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An Efficient Copper Catalyzed Sonogashira Coupling Reactions and Simulation Studies

Imran Ali[1,], Dnyaneshwar Nighot[2], Mohammad Nadeem Lone[1], Arvind Jain[2]

[1]Department of Chemistry, Jamia Millia Islamia, (Central University) New Delhi, India

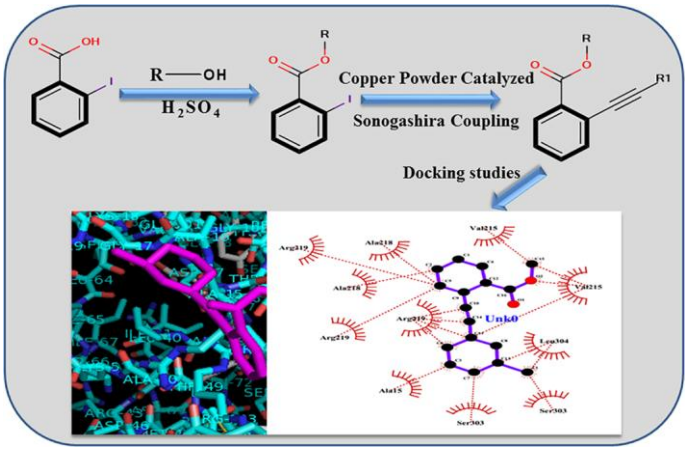
[2]Department of Chemistry, School of Basic and Applied Sciences, Galgotias University UP, India

Address Correspondence Dr. Imran Ali Department of Chemistry, Jamia Millia Islamia, (Central University) Jamia Nagar, New Delhi, India. Email: drimranchiral@gmail.com; drimran_ali@yahoo.com

Abstract

A practical copper catalyzed I-substitutions of alkyl-2-iodobenzoates with 1-octynes have been developed using Cu powder as a catalyst under solvent, co-catalyst, and base free conditions. This reaction system is new, facile, efficient, and economical that gives Sonogashira coupling products in excellent yields (up to **97%**). The coupled products (**A-J**) were characterized by CHNS, ^{1}H NMR and ^{13}C NMR and are found soluble in ethyl acetate and dichloromethane. In addition, simulation studies of **A-J** were carried out with aspulvinone dimethylallyltransferase enzyme and observe good binding affinity. The reported compounds may be future anti-cizmatics, anti-fobic disorder and inhibition of aspulvinone dimethylallyltransferase properties to control Alzheimer's, Schizophrenia etc. diseases.

Graphical Abstract



KEYWORDS: I-substitution; alkyl-2-iodobenzoates; Sonogashira coupling; Copper metal powder; Solvent free; Co-Catalyst free; Simulation studies

1. INTRODUCTION

Sonogashira coupling reactions have wide range of applications in the synthetic field such as material science, [1] pharmaceutical intermediates like isocoumarin derivatives, α-pyrons and indole derivatives, [2-4], preparation of fluorescent molecules[1] and arylbenzofurans [5]. The specialty of the reaction is that it takes place under mild conditions in the presence of a costly palladium catalyst. Besides, the functional groups like -CHO, -CN, -OCH_3 and -Cl remains unaffected. Due to these features several modifications have been reported in Sonogashira coupling reaction [6]. But, the important drawback of this reaction is the involvement of costly palladium catalyst. To avoid costly palladium catalyst, many authors developed sonogashira coupling reactions by using copper salts with phosphine ligands instead of palladium catalyst [7-10]. Moreover, the reaction conditions have been modified using iron salts along with copper salts [10,11], DABCO in solvent free conditions [12], iron salt nanoparticles [11, 13, 14]. However, the

reactions have some advantages in copper conditions over palladium. But, copper salts with phosphines are also associated with certain drawbacks like copper salt being used with phosphine ligand is poisonous in nature, longer reaction times and poor yields. Furthermore, the usage of two moles of base with dodecane is also one of major disadvantages. Recently, some reports on recent advances in copper catalyzed sonogashira coupling reactions have highlighted the beneficial effects of copper catalyzed reactions [15-16]. Keeping in view of these drawbacks, the efforts were made to carry out Sonogashira cross coupling reactions of alkyl-2-iodobenzoates with terminal alkynes using copper powder as a catalyst under solvent, co-catalyst, and base free conditions. Additionally, simulation studies have been carried out to find out the interactions with aspulvinone dimethylallyltransferase enzyme for the potential of inhibition property. The results are given herein.

