CHAPTER 2

Starch Functionalized Magnetite Nanoparticles: A Green, Biocatalyst for One-pot Multicomponent Synthesis of Imidazopyrimidine Derivatives in Aqueous Medium under Ultrasound Irradiation

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2.1 Introduction

Nitrogen-containing heterocyclic moieties get much more attention due to its biological, agrochemical and pharmaceutical properties. Imidazopyrimidines, which have two nitrogen-containing heterocyclic imidazole and pyrimidine core units, possess several biological activities (Wahe et al. 2003) like antioxidant, antibiotic, antiarrhythmic, anti-inflammatory, antiviral, antimicrobial, anti-diabetic, herbicidal, anti-cancer (Klutchko et al. 1998), calcium anagostic (Alajarin et al. 1994), antineoplastic (Badawey et al. 1995), anti-hepatitis B and as well as DNA-gyrase inhibitors and lipid peroxidation inhibitor properties (Le Corre et al. 2010, Neochoritis et al. 2011).

Several methods have been reported for the synthesis of imidazopyrimidine derivatives under different conditions and diverse catalysts like L-proline (Kalita et al. 2016), citric acid (Warekar et al. 2016), silica sulfuric acid (Wu et al. 2010), sulfamic acid (Yao et al. 2008), boric acid (Meshram et al. 2012), MgO (Sheibani et al. 2013), [PVPH]ClO_4 (Abedini et al. 2016), $ZnClO_4$ (Kaur et al. 2015), *P*-TSA (Reddy et al. 2014), NH_4OH (Hu et al. 2012), H_3PO_4–Al_2O_3 (Shaterian et al. 2014), RHA [pmim]HSO_4 (Shirini et al. 2016), Fe_3O_4@IM (Hemmati et al. 2016), [bmim][BF_4] (Yao et al. 2010).

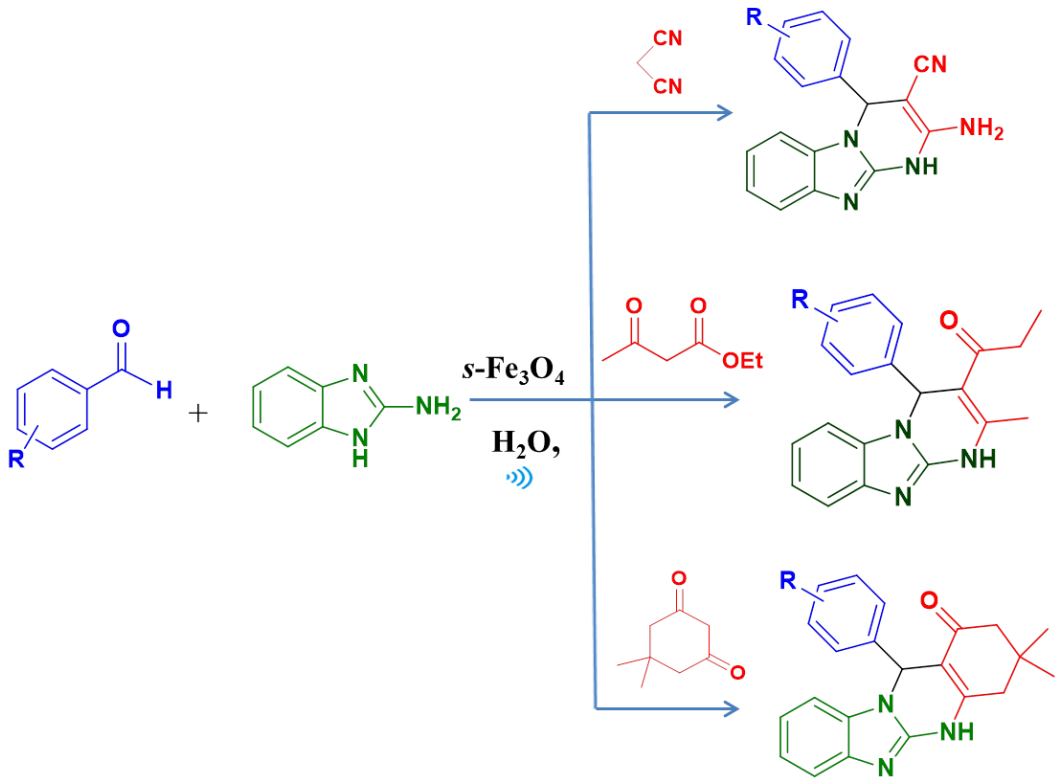
However these procedures suffer from comparatively harsh reaction conditions, longer reaction time, low yields and use of volatile organic solvents. Therefore, the development of an energy and environment efficient greener protocol for the synthesis of these heterocyclic compounds is always in demand.

In the last few decades, the construction of biologically active complex structures in a single step by multicomponent synthesis is one of the most promising areas of green chemistry. Successful implementation of this single step approach allows high atom economy, reduces reaction time, low cost due to lesser material consumption as compared to multi-step synthesis. However, limited methods have been reported for the synthesis of imidazopyrimidine derivatives via one pot. Imidazopyrimidines could be synthesized via multicomponent reaction (MCR) it reduces processing time, cost and waste materials. Another aspect of such green synthesis is the requirement of an alternative solvent like water (Khazaei et al. 2015, Rajarathinam et al. 2016, Komykhov et al. 2016, Tamaddon et al. 2014) supercritical CO_2, ethylene glycol (Survase et al. 2017, Nagarapu et al. 2013), ionic liquids (Velasco et al. 2015, Zhao et al. 2003), glycerol (Singh et al. 2016, Radatz et al. 2011) etc. which can be used instead of conventional volatile organic solvents. Among these, water is sustainable, non-toxic, inexpensive and can dissolve a variety of organic and inorganic compounds. In this respect, water has attracted much attention due to advantages in term of economic, ecological and environmental point of view. Since green synthesis procedures have generally been found to be relatively slower; therefore, workers have often

resorted to strong ultrasound irradiation (>20 Hz) for smooth conduct of the reaction. Ultrasound radiation brings physical and chemical changes due to the formation and destruction of cavitation space in the reaction mixture. Ultrasonic radiations are useful for all type of catalysts but are most effective for the catalysts which are intertwined or magnetic because ultrasound radiation helps to disperse the catalyst particulates in the reaction mixture equally (Zou et al. 2012, Tabassum et al. 2015, Cappelletti et al. 2015, Banerjee 2017, Noori et al. 2017).

Higher efficiency of green synthesis protocols for multicomponent synthesis can be achieved by using an appropriate nanocatalyst. Nowadays enzymes and biomolecules functionalized nanoparticles are being used extensively in organic synthesis as well as in biomedical sciences (Gupta et al. 2015, Gawande et al. 2012, Maleki et al. 2014, Subbiah et al. 2010, Mout et al. 2012). Functionalized nanocatalysts display improved stability against aggregation, thereby giving access to higher surface area and more catalytically active sites. Additionally, functionalization also influences the properties of active sites on the nanocatalyst (Singh et al. 2016). Because of this; the present investigation utilizes starch functionalized superparamagnetic magnetite nanoparticles for multicomponent synthesis of imidazopyridine derivatives. Starch is an excellent substrate for supporting the nanoparticles because it contains hydroxyl groups which stabilize the nanoparticles. Besides this, starch is an economical and biodegradable natural polymer of glucose. Utilization of such natural molecules for the functionalization of heterogeneous catalysts is

one of the most important thrust areas in green chemistry. To the best of our knowledge, the catalytic activity of starch functionalized magnetite nanoparticles for the one-pot multicomponent synthesis of imidazopyrimidine derivatives in aqueous medium under ultrasound irradiations has not been reported till date.



