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SFHS: Reusable catalyst for the synthesis of polyhydroquinoline derivatives and its molecular docking studies against tyrosine protein kinase

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ABSTRACT

An efficient synthesis of polyhydroquinoline derivatives is achieved via Hantzsch condensation reaction between aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in the presence of catalytic amount of SFHS in ethanol. This method gives remarkable advantages such as shorter reaction time, simple workup procedure and good to excellent yields. Furthermore the catalyst can be recovered conveniently and reused efficiently. To analyze potential anticancer activity, synthesized derivatives were docked to tyrosine protein kinase (1YJ) against 4ST and PTR binding sites.

Keywords*: Polyhydroquinoline derivatives, Multicomponent reaction, Silica supported ferric hydrogensulfate, Molecular docking.*

1. Introduction

Multi-component reactions (MCR's) have gain wide applicability in the field of synthetic organic chemistry as they increase the efficiency of the reaction and decrease the number of laboratory operations along with quantities of solvent and chemicals used. These methods also considerably reduce the reaction time and facilitate the yield of products than the normal multiple step methods.

In recent years, much attention has focused on the synthesis of 1, 4-dihydropyridine derivatives due to its wide range of pharmacological and biological activities [1]. 1, 4-Dihydropyridyl compounds possess a variety of biological activities, such as vasodilator, antiatherosclerotic, antitumor, geroprotective, and antidiabetic activity [2]. Some of 1, 4-Dihydropyridyl derivatives are considered as calcium channel modulators [3], while some derivatives are associated as antihyperglycemic and lipid modulating agent [4]. Also, some 1, 4-Dihydropyridyl compounds like amlodipine, nicardipine represent drugs for the treatment of cardiovascular diseases [5].

Janus kinase (Jak) family nonreceptor tyrosine kinase is central mediators of cytokine signaling. JaK kinase is being considered of having an active role in prostate cancer, gastrointestinal stromal tumors and lung cancer [6]. Since biological activity of polyhdydroquinolines were reported, we were encouraged to synthesize a series of polyhydroquinolines scaffolds by using novel solid supported catalyst to obtain potent JaK Kinase inhibitors suitable for the clinical development. The biologically active compounds were subjected to molecular docking and drug likeness studies to rationalize and identify the structural features required for the antitumor properties.

In view of the importance of polyhydroquinoline derivatives, many classical methods for their synthesis were reported [7], using conventional heating and refluxing approaches in the organic solvents [8]. Recently, several catalysts which are high expensive and hazardous are also have been reported such as use of $HClO_4$-SiO_2 [9], TMSI [10], PTSA [11], baker's yeast [12], CAN [13], I_2 [14], ZnO [15], $ZrCl_4$ [16], metal triflates [17], enneamolybdomanganate(IV) [18], montmorilonite K10 clay [19], ionic liquid [20], heteropolyacids [21], $[Ce(SO_4)_2.4H_2O]$ [22], organocatalysts [23] and nanoparticles [24].

These methods, however, suffer from several drawbacks such as longer reaction times, use of large quantities of volatile organic solvents, low yields and harsh reaction conditions. Therefore, it is demanding

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to develop an efficient and versatile method for the preparation of these compounds.

Recent literature revels that the use of $Fe(HSO_4)_3$ as a heterogeneous catalyst have been reported for various transformations such as Friedel-Crafts reaction [25], acetal/ketal formation [26], synthesis of β-amido ketones [27], and for the synthesis of xanthene derivatives [28], but very few attention was focused on the solid supported ferric hydrogensulfate. Recently Eshghi et.al reported the use of silica supported ferric hydrogensulfate [29] $Fe(HSO_4)_3/SiO_2$ (SFHS) for the oxidative coupling of 2-napthols.

As our interest to develop novel methods for the synthesis of biologically important scaffolds through multi-component reactions using solid supported catalyst, herewith we wish to report a four component Hantzsch condensation in the presence of silica ferric hydrogensulfate as an effective and reusable catalyst for the synthesis of polyhydroquinoline derivatives using aldehydes(1), ethyl acetoacetate(2), dimedones (3) and ammonium acetate(4) to produce the polyhydroquinoline derivatives in good to excellent yields (Scheme 1).