2. RESULTS AND DISCUSSION

A simple and successful protocol have been developed for Sonogashira coupling reactions. In this protocol, initially we synthesized derivatives of iodobenzoic acid (**I-V)** by the reaction of iodobenzoic acid with different alcohols (methanol, ethanol, *n*-butanol, iso-butanol and *sec*-butanol). Then copper powder instead of palladium has been used as a catalyst in the absence of co-catalyst under mild solvent free conditions for the successful coupling reactions of alkyl-2- iodobenzoates with terminal alkynes (**A-J**) **Scheme 1**. Besides, a reasonable mechanism for formation of Sonogashira coupled products is shown in **scheme 2**. The yield of the coupled products (**A-J**) was founded quite good in the range of 84-97%. The analytical and spectroscopic data of the coupled

products (**A-J**), supported their proposed structures. The chemical structures of initial and final coupled products are given in in **Table 1**. The structures of synthesized compounds (**A-J**) were determined by CHNS, ^{1}H NMR and ^{13}C NMR spectroscopy. The formations of products (**A-J**) were confirmed by the presence of the characteristic ^{1}H NMR signal of alkyl protons in the range of 0.91-4.41 ppm, while aromatic protons appeared in the range of 7.12-8.37 ppm. In addition to it the coupled products were found fully soluble in ethyl acetate and dichloromethane and partially soluble in *n*-hexane, *n*-heptane. For ready reference, the ^{1}H NMR of compounds **I** and **J** are shown in **Fig. 1**, While the ^{1}H NMR and ^{13}C NMR of compounds (**A-H)** are shown in **Fig. FS1 a–n (Supplementary Information)**.

The main advantages of our new protocol for the development of sonogashira coupling products are as; high yields of products, nonpoisonous nature of catalyst and mild reaction conditions.

3. OPTIMIZATION

The reaction conditions were optimized using various catalysts (**Table 2**). The yields ranged from 22-97%. A perusal of this table indicates that the copper metal powder was the best one; resulting in 98% yield. During the optimization of catalyst, reaction completed within 12 hrs using 2.5 mole % of copper metal. Furthermore, with increment of mole % of copper metal powder, the rate of reaction increased and became constant after 20 mole % **(Fig. 2)**.

4. IN SILICO STUDIES

Combinatorial chemistry and virtual screening are well reputed, possibly due to their reduction of the extremely time consuming steps of organic and inorganic synthesis and biological screening. Molecular docking is a very valuable tool for the prediction of the interactions of drugs with various biological macromolecules at a supra molecular level [17]. In biochemistry, transferase is the general name for the class of enzymes that enact the transfer of specific functional groups (e.g. a methyl or glycosyl group) from one molecule to another [18]. In enzymology, an aspulvinone dimethylallyltransferase enzyme catalyzes the chemical reaction of 2-dimethylallyl diphosphate and aspulvinone E in 2-diphosphate + aspulvinone H. The systematic name of this enzyme class is dimethylallyl-diphosphate: aspulvinone-E dimethylallyltransferase. This enzyme is also called dimethylallyl pyrophosphate: aspulvinone dimethylallyltransferase. These results showed the possible inhibitor for the aspulvinone dimethylallyltransferase enzyme to control various diseases including Alzheimer's, Schizophrenia etc.

The rigid molecular of tRNA dimethylallyltransferase docking of the ligands has been carried out using AutoDock 4.2 to find out the possible sites of the interactions of aspulvinone dimethylallyltransferase with the ligands. The docking studies of ligands were performed with aspulvinone dimethylallyltransferase (PDB ID: 2CRM). The order of binding affinity of the synthesized compounds was **F > G > J > B= C >H > E > I > A = D**. The docked models of **A**, **B** and **C** are shown in (**Fig. 3a-c**). While the docking models of the other reported compounds are shown in **Fig**. **FS2 a-g (supplementary data**). It is clear from the docked models that all the compounds interacted with tRNA