Scheme 2.1 *s*-Fe_3O_4 catalyzed synthesis of imidazopyrimidines

Moreover, superparamagnetic nanoparticles can be easily separated by placing magnet below the reaction vessel. The nanoparticles can then be reused by re-dispersing them again in fresh reaction medium after removal of the magnetic field. Thus, a new

dimension in organic synthesis for the devolvement of more efficient and green methodology for the synthesis of imidazopyridine derivatives (4) **(Scheme 2.1)** is achieved.

2.2 Results and Discussion

2.2.1 Nano-catalyst characterization

The starch functionalized superparamagnetic nanoparticles *s*-Fe_3O_4 were synthesized by co-precipitation method as reported by Prakash et al. and characterized by using different analytical and spectroscopic techniques (Singh et al. 2016). How starch was attached to the magnetite nanoparticles was investigated by FT-IR spectroscopy. The FT-IR spectrum of pure soluble starch shows characteristic peaks at 1,155 cm^{-1} for the stretching frequency of glycosidic C-O-C and 1,023 cm^{-1} for C-O bonds another peak, due to O-H stretching mode of starch, is observed at 3412 cm^{-1}. In contrast to this, the FT-IR of *s*-Fe_3O_4 displays the stretching frequencies of the C-O-C and C-O bonds at 1,150 and 1,025 cm^{-1} respectively and appearance of an intense peak at 584 cm^{-1} is due to the stretching frequency of Fe-O bond supports the formation of *s*-Fe_3O_4 (**Figure 2.1)**.

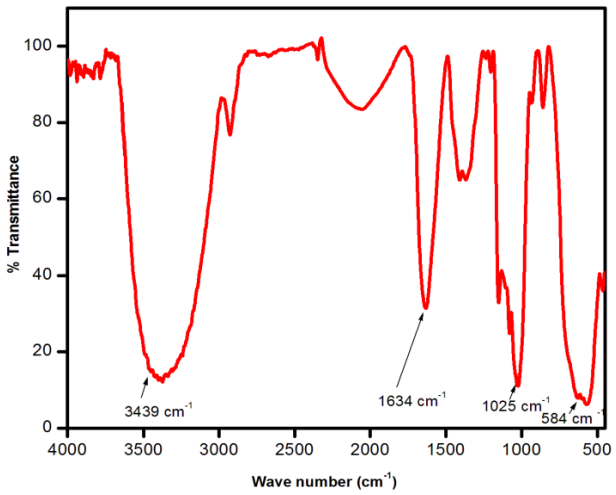


Figure 2.1 FT-IR of *s*-Fe_3O_4

The XRD diffraction spectrum of *s*-Fe_3O_4 is shown in **Figure 2.2**. The indexed planes (220), (311), (400), (422), (511), and (440) agree very well with the magnetite phase as per JCPDS card no-89-0688. The absence of any other peak indicates that only pure magnetite phase nanoparticles have been formed. Moreover, starch functionalization does not impact the XRD pattern of the magnetite phase. The SEM analysis of *s*-Fe_3O_4 was performed to investigate the effect of starch on magnetite particle morphology (**Figure 2.3**). The SEM image clearly shows the homogenous morphology and small particle size of *s*-Fe_3O_4. The presence of C, along with Fe and O in the Energy Dispersive X-Ray Analysis (EDAX), reaffirms the attachment of starch to magnetite (**Figure 2.4**). The TEM images *s*-Fe_3O_4 is spherical in nature and very fine particles in the case of *s*-Fe_3O_4 shows nano Fe_3O_4 are functionalized with starch (**Figure 2.5**).

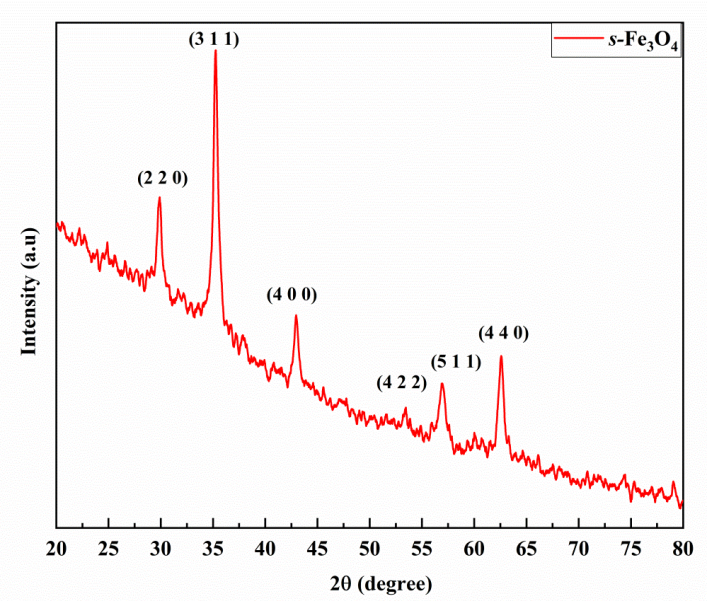


Figure 2.2 XRD pattern of *s*-Fe_3O_4

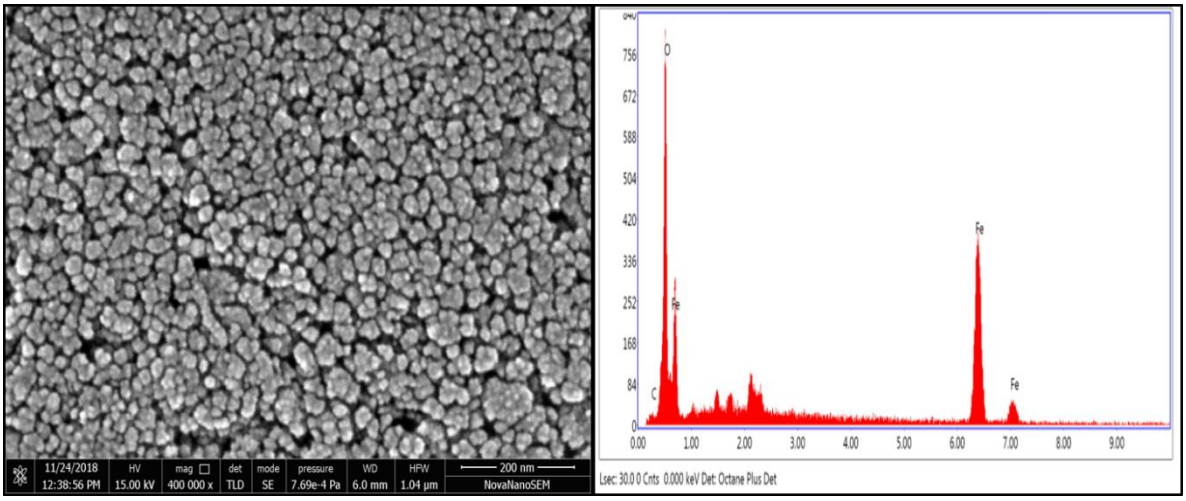


Figure 2.3 SEM image of *s*-Fe_3O_4

Figure 2.4 EDAX of *s*-Fe_3O_4.