2. Experimental

2.1. General

All reagents were purchased from s d fine & Qualigens and were used without further purification. All yields were referred to isolated products after purification. Melting points were determined by open capillary method and are uncorrected. IR spectra were recorded in KBr discs on a FT IR Jasco -4100typeA, ^{1}H NMR spectra were recorded on a Varian mercury YH-300 using tetramethylsilane (TMS) as internal standard. The progress of the reaction was monitored by TLC using silica gel-G (Merck).

2.2 Preparation of $Fe(HSO_4)_3/SiO_2$ (10 mol%) (SFHS)

Ferric hydrogensulfate (0.01 mol, 3.47 g) was ground in a mortar and the powder was added to a suspension of chromatographic grade SiO_2 (0.01 mol, 6.01 g) in absolute ethanol (50 ml). The yellowish mixture was stirred for 10 h. Then the mixture was concentrated and the solid material was filtered and dried at 120°C for 2 h. The homogeneous, free flowing and white powder catalyst (SFHS) was obtained in 99% yield (9.45 g) [29].

2.3. General procedure for the synthesis of (5a-m)

A mixture of aldehyde (2 mmol), dimedone (2 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (3 mmol) and $Fe(HSO_4)_3/SiO_2$ (10 mol %) (0.047 g, 0.050 mmol) in ethanol (5 ml) was refluxed for certain time as shown in Table 2. The Progress of the reaction was monitored by TLC (n-hexane:ethyl acetate, 8:2). After the completion of reaction, the solid catalyst was filtered in hot condition and washed with ethanol. This ethanol solution was concentrated to obtain the product in crystalline form. The products obtained showed single spot on TLC so no further purification needed.

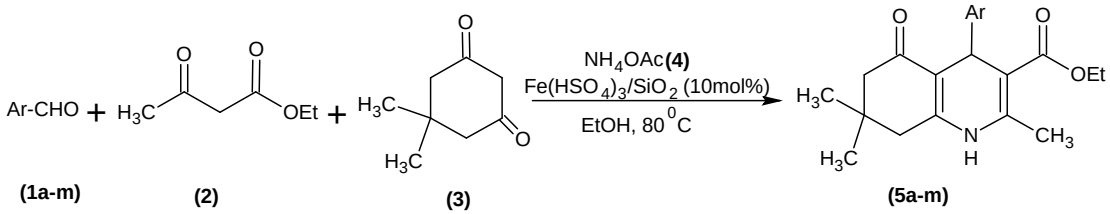
Selected spectral data

*2,7,7-Trimethyl-5-oxo-4-(4-hydroxy-3-methoxy phenyl)-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid ethyl ester (**5b**):*

White solid. m.p.= 220-220°C; FT-IR (KBr): $\bar{\nu}$ = 3410, 3288, 2960, 2872, 1676, 1219, 1078, 1030 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$): δ= 0.93 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.19 (t, 3H, *J*= 7.2Hz, CH_2 CH_3), 2.19-2.28 (m, 4H, 2 CH_2), 1.56 (s, 3H, CH_3), 2.37 (s, 3H, OCH_3), 4.05 (q, J_1=J_2= 6.8Hz, 2H, CH_2 CH_3), 5.02 (s, 1H, CH), 5.82 (s, 1H, NH), 6.56-7.08 (m, 4H, ArH) ppm. ^{13}CNMR (100 MHz, DMSO): δ= 13.75, 18.19, 26.65, 28.83, 31.90, 35.58, 50.32, 58.81, 104.20, 110.37, 112.38, 114.58, 118.53, 127.92, 144.13, 148.54, 149.17, 156.25, 167.07, 194.73 ppm. MS (ESI+): m/z= 386 $(M+H)^+$.