dimethylallyltransferase enzyme *via* different sites. The number of H- bonds formed by the compounds **A–J** is given in **Table 3**. The number of hydrogen bonds were zero (**F-J**), one (**A, B and E**), two (**D**), three (**C**). The common moities of ligands involved in hydrogen bonding were carbonyl and ether groups and residues of receptor involved were ALA-215H01, ARG-219H01, ASP-20H01, GLY-17H01, SER-303H01, GLU-229H01, ARG-225H01 and ALA-218H01. In addition to hydrogen bondings, hydrophobic interactions were also observed **(Table 3)**. In addition, hydrophobic interactions were also observed. The common residues involved Arg282, Ala221, Glu222, Arg225, Ser303, Val215, Leu21, Leu304, Ser303 and Tyr270. The different simulation parameters of the final compounds (**A-J**) are given in **Table 3**.

5. IMPORTANCE OF WORK

The iodoarenes are higher reactive than chloro, bromo ones for the synthesis of substituted arynes/alkynes. As per the literature, the iodoarenes used in coupling reactions by a palladium catalyst resulted poor yields because of poisonous palladium catalyst [19-21]. But in this research article, the coupling reactions were performed with iodoarenes by copper catalyst. The copper catalyst is not poisoned by iodoarenes; leading to good yields of substituted arynes/alkynes. In addition to it, our method is found to be eco-friendly involving no use of ligands, co-catalyst, base and solvent that is the main speciality of our work. Furthermore, the prediction of the activities of the synthesized compounds was carried out by online software (pass prediction). It was observed that the compounds have anti-cizmatics, anti-fobic disorder and inhibition of aspulvinone dimethylallyltransferase properties. Besides, in silico studies also indicated the prepared

compounds may act as inhibitor for aspulvinone dimethylallyltransferase enzyme to control Alzheimer's, Schizophrenia etc. diseases.

6. CONCLUSIONS

In summary, we have reported a mild and efficient method for copper-catalyzed I-substitution of alkyl-2-iodobenzoates with alkynes under solvent free conditions (Sonogashira coupling reactions). The reactions were performed smoothly to generate the desired products (**A-J**) in moderate to excellent yields (**84-97%**). This method offers one of the important motifs for the synthesis of Sonogashira coupled products. Furthermore, **A-J** compounds were soluble in ethyl acetate and dichloromethane. The docking affinities varied from 3.3 to 4.6 kcal/mol, and the compounds formed 1-3 hydrogen bonds with the amino acid residues of aspulvinone dimethylallyltransferase enzyme. The reported compounds may be future anti-cizmatics, anti-fobic disorder and inhibition of aspulvinone dimethylallyltransferase properties to control Alzheimer's, Schizophrenia etc. diseases.

7. EXPERIMENTAL

2.3. Synthesis Of Alkyl 2-Benzoates (I-V)

Iodobenzoic acid (10 g) was added to 60 mL of alcohol derivatives (methanol, ethanol, *n*-butanol, iso-butanol and *sec*-butanol) in 5 mL conc. H_2SO_4, separately. The reaction mixtures were stirred electromagnetically in an oil bath at 65, 78, 100, 105 and 95°C for 24, 5, 2, 4 and 4 hrs, respectively. Then excess alcohol derivatives were removed under vacuum rotary evaporator. Then water and ethyl acetate were added to final residues and

organic layer was separated and washed three times with water and with a saturated bicarbonate solution. Finally, the mixtures were dried over Na_2SO_4 and excess solvent was removed by distillation that resulted 97% yield of methyl-2-iodobenzoate, 99% yield of ethyl 2-iodobenzoate, 95% yield of *n*-butyl 2-iodobenzoate, 96% yield of 2-methylpropyl-2-iodobenzoate and 98% yield of butan-2-yl- 2-iodobenzoate, respectively. **(Scheme 1, Table 1)**.

2.4. Synthesis Of Final Coupled Products (A-J)

Reaction mixtures of **1-V** (10 mL, 10 mM) separately, 1-octyne (12 mL, 12 mM), copper powder (7.8mM, 0.5 g) in dichloromethane (DCM) were stirred electromagnetically at 120°C for 12 hrs. Filtration removed the catalyst. The crude products were purified over silica gel column chromatography in 0.25% ethyl acetate with *n*- hexane solvent system and resulted **A-E** products.