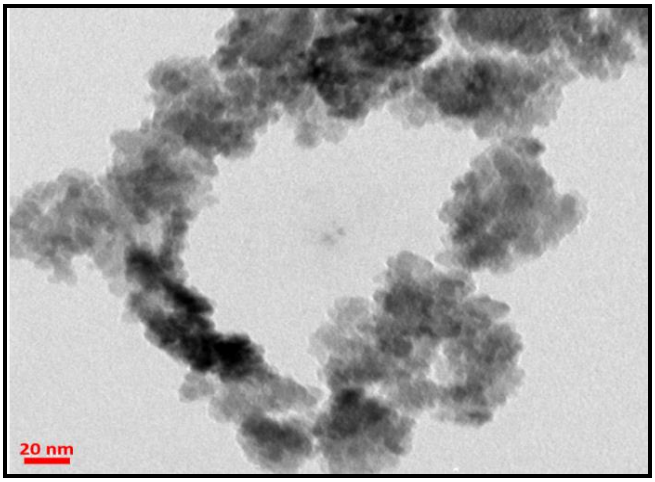


Figure 2.5 TEM image *s*-Fe_3O_4

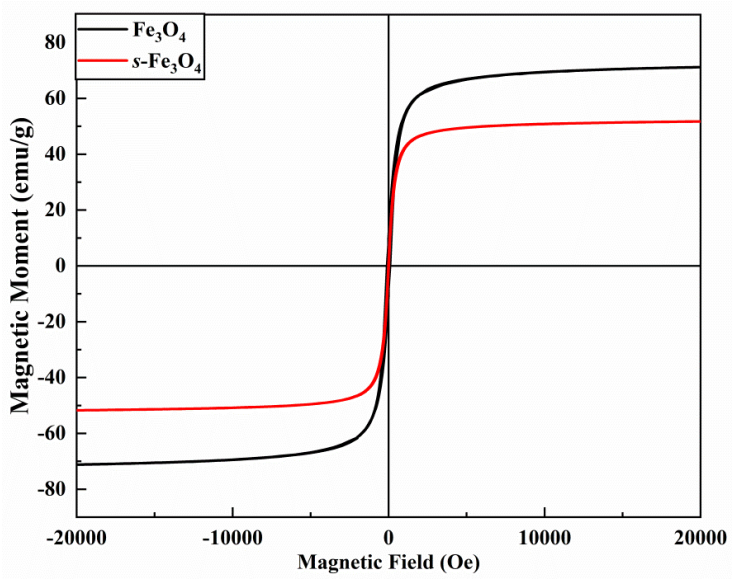


Figure 2.6 MPMS analysis; Magnetic moment versus magnetic field graph of Fe_3O_4 and *s*-Fe_3O_4

The magnetic properties of the starch functionalized magnetite nanoparticles were analyzed by Mission Planning and Monitoring System (MPMS) **Figure 2.6** shows the magnetization curve of *s*-Fe_3O_4. The absence of hysteresis loop shows that *s*-Fe_3O_4 is superparamagnetic. Furthermore, the magnetic moment of *s*-Fe_3O_4 (51.9 emu/g) is lower than Fe_3O_4 (71.3 emu/g) due to starch functionalization.

2.2.2 Optimization of Reaction Conditions

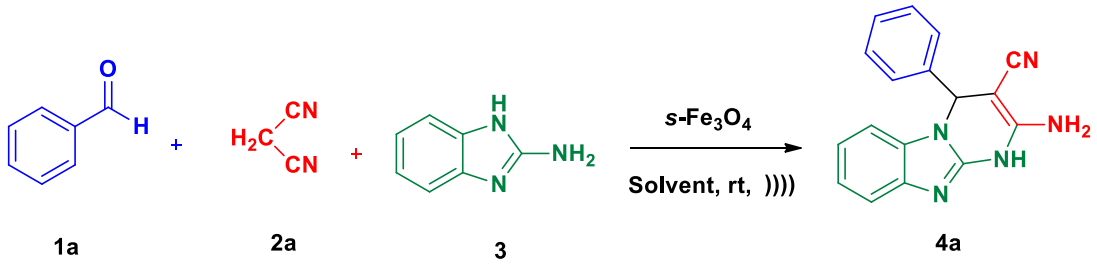
To establish the optimized conditions benzaldehyde (**1a**), malononitrile (**2a**) and 2-aminobenzimidazole (**3**) in (1.2: 1.2: 1 molar ratio) was chosen as a model reaction for the synthesis of imidazopyrimidine (**4a**).

The model reaction was carried out in reflux and ultrasound irradiation method to compare the effectiveness of this methodology. When model reaction was done under reflux, the reaction was completed in 2h and gave 80% yield of the product. While in ultrasound irradiation method it gave 98% of the product in 3 min because catalyst *s*-Fe_3O_4 was homogenized in reaction mixture by ultrasound irradiation so all other optimization was carried out by ultrasound method. To find a suitable solvent the model reaction was carried out with 5 mg of *s*-Fe_3O_4 in various solvents at room temperature under ultrasound irradiation. In non-polar solvents such as xylene, toluene, benzene no product was obtained after 1h (**Table 2.1, entries 1-3**). Polar-aprotic solvents such as 1,4-dioxane, acetonitrile, dichloromethane gave the imidazopyrimidine (**4a**) in 25-40% yield after one hour (**Table 2.1, entries 4-6**). In the case of polar- protic solvents like methanol, ethanol, and water

gave the product (**4a**) in 40-98% yield (**Table 2.1, entries 7-9**). The best result was obtained in water almost complete conversion of the reactants into the product (**4a**) was achieved with an isolated yield of 98% in 3 minutes (**Table 2.1, entry 9**). To understand the effectiveness of *s*-Fe_3O_4 nano catalyst in the synthesis of imidazopyrimidines some controlled experiments have been done with the model reaction under the same reaction conditions. The model reaction mixture was irradiated under ultrasound without catalyst *s*-Fe_3O_4 in water at r.t. However, there was no formation of 2-amino-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (**4a**) in 1h (**Table 2.1, entry 10**). In another controlled experiment, the reaction was also performed in the presence of starch only (no *s*-Fe_3O_4) but no product was formed in this case. The reaction was attempted with nano Fe_3O_4 (without starch functionalization) separately again, in this case, only 30% of the product was obtained under the same reaction conditions (**Table 2.1, entry 11, 12**).

Furthermore, optimization of catalyst loading was investigated with catalyst concentration 2, 3 and 4 mg gave 50%, 80%, and 98% yields of the desired product respectively (**Table 2.1, entries 13–15**), the results show that 4 mg of *s*-Fe_3O_4 was optimal and excessive amount of catalyst did not increase the rate and yield of the product. The product (**4a**) was characterized by spectral data (IR, ^1H, ^{13}C NMR) and confirmed by comparing with the reported.

Table 2.1 Evaluation of solvents and amount of the catalyst for the synthesis of 4a[a]



Entry	Solvent	Catalyst	Catalyst Amount (mg)	Time (min)	% Yield[b]
1	Xylene	*s*-Fe_3O_4	5	60	NA
2	Toluene	*s*-Fe_3O_4	5	60	NA
3	Benzene	*s*-Fe_3O_4	5	60	NA
4	1,4-Dioxane	*s*-Fe_3O_4	5	60	25
5	Acetonitrile	*s*-Fe_3O_4	5	40	35
6	Dichloromethane	*s*-Fe_3O_4	5	60	40
7	Ethanol	*s*-Fe_3O_4	5	40	50
8	Methanol	*s*-Fe_3O_4	5	60	40
9	Water	*s*-Fe_3O_4	5	3	98
10	Water	-	-	60	NA
11	Water	nano-Fe_3O_4	5	60	30
12	Water	Starch	5	60	NA
13	Water	*s*-Fe_3O_4	4	3	98

14	Water	*s*-Fe_3O_4	3	10	80
15	Water	*s*-Fe_3O_4	2	15	50

[a] **Reaction conditions:** Benzaldehyde 1a (1.2 mmol), malononitrile 2a (1.2 mmol) and 2-aminobenzimidazole 3 (1.0 mmol) in the presence of *s*-Fe_3O_4 at room temperature under ultrasound irradiation, [b]Isolated yield.