*2,7,7-Trimethyl-5-oxo-4-(2-hydroxy)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (**5d**):*

White solid. m.p.= 212-214°C. FT-IR (KBr): $\bar{\nu}$ = 3476, 3275, 2959, 2936, 1681, 1647, 1217, 1076 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$): δ= 0.92 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.19 (t, 3H, *J*= 7.2Hz, CH_2 CH_3), 2.11-2.28 (m, 4H, 2 CH_2), 2.36 (s, 3H, CH_3), 4.05 (q, J_1=J_2= 6.8Hz, 2H, CH_2 CH_3),5.02 (s, 1H, CH) 5.38 (s,1H, NH), 6.35 (s, 1H, OH), 7.17-7.26 (m, 4H, ArH) ppm. ^{13}CNMR (100 MHz, DMSO): δ= 13.72, 18.24, 26.48, 28.96, 31.92, 34.88, 50.29, 58.84, 104.93, 110.99, 114.73, 128.27, 138.30, 143.70, 148.83, 154.55, 167.24, 195.05 ppm. MS (ESI+): m/z= 374 $(M+H)^+$.



Scheme 1. Synthesis of polyhydroquinoline derivatives in the presence of SFHS.

*2,7,7-Trimethyl-5-oxo-4-(3,4,5-trimethoxy)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (**5f**):*

White solid. m.p.= 199-200°C. FT-IR (KBr): $\bar{\nu}$ = 3275, 2996, 3076, 2957, 1693, 1215, 1069 cm^{-1}. ^{1}HNMR (400 MHz, DMSO): δ= 0.93 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.19 (t, 3H, *J*= 7.2Hz, CH_2 CH_3), 2.26 (s, 3H, CH_3), 1.98-2.51 (m, 4H, 2 CH_2), 3.34 (s,3H,OCH_3), 3.65 (s,3H,2 OCH_3), 4.03(q, J_1=J_2= 6.8Hz, 2H, CH_2 CH_3), 4.77 (s, 1H, CH), 6.37 (s, 2H, ArH), 8.04 (s, 1H, NH) ppm. ^{13}CNMR (100 MHz, DMSO): δ= 14.26, 18.20, 26.23, 29.33, 32.07, 35.30, 50.28, 55.82, 58.99, 104.03, 105.03, 109.91, 133.90, 138.07, 144.35, 147.42, 149.47, 167.04, 194.39 ppm. MS (ESI+): m/z= 415 $(M+H)^+$.

*2,7,7-Trimethyl-5-oxo-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (**5h**):*

White solid. m.p.= 222-224°C. FT-IR (KBr): $\bar{\nu}$ = 3273, 3076, 2958, 1705, 1647, 1215, 1070 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$): δ= 0.92 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.19 (t, 3H, *J*= 7.2Hz, CH_2 CH_3), 2.11-2.28 (m, 4H, 2 CH_2), 2.36 (s, 3H, CH_3), 4.05 (q, J_1=J_2= 6.8Hz, 2H, CH_2 CH_3), 5.02(s, 1H, CH), 6.35 (s, 1H, NH), 7.17-7.26 (m, 4H, ArH) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ= 14.18, 19.24, 27.03, 29.40, 32.61, 36.24, 40.83, 50.70, 59.85, 105.61, 111.57, 127.94, 129.38, 131.38, 143.86, 145.65, 148.83, 167.23, 195.63 ppm. MS (ESI+): m/z= 374 $(M+H)^+$.

*2,7,7-Trimethyl-5-oxo-4-(2-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (**5i**):*

White solid. m.p.= 202-204°C. FT-IR (KBr): $\bar{\nu}$ = 3292, 3072, 2958, 1697, 1637, 1213**,** 1072 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$): δ= 0.97 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.21 (t, 3H, *J*= 7.2Hz, CH_2 CH_3), 2.16-2.27 (m, 4H, 2 CH_2), 2.30 (s, 3H, CH_3), 4.08 (q, J_1=J_2= 6.8Hz, 2H, CH_2 CH_3),5.43(s, 1H, CH), 6.73 (s, 1H, NH), 7.06-7.45 (m, 4H, ArH) ppm. ^{13}CNMR (100 MHz, DMSO): δ= 13.82, 18.40, 26.70, 29.01, 31.94, 35.14, 50.35, 59.08, 104.07, 110.28, 125.87, 126.57, 128.92, 131.44, 132.46, 144.47, 149.28, 167.23, 194.86 ppm. MS (ESI+): m/z= 374 $(M+H)^+$.