Reaction mixtures of **1-V** (10 mL, 10 mM) separately, 1-chloro-3-ethynylbenzene, 1-chloro-3-ethynylbenzene, phenylacetylene, phenylacetylene, phenylacetylene (12 mL, 12 mM), respectively, copper powder (0.5 g) in dichloromethane (DCM) were stirred electromagnetically at 120°C for 12 hrs. Filtration removed the catalyst. The crude products were purified over silica gel column chromatography in 0.25% ethyl acetate with *n*- hexane solvent system and resulted **F-J** products (**Scheme 1**, **Table 1**).

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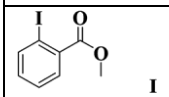
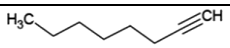
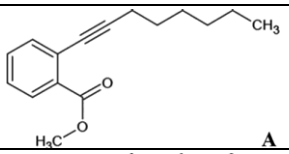
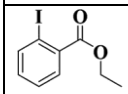
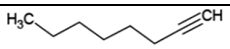
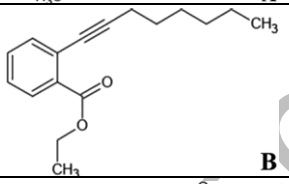
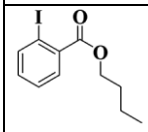
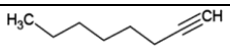
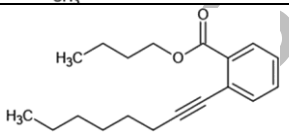
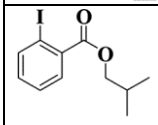
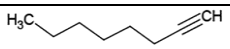
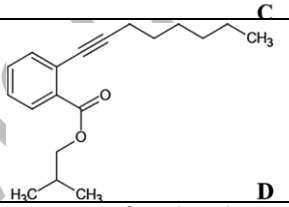
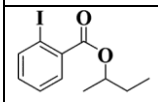
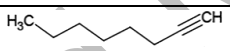
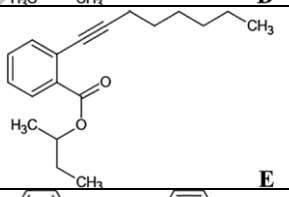
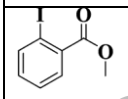
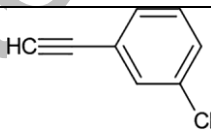
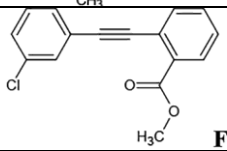
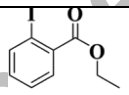
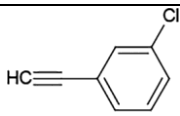
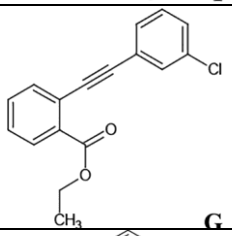
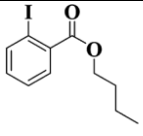
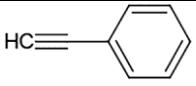
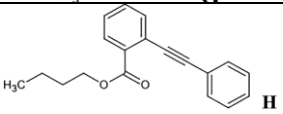
Table 1: Chemical structures and percentage yields of **I-V** and **A-J.**

Iodobenzoates	Alkynes	Coupled products	Yields (%)
 **I**		 **A**	97
 **II**		 **B**	95
 **III**		 **C**	93
 **IV**		 **D**	86
 **V**		 **E**	89
 **I**		 **F**	90
 **II**		 **G**	94
 **III**		 **H**	91

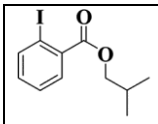
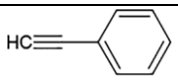
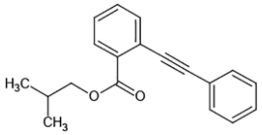
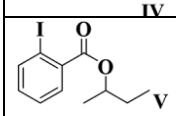
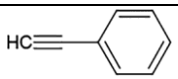
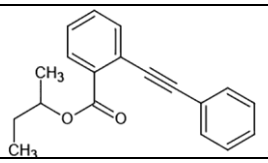
 IV		 I	92
 V		 J	84

Table 2: Catalytic screening during optimization.