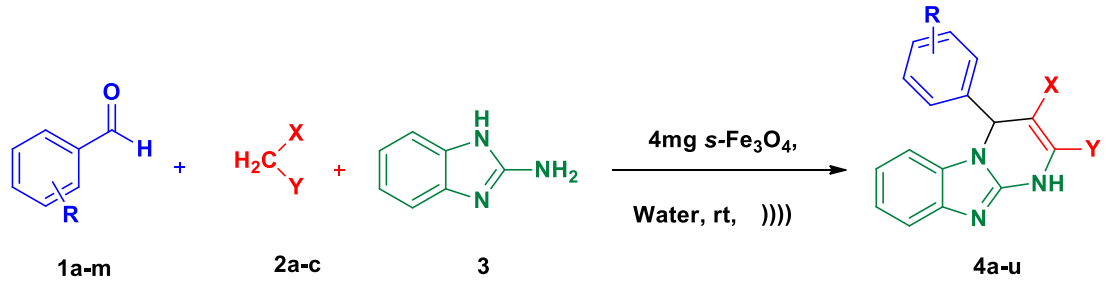
2.2.3 Substrate Scope

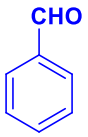
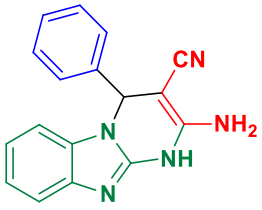
With optimized conditions in hand (**Table 1, entry 13**), the scope of this *s*-Fe_3O_4 catalyzed protocol was investigated with a variety of aromatic aldehydes such as benzaldehyde (**1a**), 2-methylbenzaldehyde (**1b**), 4-methoxybenzaldehyde (**1c**), 2-naphthaldehyde (**1d**), 2-nitrobenzaldehyde (**1e**), 4-nitrobenzaldehyde (**1f**), 2-chlorobenzaldehyde (**1g**), 3-chlorobenzaldehyde (**1h**), 4-chlorobenzaldehyde (**1i**), 2,3-dichlorobenzaldehyde (**1j**), 4-fluorobenzaldehyde (**1k**), 4-bromobenzaldehyde (**1l**) and malononirile (**2a**) with 2-aminobenzimidazole (**3**) which leads to a series of imidazopyrimidine derivatives viz. 2-amino-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (**4a**), 2-Amino-4-(o-tolyl)-1,4-dihydrobenzo[4,5]imidazolo[1,2-a]pyrimidine-3-carbonitrile (**4b**), 2-amino-4-(4-methoxyphenyl)-1,4 dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3 carbonitrile (**4c**), 2-amino-4-(naphthalen-1-yl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (**4d**), 2-amino-4-(2-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile **(4e)**, 2-amino-4-(4-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile **(4f)**, 2-amino-4-(2-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile **(4g),** 2-amino-4-(3-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-

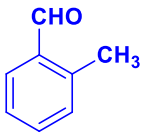
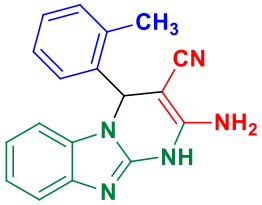
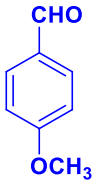
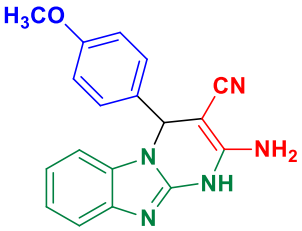
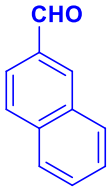
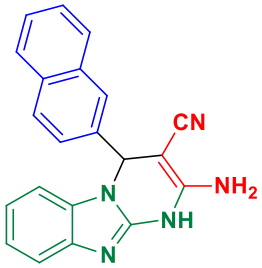
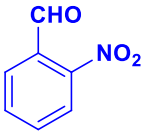
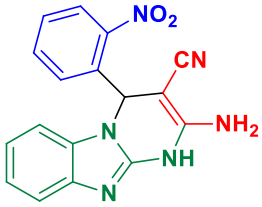
carbonitrile **(4h)**, 2-amino-4-(4-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazolo[1,2-a]pyrimidine-3-carbonitrile **(4i)**, 2-amino-4-(2,3-dichlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile **(4j)**, 2-Amino-4-(4-fluorophenyl)-1,4-dihydrobenzo[4,5]imidazolo[1,2-a]pyrimidine-3-carbonitrile **(4k),** 2-Amino-4-(4-bromophenyl)-1,4-dihydrobenzo[4,5]imidazolo[1,2-a]pyrimidine-3 carbonitrile **(4l)** in high-to-excellent yields. **Table 2.2**, reveal that nitro, chloro, fluoro, bromo electron-withdrawing groups on benzaldehyde leads to excellent yields in shorter reaction time than electro donating groups like methoxy, methyl. Further under the same optimized conditions the reaction of different active methylene compounds like ethyl acetoacetate (**2b**), dimedone (**2c**) with various aldehydes (**1**) and 2-aminobenzimidazole (**3**) 1-(2-methyl-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-3-yl)propan-1-one (**4m**), 1-(4-(4-methoxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-3 yl)propan-1-one (**4n**), 1-(4-(4-chlorophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-3-yl)propan-1-one **(4o),** 1-(2-methyl-4-(4-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-3-yl)propan-1-one **(4p),** 3,3-dimethyl-12-phenyl-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one **(4q),** 12-(4-methoxyphenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one **(4r),** 3,3-dimethyl-12-(naphthalen-2-yl)-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one **(4s),** 3,3-dimethyl-12-(4-nitrophenyl)-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one **(4t),** 12-(4-chorophenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-

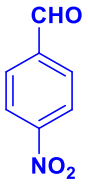
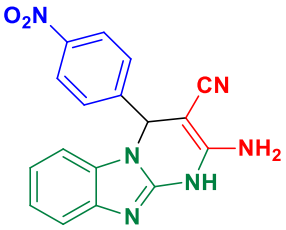
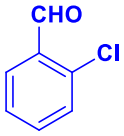
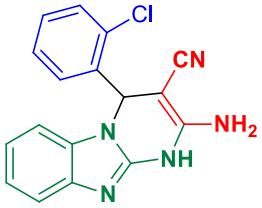
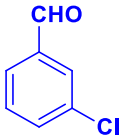
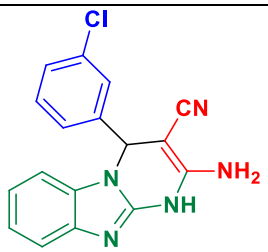
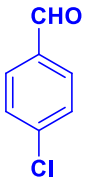
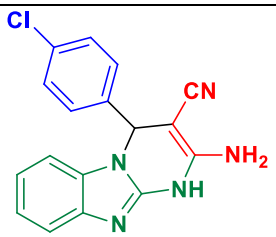
one **(4u),** gave desired products in excellent yields but it took slightly longer reaction time than malanonitrile. Excellent chemoselectivity is an important aspect of this reaction it gave only (**4**) as the major product in very high yields and the other possible product (**5**) was not observed in this methodology (**Scheme 2.2**).