*2,7,7-Trimethyl-5-oxo-4-(3-Nitro)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (**5k**):*

White solid. m.p.= 192-194°C. FT-IR (KBr): $\bar{\nu}$ = 3273, 3076, 2958, 1705, 1647, 1523, 1347, 1215, 1070 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$): δ= 0.93 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.19 (t, 3H, *J*= 7.2Hz, CH_2 CH_3), 2.17-2.36 (m, 4H, 2 CH_2), 2.41 (s, 3H, CH_3), 4.06(q, J_1=J_2= 7.0Hz, 2H, CH_2 CH_3), 5.15 (s, 1H, CH), 6.00 (bs, 1H, NH), 7.27 (t, 1H, ArH), 7.73 (d, 1H, ArH), 8.00 (d, 1H, ArH), 8.11 (s, 1H, ArH) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ= 14.17, 19.64, 27.14, 29.36, 32.80, 36.95, 41.19, 50.55, 60.08, 111.51, 121.31, 122.83, 128.53, 134.86, 144.09, 148.17, 148.37, 149.10, 166.82, 195.21 ppm. MS (ESI+): m/z= 385 $(M+H)^+$.

*2,7,7-Trimethyl-5-oxo-4-(4-methoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylicacid ethyl ester (**5l**):*

White solid. m.p.= 220-222°C. FT-IR (KBr): $\bar{\nu}$ = 3275, 2956, 2931, 1699, 1647, 1215, 1072 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$): δ= 0.92 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.20 (t, 3H, *J*= 7.2Hz, CH_2 CH_3), 2.19-2.32 (m, 4H, 2 CH_2), 2.34 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.05 (q, J_1=J_2= 6.8Hz, 2H, CH_2 CH_3),4.98(s, 1H, CH), 6.19 (s, 1H, NH), 6.72 (d, 2H, ArH), 7.21 (d, 2H, ArH) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ= 14.20, 19.12, 27.02, 29.42, 32.53, 35.68, 40.62, 50.74, 55.02, 59.70, 106.04, 111.81, 113.14, 128.86, 139.70, 143.57, 149.07, 157.68, 167.57, 195.88 ppm. MS (ESI+): m/z= 370 $(M+H)^+$.

3. Results and discussion

3.1. General

Initially, 4-chlorobenzaldehyde was selected as a probe aldehyde to optimize the reaction conditions and the results are listed in Table 1. The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields of polyhydroquinoline. The formation of the **5h** did not proceed in absence of the catalyst SFHS even after refluxing the above same reaction mixture for 24 hrs. Obviously, the amount of catalyst had important effects on the reaction. Yields of **5h** increased from 92% to 95% as the amount increased from 23 mg (0.025mmol) to 47 mg (0.050 mmol). Increase in the amount of catalyst to 94mg (0.1mmol) does not increase in the yield and time remains the same. Therefore, it was reasonable to conclude the best conditions were 47 mg of $Fe(HSO_4)_3/SiO_2$ (10 mol %), where the maximum yield of 95% obtained.

To select the best solvent, various solvents were studied for the probe reaction with 47 mg, 10 mol% of the SFHS as catalyst at reflux condition. It has been observed that the poor yield was obtained with distilled water as a solvent while best yield was obtained in ethanol. Results of other solvents are summarized in Table 1.

From these results, other aromatic aldehydes have been reacted with dimedone, ammonium acetate and ethyl acetoacetate in ethanol and the results are listed in Table 2. It was evident that several aromatic aldehydes converted to the corresponding products in high yields over the SFHS catalyst. Benzaldehyde (entry 1) and other aromatic aldehydes containing electron-withdrawing groups such as nitro group (entry 10,11), halide (entry 8,9) or electron donating groups such as hydroxyl group (entry 2,3,4,7), alkoxyl group (entry 2,3,6,12) and heterocyclic aldehyde (entry 5) were employed and reacted well to give the corresponding polyhydroquinoline derivatives in good to excellent yields.

