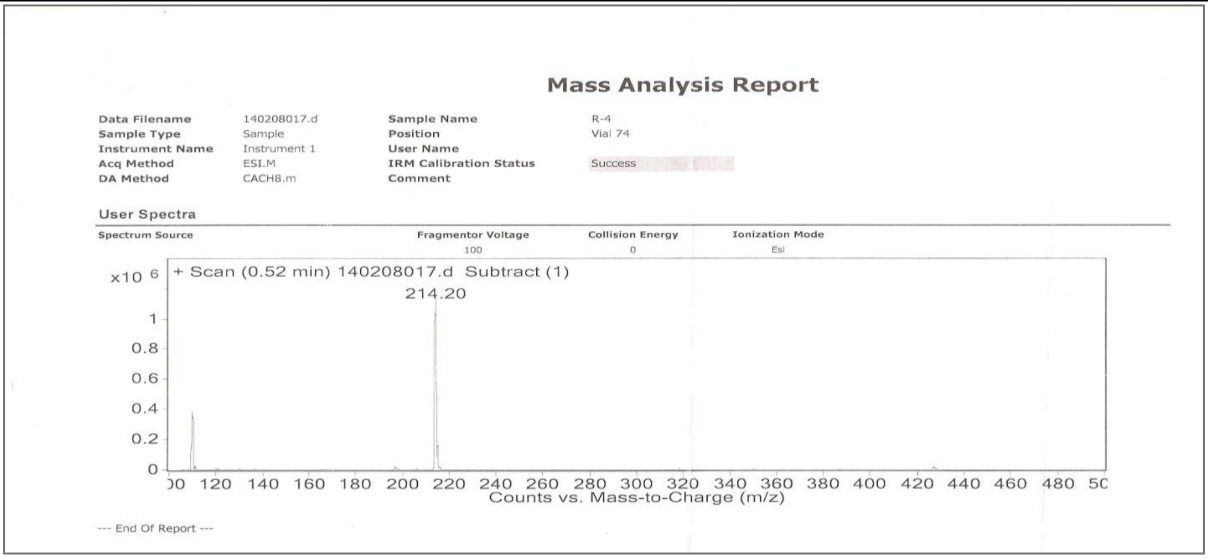


Figure 3. LCMS of product of scheme 2

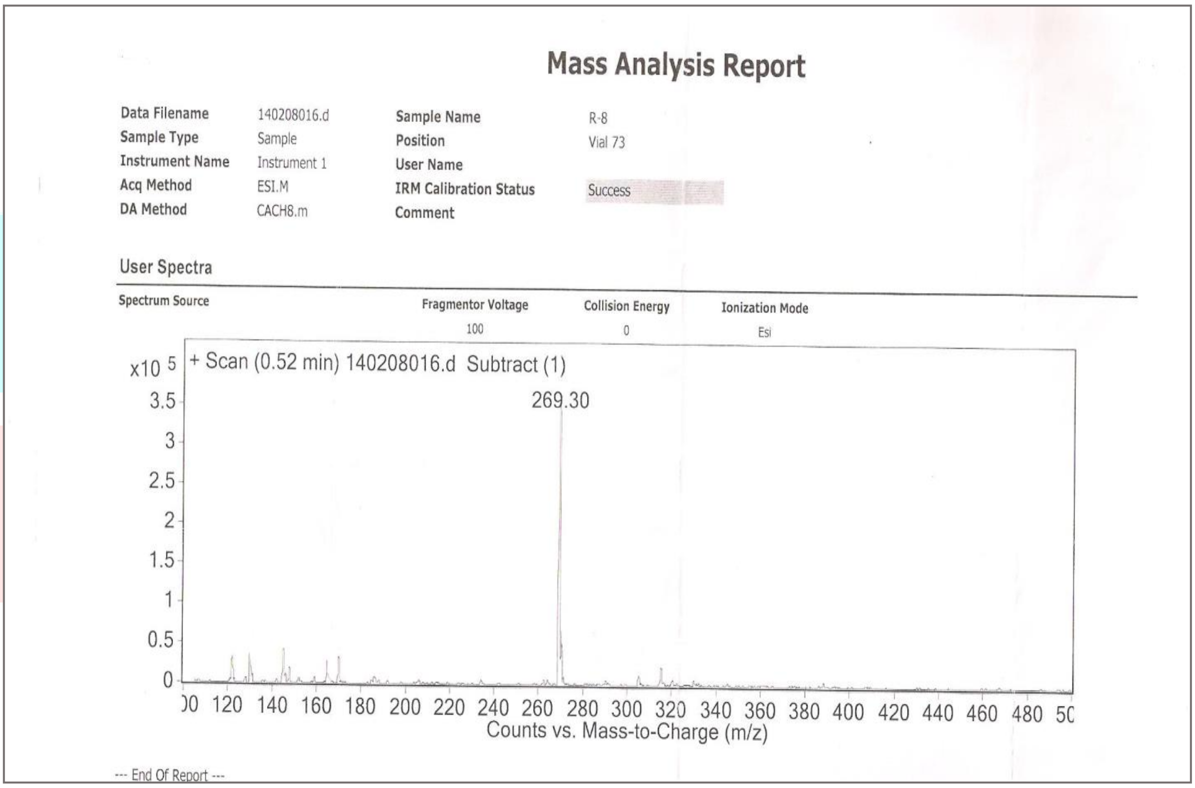


Figure 4. LCMS spectrum of N, N'- disalicylethelyenediamine.