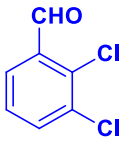
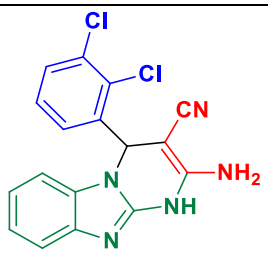
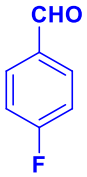
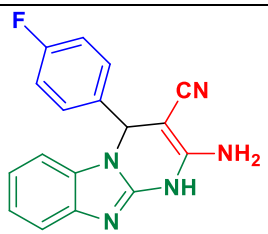
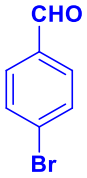
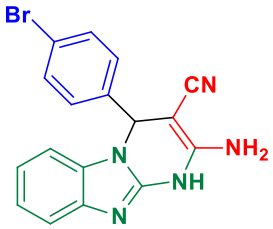
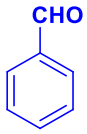
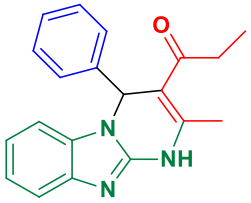
Table 2.2 Starch functionalized magnetite nanoparticles catalyzed the multicomponent synthesis of imidazopyrimidines (4a-u).

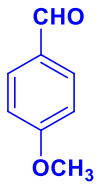
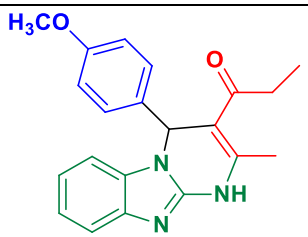
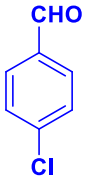
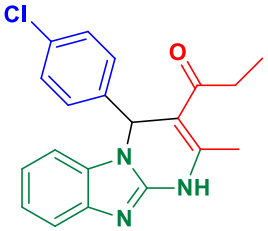
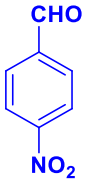
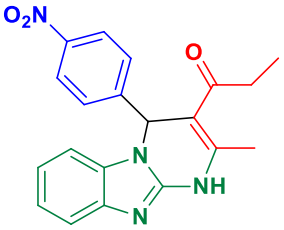
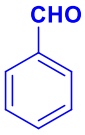
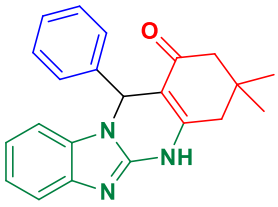


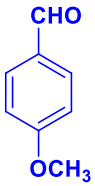
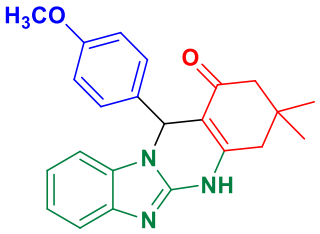
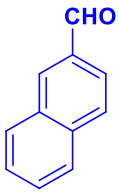
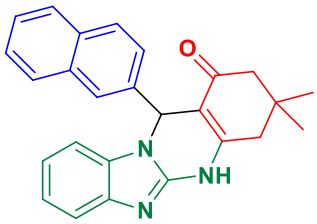
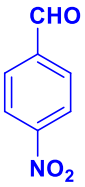
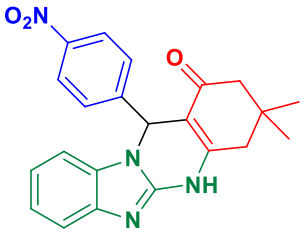
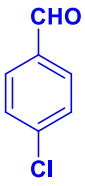
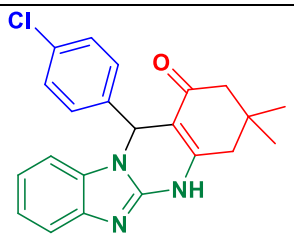
Entry	Reactant	Product	Time (min)	% Yield[b]
1	 1a	 4a	3	98

2	 1b	 4b	5	95
3	 1c	 4c	6	93
4	 1d	 4d	4	96
5	 1e	 4e	3	96

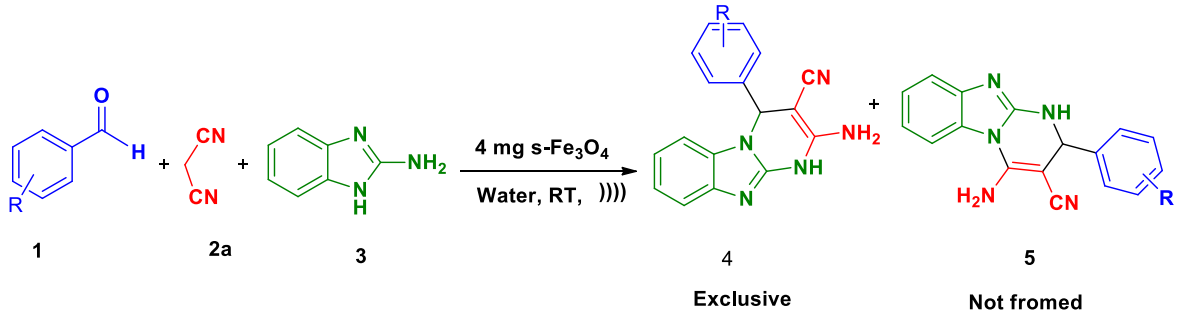
6	 1f	 4f	2	98
7	 1g	 4g	3	95
8	 1h	 4h	5	94
9	 1i	 4i	3	97

10	 1j	 4j	4	96
11	 1k	 4k	3	98
12	 1l	 4l	4	97
13	 1a	 4m	6	95

14	 1c	 4n	8	96
15	 1i	 4o	6	97
16	 1f	 4p	6	97
17	 1a	 4q	9	96

18	 1c	 4r	9	98
19	 1d	 4s	8	95
20	 1f	 4t	7	98
21	 1i	 4u	7	98

[a] **Reaction conditions:** Benzaldehyde derivatives 1a-l (1.2 mmol), active methylenic compounds 2a-c (1.2), 2-amino benzimidazole 3 (1.0 mmol) and *s*-Fe_3O_4 (4 mg) in 5 mL water under ultrasound irradiation method, b isolated yield



Scheme 2.2 Chemoselective synthesis of 4

2.2.4 Reusability of *s*-Fe_3O_4 nanocatalyst

The reusability of *s*-Fe_3O_4 nanocatalyst was also examined under the optimized reaction conditions up to 6 runs (**Figure 2.7**). The catalyst was separated by an external magnet after completion of the reaction, first washed with water and then methanol (3x10mL), dried at 60 ^oC and used in next reaction. The collected catalyst could be reused numerous times in the succeeding runs without a significant loss of catalytic activities. Comparison of XRD pattern (**Figure 2.9**) and FT-IR spectra (**Figure 2.8**) of the fresh and recycled catalyst *s*-Fe_3O_4 has shown that the reaction conditions do not affect the structure and chemical nature of the catalyst.