One of the special features of silica ferric hydrogensulfate is its insolubility in organic solvents

Table 1. Effect of various solvents on the SFHS catalyzed synthesis of polyhydroquinoline **5h.**

Entry	Solvent	Time (h)	Yield (%)
1	Ethyl acetate	3.5	85.00
2	THF	5.0	67.00
3	Acetonitrile	1.5	56.00
4	Ethanol	1.0	95.00
5	Water	4.0	51.00

Reaction condition: 4-Chloro benzaldehyde (2 mmol), dimedone (2 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (3 mmol) and catalyst-47mg in solvent (5 ml), at reflux temperature.

which makes its recovery very convenient. After completion of the reaction, the catalyst was simply recovered by filtration in hot condition. The catalyst was then washed with acetone, and dried in air. Recycling performance of $Fe(HSO_4)_3/SiO_2$ was investigated in the reaction of 4-chlorobenzaldehyde with dimedone, ethyl acetoacetate and ammonium acetate. The $Fe(HSO_4)_3/SiO_2$ could be reused without significance loss of its catalytic activity until five runs as shown in Fig. 1.

3.2. Molecular docking study

Molecular docking studies was employed for the analysis with training set composed of our synthesized compound whose inhibitory activity is unknown. In order to find out the molecular facilities responsible for biological activities, thirteen derivatives were taken for docking study.

The role of tyrosine kinases in the cell cycle regulation, cell metabolism, cell migration, cell proliferation, cell differentiation and cell survival make it potential anti-cancer drug target in humans.

Janus kinase (JAK3) is a tyrosine kinase act as central mediators of cytokine signaling require for immune cell development. Targeting JAK3 is an important approach to discover novel immunosuppressant drugs vital in cancer therapy. Therefore crystal structure of JAK3 kinase domain (PDB ID 1YVJ) from homosapiens was extracted from protein data bank.

Table 2. SFHS catalyzed synthesis of polyhydroquinoline derivatives.[a]

Entry	Molecule name	Ar	Product	Time (min.)	Yield (%)[b]	m.p.(°C)		Ref.
						Found[c]	Reported	
1.	PHQ-1	C_6H_5-	5a	60	89	208-210	204-205	[16b]
2.	PHQ-2	4-(OH), 3-(OCH_3) C_6H_3-	5b	60	95	220-222	225-227	[7]
3.	PHQ-3	4-(OH), 3,5-$(MeO)_2C_6H_2$-	5c	30	92	202-204	197-199	[24b]
4.	PHQ-4	2-(OH)C_6H_4-	5d	60	95	212-214	-------	[24a]
5.	PHQ-5	2-Furyl	5e	60	90	200-202	210-212	[8]
6.	PHQ-6	3,4,5-$(OCH_3)_3C_6H_2$-	5f	30	74	220-222	199-200	[4]
7.	PHQ-7	4-(OH)C_6H_4-	5g	90	85	218-220	220-222	[8]
8.	PHQ-8	4-(Cl)C_6H_4-	5h	60	95	222-224	234-235	[9]
9.	PHQ-9	2-(Cl)C_6H_4-	5i	60	77	202-204	206-208	[11]
10.	PHQ-10	2-(NO_2)C_6H_4-	5j	60	85	202-204	204-206	[15]
11.	PHQ-11	3-(NO_2)C_6H_4-	5k	60	83	192-194	198-200	[8]
12.	PHQ-12	4-(OCH_3) C_6H_4-	5l	60	95	220-222	193-195	[7]
13.	PHQ-13	4-(NMe_2)C_6H_4-	5m	45	70	214-216	222-223	[7]

[a]Reaction condition: Aldehyde (2 mmol), dimedone (2 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (3 mmol) and catalyst-47mg in ethanol (5 ml), 80°C.

[b]Isolated yields.

[c]After recrystallization.