Mass analysis (Figure 3. & 4.) confirmed the formation of Schiff bases.

Further the catalyst is studied with Swiss ADME. First of all, the selected molecules (TiO_2, polyaniline and TiO_2 with polyaniline) have been modelled to obtain the corresponding SMILES by Swiss ADME web tool and it is shown in Table 1. The concern bioavailability radar of all the studied molecules (shown in Table 3) have been obtained by running the programme of SMILES. It is known that the studied molecules are possessing the characteristic properties namely lipophilicity, size, polarity, insolubility, and flexibility within the optimal range of pink area present in the bioavailability radar. In contrast, only insaturation of the molecules exceeds the optimum level.

Table 2. Physicochemical properties of the selected molecules by SWISSADME web tool

Molecule	SMILES	M.F.*	M.W.*	NHD*	NHA*	M.R.*
Titanium dioxide	O=[Ti]=O	TiO_2	79.87	1	2	1.37
Polyaniline	Nc1ccccc1	C_6H_7N	93.13	1	0	30.85
Polyaniline- Titanium dioxide	Nc1ccccc1.O=[Ti]=O	$C_6H_7NO_2Ti$	172.99	1	2	32.22

*M.F. = Molecular formula; M.W. = Molecular weight; NHD = No. of hydrogen bond donor; NHA = No. of hydrogen bond acceptor; M.R. = Molecular refractivity

Table 3. ADME properties of the selected molecules by SWISSADME web tool

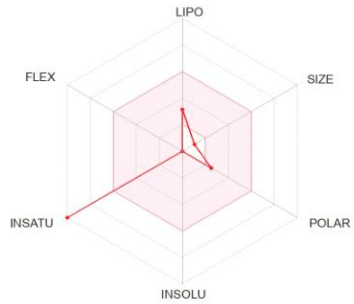
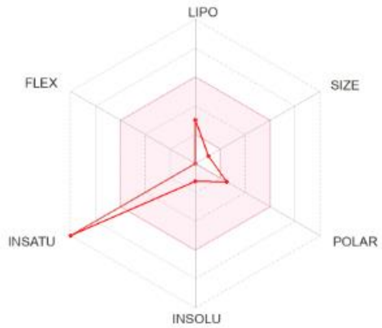
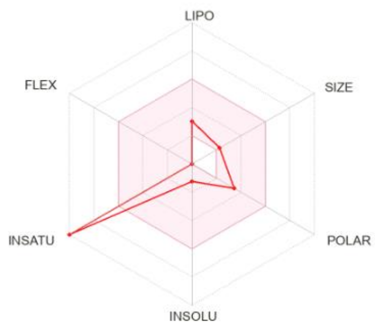
Molecule	Bioavailability Radar
Titanium dioxide	
Polyaniline	
Polyaniline- Titanium dioxide	

Table 4. ADME properties of the selected molecules by SWISSADME web tool

Molecule	Lipophilicity	Solubility	GI	BBB	Skin permeation Log K_p (cm/s)
Titanium dioxide	0.31	Very soluble	High	Yes	-7.50
Polyaniline	1.22	Very soluble	High	Yes	-6.23
Polyaniline-Titanium dioxide	0.31	Very soluble	High	Yes	-7.50

Table 5. Medicinal properties of the selected molecules by SWISSADME web tool

Molecule	Lipinski[7]	Bioavailability Score	Leadlikeness	Synthetic Accessibility
Titanium dioxide	Yes; 0 violation	0.55	No; 1 violation: MW<250	1.00
Polyaniline	Yes; 0 violation	0.55	No; 1 violation: MW<250	1.00
Polyaniline-Titanium dioxide	Yes; 0 violation	0.55	No; 1 violation: MW<250	1.00

The physicochemical properties and ADME measurements of the selected molecules have been listed in Table 2 & 4. The results show that all the studied molecules are possessing good lipophilicity, solubility and Gastrointestinal absorption properties also. As the molecular weight increases molar refractivity also enhances. In addition, the presence of TiO_2 allows the molecule to possess more skin permeation and BBB permeation may be due to the availability of hydrogen bond acceptors.

The medicinal properties of the studied candidates are shown in Table 5. The result reveals the following points.

- All the studied molecules are obeying Lipinski's rule (Lipinski, C.A. et.al., 2001) by which it is possible to have the ability of acting as an oral drug.
- Bioavailability score is good for all the candidates.
- Although molecular weight is less than the limitation, the molecules have some expected medicinal properties.
- All the candidates have pronounced synthetic accessibility.

IV. CONCLUSION

This paper reveals the greener, faster, cleaner and solvent free approach of TiO_2-PANI photocatalyst with enhanced performance in synthesis of Schiff bases over the traditional method of condensation using acidic and basic medium. Reaction also reduces the side reaction and unwanted polymerization. Workup is simple which results in maximum efficiency. We believe that TiO_2-PANI can be further applied to more diverse photochemical transformations. TiO_2-PANI photocatalyst shows good reusability as well as availability of medicinal properties of TiO_2 with polyaniline nanomaterial in such a way that the candidates under study have high GI absorption, good BBB and Skin permeation along with upright bioavailability score and worthy synthetic accessibility.

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