Sl. No.	Catalysts	% Yields
1	CuI/Orthophenylenediamine	77
2	CuI /Binap complex	89
3	Vanillin Cu Complexes	83
4	$CuBr_2(PPh3)_3$	91
5	Fe Powder	Traces
6	CuI	55
7	**Copper metal powder**	**97**
8	$CuBr_2$	22

The reaction was conducted at110° C in presence of DMF, Idobenzene and 1-Octyne used as reactant.

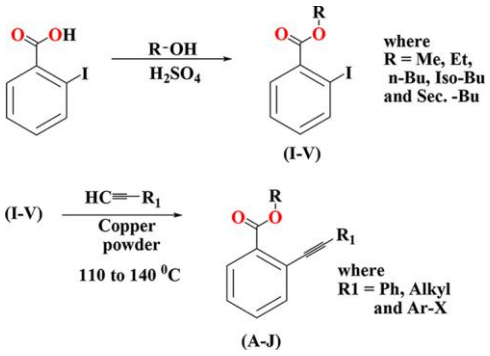
Table 3: The different simulation parameters of **A-J** with aspulvinone dimethylallyltransferase.

Compounds	Binding affinity (kcal/mol)	Number of hydrogen bonds	Residues involved in H-bonding *(Bond length)*	Residues involved in hydrophobic attractions
A	-3.3	1	**A:** ALA-215H01:: O of carbonyl group *(3.4)*	Arg282:: C1&C2, Ala218::C10 Ala221:: C1,C7,C9,C12&C14 Glu222::C3,C4,C8&C11 Arg225::C4, C5,C9
B	-3.8	1	**A:** ARG-219H01:: O of ester group *(3.5)*	Ser303::C1,C5,C9&C14 Arg219::C4,C7,C10,c16,C17&O 2 Val215::C4,C7, Asp20::C2,C9 Leu304::C8,C11&C12
C	-3.8	3	**A:** ASP-20H01::O of carbonyl group *(3.5)* **B:** GLY-17H01:: O of carbonyl group *(3.5)* **C:** SER-303H01:: O of ester group *(3.2)*	Arg219::C1, Leu21::C8 Asp20::C4,C5,C8,C9,C13&C19 Ala16::C11, Leu304::C11 Ser303::C11,C17&C19 Ala304::C12, Ala305::C12,C18
D	-3.3	2	**A:** GLU-229H01:: O of carbonyl group *(3.5)*	Tyr270::C2,C3,C5 Glu226::C4&C9, Glu222::C6 Arg225::C5,C6,C10,C13&C14

			B: ARG-225H01:: O of carbonyl group *(3.3)*	Glu229::C18,C19,01&O2
E	-3.6	1	**A:** ALA-218H01:: O of carbonyl group *(3.4)*	Ser303::C1&C2 Val215::C16 Ala15&Pro210::C1 Ala16::C3,Ala15::C5 Glu222::C4,C6,C8,C9, Ala218::O1Ala219::C5,C10,C10 ,C16C17,O1
F	-4.6	0	-	Ala218::C2,C5,Ala15::C3 Arg219::C5,C6,C10,C11&C14 Ser303::C7,Cl,Leu304::C13&Cl, Val215::C11,C15&O2
G	-4.4	0	-	Ala16::C1,Ala15::C1 Pro210::C1,C2,Arg219::C5,C11, C16,Ala218::C3,C7 Ala215::C2,C5,C6, Leu304::O1 Ser303::C1,Leu216::C2, Val215::C6,C10,C11C15
H	-3.7	0	-	Arg225::C2,C6,C7,C9C10C13,C 15&C17,Glu229::C2,C3,C15 Glu222::C4,C10,C14 Glu226::C6&C9

I	-3.5	0	-	Arg225::C10,C15,C13,C9,C5&O1,Gln226::C2&C5 Glu222::C14,C17,C9&C5
J	-3.9	0	-	Ala218::C1&C4, Gln226::C5 Ala221::C10,Arg225::C15,C13,C5&O1 Gln222::C10,C9,C17,C15,C8,

Scheme 1. Syntheses of alkyl 2-iodobenzoates and their coupling products.



Scheme 2. A reasonable proposed mechanism for formation of coupling products.