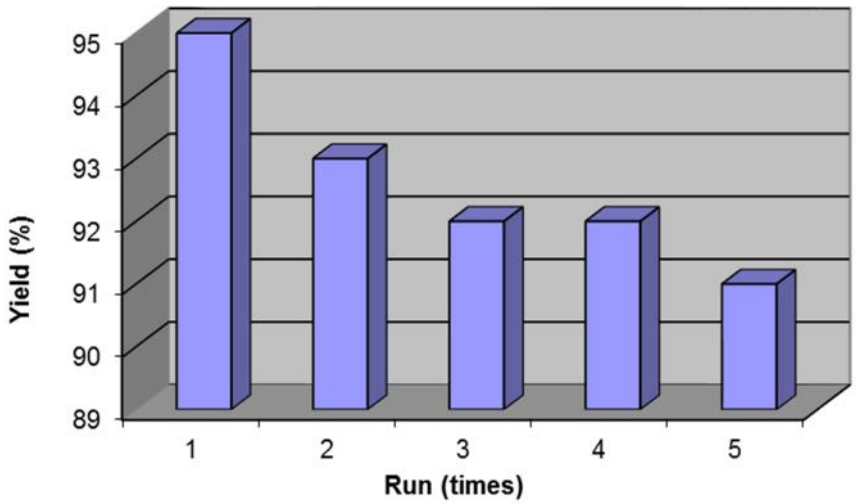


Fig. 1. Recycling of ferric hydrogen sulfate in the reaction between 4- chlorobenzaldehyde, dimedone, ethyl acetoacetate and ammonium acetate.

By using PROCHECK, tertiary structure validation of 1YVJ has been done which revealed high quality structure with 90% residues in most favored region. Due to its well confirmed stereochemistry 1YVJ was considered for docking study.

3.2.1. Receptor preparation

1YVJ as receptor was prepared using AUTODOCK 4.2 tools. The Autodock Tools package version 1.4.6 was used to generate the docking input files. Co-crystallized Ligand molecule was removed from the enzyme active site.4ST and PTR binding site of 1YVJ was considered for potential docking sites. For the docking, a grid spacing of 0.375 Å and 60×60×60 number of points was used. Before docking all water molecules were removed from the protein structure followed by addition of Hydrogen atoms to receptor and merging non-polar hydrogens. Receptor protein was assigned by Kollman united atom charges and solvation parameters while ligands were assigned by Gasteiger charge. Rigid roots were also assigned to the ligand and five bonds were made rotatable.

3.2.2. Ligand preparation

The synthesized compounds were taken for prediction of 3D structures by using Cambridge software. The energy minimization was done by using open babel in Pyrx virtual screening tool with UFF force field and conjugate gradient optimization algorithm.

Receptor grid generation was done by auto dock 4.2. In the receptor Grid Generation the receptor structure was defined by excluding cocrystallized ligand, determining the position and size of the active site as it will be represented by receptor grids.

Docking simulation was done using AutoDock Vina suite as molecular-docking tool. The default optimization parameters were used with the Lamarckian Genetic Algorithm with a population size of 150 dockings. Autodock Vina tool generated 10 possible binding conformations, i.e. 10 runs for each docking by using Genetic Algorithm (GA-LS) searches. A default protocol constituting a maximum number of 2.5×10^5 energy evaluations, a maximum number of 2.7×10^4 generations and an initial population of 150 randomly placed individuals were applied. A mutation rate of 0.02 and a crossover rate of 0.8 were used. The grid box used for specifying the search space was set at 60 × 60 × 60 centered on of JAK Kinase with a default grid point spacing of 0.375 Å. Autogrid was used to obtain pre-calculated grid maps. After completion of docking, most suitable conformation was chosen based on lowest docked energy. Docking protocol was verified by redocking of the co-crystallized ligand 1,2,3,4 tetra hydrogen taurosporin in the vicinity of the active site of 1YVJ. Selected conformations were analyzed using Pymol software.

The PHQ-6 compound tested for docking study showed high affinity with low energy of -8.7 kcal/mol with 4ST binding site and -6.3kcal/mol with PTR binding site of tyrosine protein kinase.