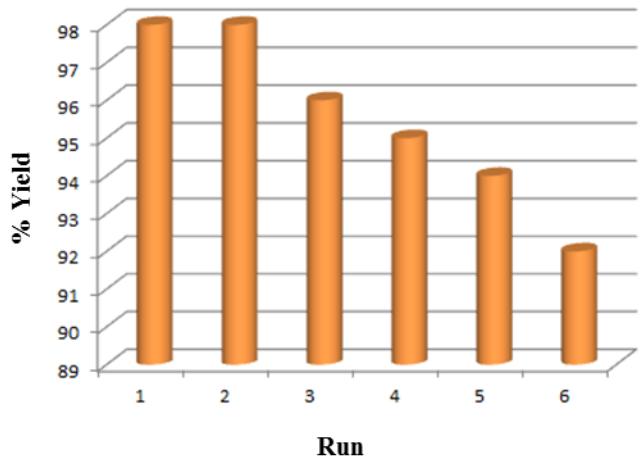


Figure 2.7 Recyclability of catalyst upto 6 runs

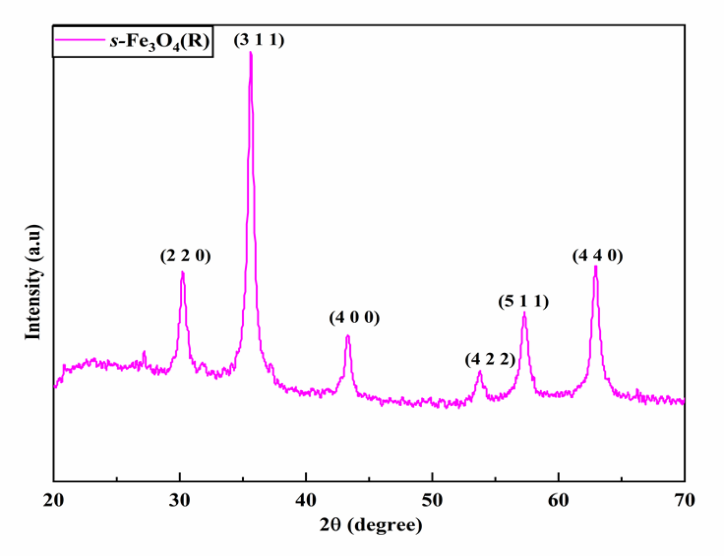


Figure 2.8 XRD pattern of reused *s*-Fe_3O_4

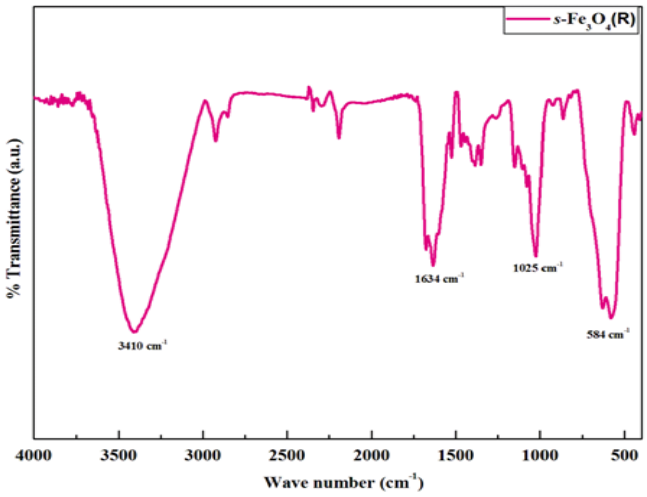


Figure 2.9 FT-IR of reused *s*-Fe_3O_4

2.2.5 Proposed Mechanism

A proposed mechanism for the *s*-Fe_3O_4 catalyzed synthesis of imidazopyrimidine based on the product analysis is shown in **Figure 2.10**. In the presence *s*-Fe_3O_4 catalyst the carbonyl group of aldehyde get polarized and its electrophillicity that help the condensation with malanonitrile to from arylidenemalononitrile intermediate (**I**) by Knoevenagel reaction. In the next step, Michael addition by ring nitrogen atom of 2-aminobenzimidazole (**3**) to arylidenenitrile (**I**) followed by intermolecular cyclization (**II**) *in situ* and gives the product (**4**).

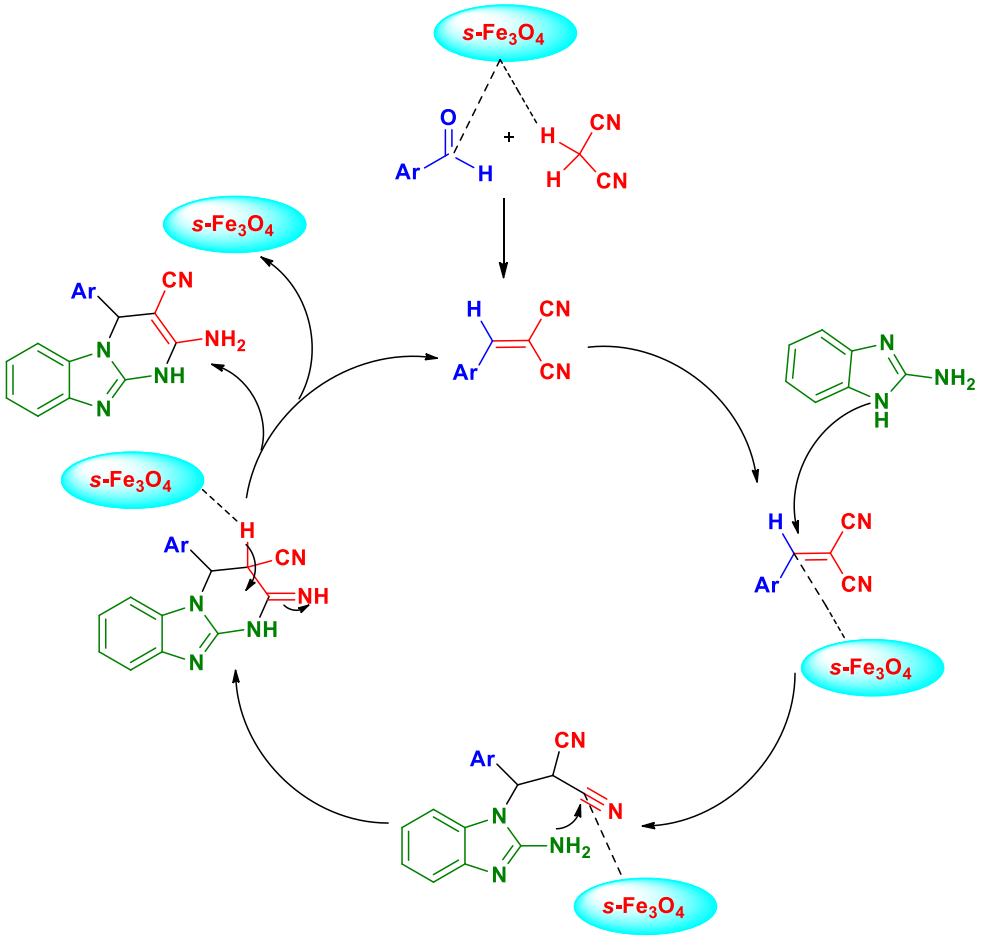


Figure 2.10 Plausible mechanism for *s*-Fe_3O_4 catalyzed synthesis of imidazopyrimidine

2.3 Experimental Section

2.3.1 General experimental procedure for the synthesis of imidazo pyrimidine derivatives (4a-u)

Aldehyde (1.2 mmol), active methylene compound (1.2 mmol), 2-aminobenzimidazole (1.0 mmol) and starch functionalized Fe_3O_4 (4 mg) were sonicated

in water (5 mL) and progress of the reaction was monitored by TLC. The catalyst was collected by an external magnet, after completion of the reaction. The reaction mixture was extracted with ethyl acetate (3×10 mL), washes with brine (3×10 mL) and dried over sodium sulphate. The solvent was evaporated under vacuum and the solid obtained was purified by recrystallization.