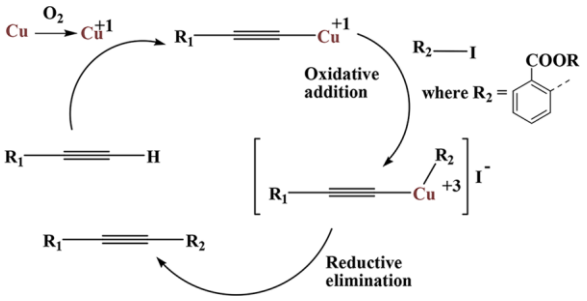


Fig. 1. ^{1}H NMR spectra of compounds **I** and **J**

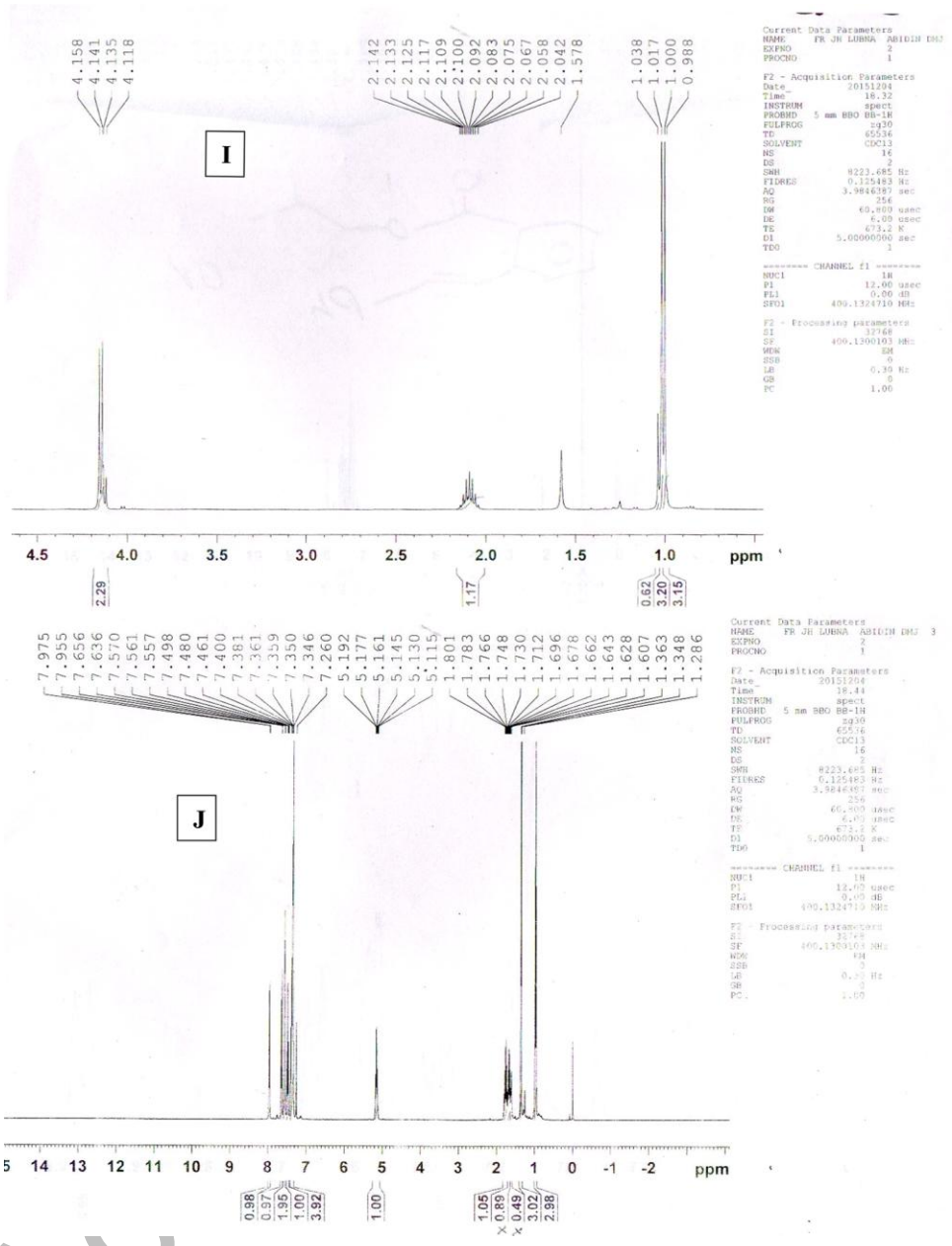


Fig. 2. Effect of mole percentage catalyst on rate of reaction.