Molecular descriptor analysis and toxicity studies were performed to find the molecular properties of synthesized compounds is shown in Table 3. TPSA analysis also showed minimum TPSA value for PHQ-6.Thus 6PHQ was selected for further Absorption, Distribution, Metabolism, and Excretion ADME/TOX analysis.

PHQ-6 showed maximum 70%, oral bioavailability, chemical stability at acidic pH less than 2, have good passive absorption (>70%) against intestinal barrier with 100% passive absorption with transcellular route, does not show first pass metabolism in stomach or intestine and no active transport, its Permeability on

Table 3. QSAR/ADME TOX study of synthesized polyhydroquinoline derivatives.

Molecule	Energy Value (Kcal/mol)[a]	Molecular Wt.	log*P*	HD	HA	Energy Value (Kcal/mol)[b]	TPSA
PHQ-1	-5.3	309.4	3.81	1	3	-7.6	46.700
PHQ-2	-6.1	339.43	3.61	2	4	-7.7	66.400
PHQ-3	-6.0	353.46	4.34	2	4	-8.0	66.397
PHQ-4	-5.4	325.40	3.27	2	4	-7.5	66.397
PHQ-5	-4.9	299.37	2.59	1	4	-7.9	59.309
PHQ-6	-6.3	351.49	4.59	1	3	-8.7	46.169
PHQ-7	-5.6	325.41	3.33	2	4	-7.5	66.397
PHQ-8	-5.6	343.85	4.48	1	3	-7.6	46.169
PHQ-9	-5.6	377.88	4.65	1	4	-7.5	55.403
PHQ-10	-5.4	323.43	3.74	1	3	-7.4	46.169
PHQ-11	-5.6	323.43	4.23	1	3	-8.0	46.169
PHQ-12	-5.9	323.43	4.25	1	3	-7.1	46.169
PHQ-13	-5.7	352.47	3.91	1	4	-7.7	49.410

[a]PTR binding site.

[b]4ST binding site.

human jejunum scale is 7.37×10^{-4} cm/s with Ld 50 in mouse intraperitoneal is 310mg/kg with moderate reliability. Molecular descriptor studies of the ligand reveal that all selected ligands were passed, and acted as hydrophilic or moderately hydrophobic basic drug molecule by their adherence to the properties.

Docking simulation was performed between tyrosine protein kinase with 13 synthesized compounds to find out the binding orientation and binding affinities of the ligands. According to ADME/TOX studies PHQ-6 was identified as a possible better inhibitor against tyrosine protein kinase and follows most of the ADME properties, leading to a hydrophilic acidic drug candidate as lymphocyte specific immunosuppressant. Thus with the least binding energy, least TPSA, with a reasonable hydrogen bond interaction and with no toxicity risk at all ensures this ligand is a better source for inhibiting the tyrosine protein kinase. The docking study revealed the binding orientation is in the PTR binding pocket (Fig. 2). Carbon at 15, 16 and 17 are being derivatised. Out of these in methoxy derivatisation carbon 17 shows significant activity. Methoxy derivative at C17 position showed maximum binding to tyrosine protein kinase. Interaction with nonpolar uncharged amino acids alanine, methionine, valine and glycine are important for inhibitory activity of molecules. On the basis of oral bioavailability, chemical stability at acidic pH, absorption against intestinal barrier, 2,7,7-Trimethyl-5-oxo-4-(3,4,5 trimethoxy phenyl)-1,4,5,6,7,8-hexahydro quinoline-3-carboxylic acid ethyl ester (PHQ-6) can act as basic hydrophilic tyrosine protein kinase inhibitor drug molecule resulting in antitumor activity.

4. Conclusions

In conclusion, Fe $(HSO_4)_3$ /SiO_2 (10 mol %) can be prepared by simple procedure from commercially and relatively cheap starting materials, which efficiently catalyze the synthesis of polyhydroquinoline derivatives. The catalyst can be recovered and reused for several reaction cycles without significant loss of its activity. Moreover, short reaction time, simple work- up in isolation of the products and good yields with high purity are features of the present method.