2.4 Analytical data

2-Amino-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (4a) Yield 98%; yellow powder; m.p. 234–236°C; **IR** (KBr) 3354, 3115, 2176 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.57 (s, 1H, NH), 7.36-7.33 (t, 1H), 7.29-7.27(d, 2H), 7.23-7.22 (d, 1H), 7.13-7.10 (t, 1H), 7.02-6.99 (t, 1H), 6.79 (s, 2H), 5.21 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.39, 148.80, 143.13, 142.50, 128.89, 128.42, 127.60, 125.56, 123.12, 119.68, 118.85, 115.77, 112.02, 61.60, 52.89.

2-Amino-4-(o-tolyl)-1,4-dihydrobenzo[4,5]imidazolo[1,2-a]pyrimidine-3-carbonitrile (4b) Yield 95%; white powder; m.p. 235–236°C; **IR** (KBr) 3398, 3348, 2185 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.33 (s, 1H, NH), 7.66-7.64 (d, 2H), 7.23-7.17 (m, 3H), 7.13-7.10 (t, 2H), 7.02–6.99 (t, 1H), 6.78 (s, 2H), 5.48 (s, 1H), 2.41 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.56, 148.97, 143.22, 139.70, 134.63, 130.34, 128.90, 127.45, 126.11, 126.09, 122.95, 119.50, 118.48, 115.60, 111.97, 61.42, 49.95, 18.52.

2-Amino-4-(4-methoxyphenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3 carbonitrile (4c) Yield 93%; white powder; m.p. 265–266°C; **IR** (KBr) 3392, 3343, 2179 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.49 (s, 1H, NH), 7.63-7.62 (d, 1H), 7.22-7.19 (t, 3H), 7.12-7.09 (t, 1H), 7.01-6.98 (t, 1H), 6.91-6.90 (d, 2H), 6.78 (s, 2H), 5.14 (s, 1H), 3.71 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 158.42, 151.27, 148.56, 143.13, 134.33, 128.81, 126.79, 122.80, 119.32, 118.70, 115.54, 113.53, 111.89, 61.82, 54.61, 52.27.

2-Amino-4-(naphthalen-1-yl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (4d) Yield 96%; white powder; m.p. 228–229°C; **IR** (KBr) 3390, 3340, 2183 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.66 (s, 1H, 1NH), 7.93-7.88 (m, 4H), 7.78 (s, 1H), 7.66-7.64 (d, 1H), 7.52-7.50 (m, 1H), 7.47-7.45 (m, 1H), 7.24-7.23 (d, 1H), 7.14-7.10 (t, 1H), 7.02-6.99 (d, 1H), 6.86 (s, 2H), 5.41 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.21, 148.73, 143.00, 139.59, 132.09, 128.81, 128.19, 127.39, 127.06, 126.01, 125.73, 124.06, 123.89, 122.84, 119.38, 118.67, 115.58, 114.52, 111.93, 61.31, 53.10.

2-Amino-4-(2-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (4e) Yield 96%; brown powder; m.p. 233–235 °C; **IR** (KBr) 3319, 2182, 1670, 1645, 1565 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.59 (s, 1H, NH), 7.62-7.61 (d, 1H), 7.56-7.55 (d, 1H), 7.25-7.22 (t, 2H), 7.13-7.10 (t, 1H), 7.02-6.99 (t, 2H), 6.85 (s, 2H), 5.23 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.18, 148.88, 143.18,

141.47, 131.28, 128.84, 127.90, 123.12, 120.66, 119.69, 118.68, 115.79, 112.06, 60.99, 52.26.

2-Amino-4-(4-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (4f) Yield 98%; brown powder; m.p.> 300 °C; **IR** (KBr) 3329, 2180, 1677, 1640, 1560 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.75 (s, 1H), 8.25-8.23 (d, 2H), 7.64-7.62 (d, 1H), 7.56-7.55 (d, 2H), 7.26-7.24 (d, 1H), 7.14-7.11 (t, 1H), 7.03-7.00 (t,1H), 6.95 (s, 2H), 5.44 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 150.97, 149.69, 148.99, 146.60, 128.76, 126.78, 123.63, 123.05, 119.63, 118.48, 115.77, 112.08, 60.15, 52.05.

2-Amino-4-(2-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (4g) Yield 95%; white powder; m.p. 232-234°C; **IR** (KBr) 3425, 3310, 2190 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.53 (s, 1H, NH), 7.66-7.65 (d, 1H), 7.48 (s, 1H), 7.34 (s, 1H), 7.25-7.23 (d, 1H), 7.15-7.12 (t, 1H), 7.04-7.01 (t, 1H), 6.88 (s, 2H), 5.64 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.27, 149.14, 143.00, 138.86, 131.00, 129.33, 128.75, 128.03, 127.54, 123.08, 119.70,118.14,115.70, 112.07, 60.38, 50.45.

2-Amino-4-(3-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (4h) Yield 94%; white powder; m.p. 240–242 °C; **IR** (KBr) 3255, 2190, 1680, 1635, 1540 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.60 (s, 1H, NH), 7.84-7.83 (d, 1H), 7.80-7.79 (d, 1H), 7.63-7.55 (m, 1H), 7.38-7.34 (d, 1H), 7.25-7.24 (d, 2H), 7.13-7.10

(t, 1H), 7.02-6.99 (t, 1H), 6.88 (s, 2H), 5.24 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.08, 148.74, 143.05, 141.73, 131.12, 130.92, 130.22, 128.75, 127.76, 122.89, 122.43, 120.47, 119.45, 118.55, 115.63, 111.97, 110.84, 60.88, 52.11.

2-Amino-4-(4-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazolo[1,2-a]pyrimidine-3-carbonitrile (4i) Yield 97%; yellow powder; m.p. 234-235°C; **IR** (KBr) 3443, 3315, 2185 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.59 (s, 1H, NH), 7.63-7.61 (d, 1H), 7.43-7.42 (d, 2H), 7.31-7.29 (d, 1H), 7.24-7.22 (d, 1H), 7.13-7.12 (d, 1H), 7.02-7.00 (d, 1H), 6.86 (s, 2H), 5.25 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.11, 148.77, 143.07, 141.30, 131.97, 130.35,128.67, 128.24, 127.38, 122.94, 119.50, 118.58, 115.67, 111.99, 60.93, 51.78.

2-Amino-4-(2,3-dichlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (4j) Yield 96%; white powder; m.p. 245–246°C; **IR** (KBr) 3422, 3310, 3208, 2902, 2198 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.48 (s, 1H, NH), 7.65 – 7.63 (m, 1H), 7.45-7.43 (d, 1H), 7.38-7.36 (d, 1H), 7.25-7.24 (d, 1H), 7.15-7.12(t, 1H), 7.04-7.01 (t, 1H), 6.88 (s, 2H), 5.63 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.30, 149.40, 143.08, 137.88, 133.25, 132.26, 129.75, 128.94, 127.87,123.40, 120.05, 118.22, 115.97, 112.09, 59.42, 50.34.

2-Amino-4-(4-fluorophenyl)-1,4-dihydrobenzo[4,5]imidazolo[1,2-a]pyrimidine-3-carbonitrile (4k) Yield 98%; yellow powder; m.p. 266–268 °C; **IR** (KBr) 3424, 3314, 3206, 3052, 2890 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.57 (s, 1H, NH), 7.64-

7.62 (d, 1H), 7.34-7.31 (t, 1H), 7.24-7.17 (m, 3H), 7.13-7.10 (t, 1H) 7.02-7.00 (t, 1H), 6.84 (s, 2H), 5.25 (s, 1H); **^{13}C NMR** (125 Hz, DMSO-d_6) δ (ppm): 150.91, 149.11, 147.39, 144.58, 143.00, 132.31, 130.02, 128.74, 123.04, 122.42, 120.35, 120.35, 119.62, 118.51, 115.75, 112.05, 60.10, 51.84.