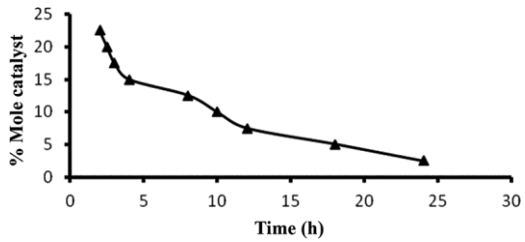
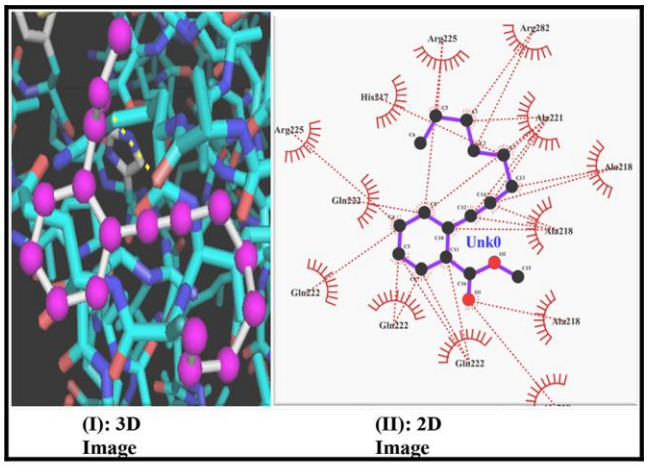
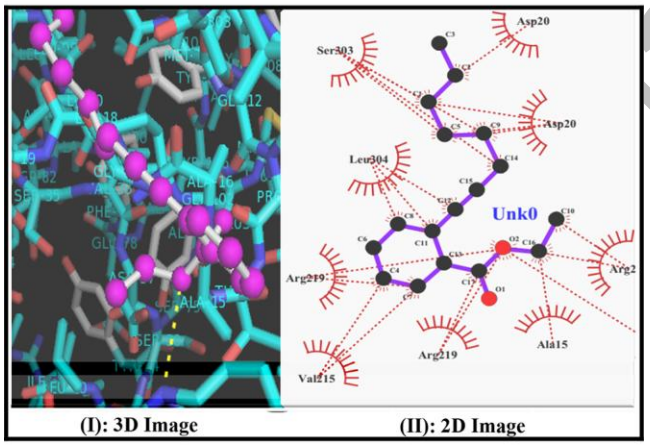


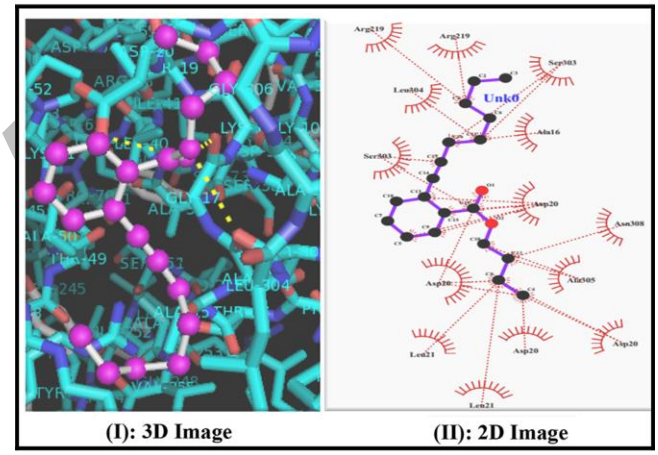
Fig. 3. a. 2D and 3D docking poses of **A** with aspulvinone dimethylallyltransferase.; **b.** 2D and 3D docking poses of **B** with aspulvinone dimethylallyltransferase; **c:** 2D and 3D docking poses of **C** with aspulvinone dimethylallyltransferase.



(a)



(b)



(c)