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PHQ-3

PHQ-6

PHQ-8

PHQ-11

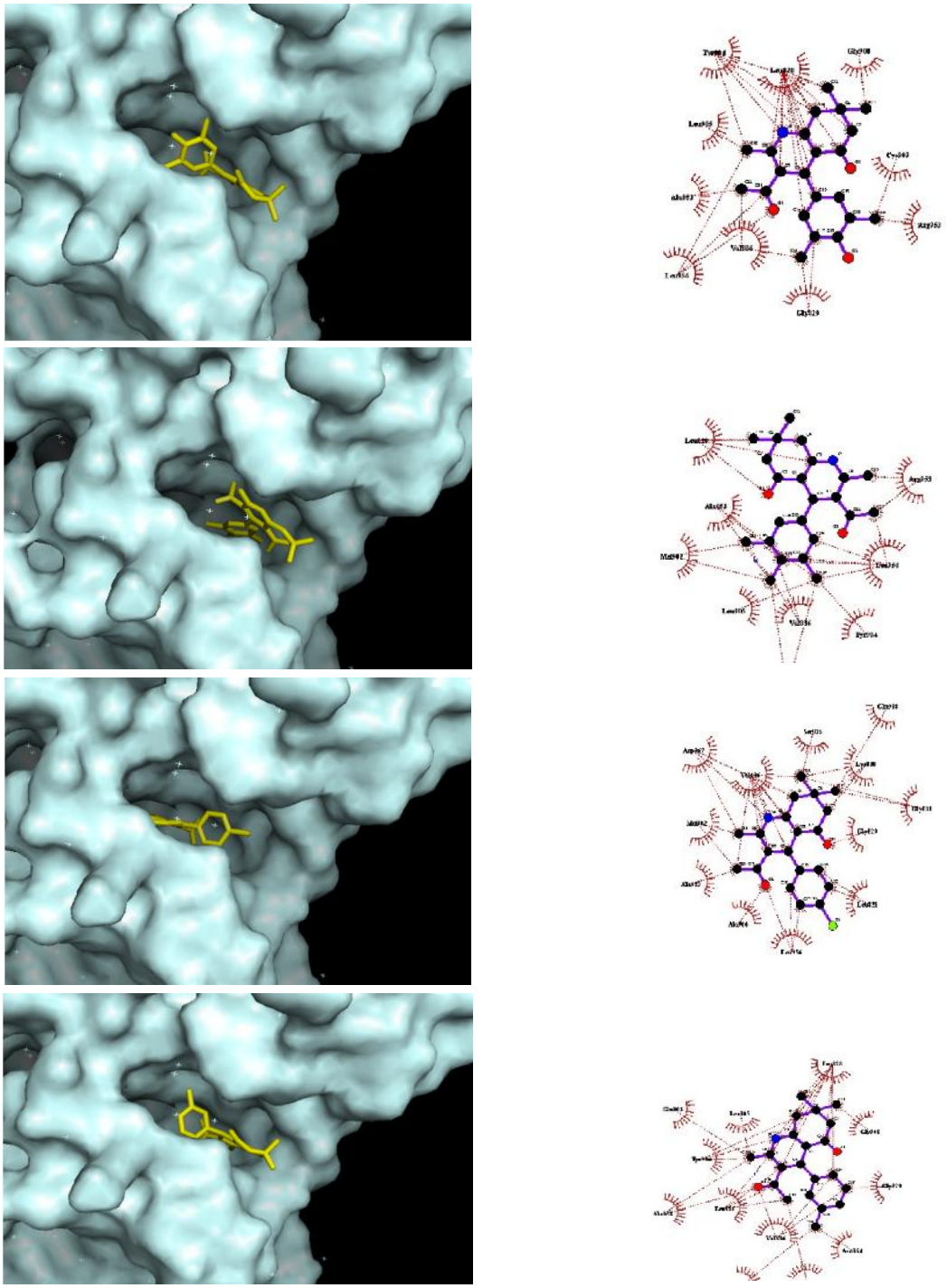

Fig. 2. Docked polyhydroquinolines with tyrosine protein kinase.

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