2-Amino-4-(4-bromophenyl)-1,4-dihydrobenzo[4,5]imidazolo[1,2-a]pyrimidine-3 carbonitrile (4l) Yield 97%; yellow powder; m.p.> 300 °C; **IR** (KBr) 3326, 2185, 1675, 1470, 1420 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.59 (s, 1H, NH), 7.62-7.61 (d, 1H), 7.56-7.55 (d, 2H), 7.25-7.22 (t, 2H), 7.13-7.10 (t, 1H), 7.02-6.99 (t, 1H), 6.85 (s, 2H), 5.23 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.18, 148.88, 143.01, 141.79, 131.28, 128.84, 127.90, 123.12, 120.66, 119.69, 118.68, 115.79, 112.06, 60.06, 52.26.

1-(2-methyl-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-3-yl)propan-1-one (4m) Yield 95%; White powder; m.p 288-289°C; **IR** (KBr) 3025, 2975, 2940, 1695, 1580 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 10.79 (s, 1H), 7.35-7.33 (m, 3H), 7.27-7.23 (m, 3H), 7.19-7.16 (t, 1H), 7.05-7.02 (t, 1H), 6.96-6.93 (t, 1H), 6.41 (s, 1H), 4.02-3.97 (m, 2H), 2.45 (s, 3H), 1.14-1.12 (t, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 164.74, 146.12, 145.18, 141.27, 131.12, 128.00, 127.43, 126.70, 121.43, 119.85, 116.38, 109.46, 97.58, 59.23, 55.09, 18.20, 13.53.

1-(4-(4-methoxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-3-yl)propan-1-one (4n) Yield 96%; White powder; m.p. 270-274°C; **IR** (KBr) 3050, 2980, 2958, 1615, 1575, 1260 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 10.79 (s, 1H),

7.34-7.33 (d, 1H), 7.28-7.25 (m, 3H), 7.05-7.02 (t, 1H), 6.96-6.93 (t, 1H), 6.81-6.79 (d, 2H), 6.37 (s, 1H), 4.02–4.00 (m, 2H), 3.57 (s, 3H), 2.45 (s, 3H), 1.16-1.13 (t, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 165.23, 164.74, 158.13, 145.82,145.62, 145.14, 145.12, 141.81, 133.66, 131.00, 127.79, 127.62, 121.19, 119.63, 119.58, 116.23, 113.24, 113.14, 109.38, 97.68, 97.60, 58.99, 54.21, 50.29, 18.13, 13.59.

1-(4-(4-chlorophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-3-yl)propan-1-one (4o) Yield 97%; White powder; m.p. 267-268°C; **IR** (KBr) 3061, 2935, 2840, 1620, 1573, 1270 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 10.86 (s, 1H), 7.39-7.36 (t, 3H), 7.34-7.32 (t, 3H), 7.26-7.24 (d, 1H), 7.06-7.03 (t, 1H), 6.97-6.94 (t, 1H), 6.45 (s, 1H), 4.03-4.02 (t, 2H), 2.46 (s, 3H), 1.16-1.13 (t, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 165.58, 147.33, 145.92, 142.77, 141.51, 132.80, 131.93, 129.53, 128.90, 122.38, 120.77, 117.36,110.34, 97.98, 59.93, 55.74, 19.16, 14.57.

1-(2-methyl-4-(4-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-3-yl)propan-1-one (4p) Yield 97%; White powder; m.p. 276-278°C; **IR** (KBr) 3055, 2940, 2837, 1675, 1570, 1260 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 10.97 (s, 1H), 8.14-8.12 (d, 2H), 7.66-7.64 (d, 2H), 7.37-7.35 (d, 1H), 7.27-7.26 (d, 1H), 7.06-7.03 (t, 1H), 6.97-6.64 (t, 1H), 6.60 (s, 1H), 4.03-4.01(m, 2H), 2.47 (s, 3H), 1.16-1.14(t, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 165.42, 148.51, 146.98, 146.42, 144.73, 141.73, 130.83, 128.01, 123.20, 121.53, 119.94, 116.47, 109.27, 96.29, 59.04, 54.73, 17.89, 13.54.

3,3-Dimethyl-12-phenyl-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one (4q) Yield 96%; White powder; m.p.> 300 °C; **IR** (KBr) 3431, 2890, 1640, 1622, 1588 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 11.12 (s, 1H, NH), 7.36-7.32 (d, 3H), 7.25 (s, 3H), 7.15 (s, 1H), 7.04 (s, 1H), 6.95 (s, 1H), 6.41 (s, 1H), 2.65-2.62 (d, 2H), 2.27-2.24 (d, 1H), 2.07-2.04 (d, 1H), 1.06 (s, 3H), 0.93 (s, 3H).

12-(4-methoxyphenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one (4r) Yield 98%; White powder; m.p.> 300 °C; **IR** (KBr) 3432, 2892, 1645, 1620, 1590 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 11.00 (s, 1H, NH), 8.17 (s, 1H), 7.33-732 (d, 1H), 7.23-7.21 (d, 2H), 7.17-7.15 (d, 1H), 7.03-7.00 (t, 1H), 6.93-6.90 (t, 1H), 6.75-6.73 (s, 1H), 6.30 (s, 1H), 3.64 (s, 3H), 2.60-2.56 (d, 2H), 2.23-2.20 (d, 1H), 2.06-2.02 (d, 1H), 1.06 (s, 3H), 0.94 (s, 3H).

3,3-dimethyl-12-(naphthalen-2-yl)-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one (4s) Yield 95%; White powder; m.p.> 300 °C; **IR** (KBr) 3427, 2923, 2992, 1647, 1576 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 11.11 (s, 1H, NH), 8.15 (s, 1H), 7.96 (s, 1H), 7.84-7.83 (d, 1H), 7.74-7.69 (m, 1H), 7.44-7.29 (m, 4H), 7.19-7.18 (d, 1H), 7.00-6.97 (t, 1H), 6.89-6.86 (t, 1H), 6.53 (s, 1H), 2.64-2.54 (m,2H), 2.24-2.21 (d, 1H), 2.05-2.01 (d, 1H), 1.07 (s, 3H), 0.93 (s, 3H).

3,3-dimethyl-12-(4-nitrophenyl)-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one (4t) Yield 98%; White powder; m.p.> 300 °C; **IR** (KBr) 3542, 3043, 1645, 1600, 1590 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 11.28 (s, 1H), 8.12-

8.11 (d, 2H), 7.61-7.60 (d, 2H), 7.40-7.38 (d, 1H), 7.22-7.21 (d, 1H), 7.08-7.05 (t, 1H), 6.98-6.95 (t, 1H), 6.59 (s, 1H), 2.66-2.63 (t, 1H), 2.55-2.54 (t, 1H), 2.28-2.25 (d, 1H), 2.07-2.04 (d, 1H), 1.05 (s, 3H), 0.90 (s, 3H).

12-(4-chorophenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one3 (4u) Yield 98%; White powder; m.p.> 300 °C; **IR** (KBr) 3442, 2956, 1646, 1617, 1590, 1569 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 11.03 (s, 1H, NH), 8.18 (s, 1H), 7.34-7.30 (m, 2H), 7.22-7.19 (t, 2H), 7.14-7.12 (d, 1H), 7.03-7.00 (t, 1H), 6.93-6.90 (t, 1H), 2.60-2.57 (d, 1H), 2.39-2.36 (d, 1H), 2.24-2.20 (d, 1H), 2.07-2.04 (d, 1H), 1.07 (s, 3H), 0.94 (s, 3H).

2.5 Spectral data of product for few products

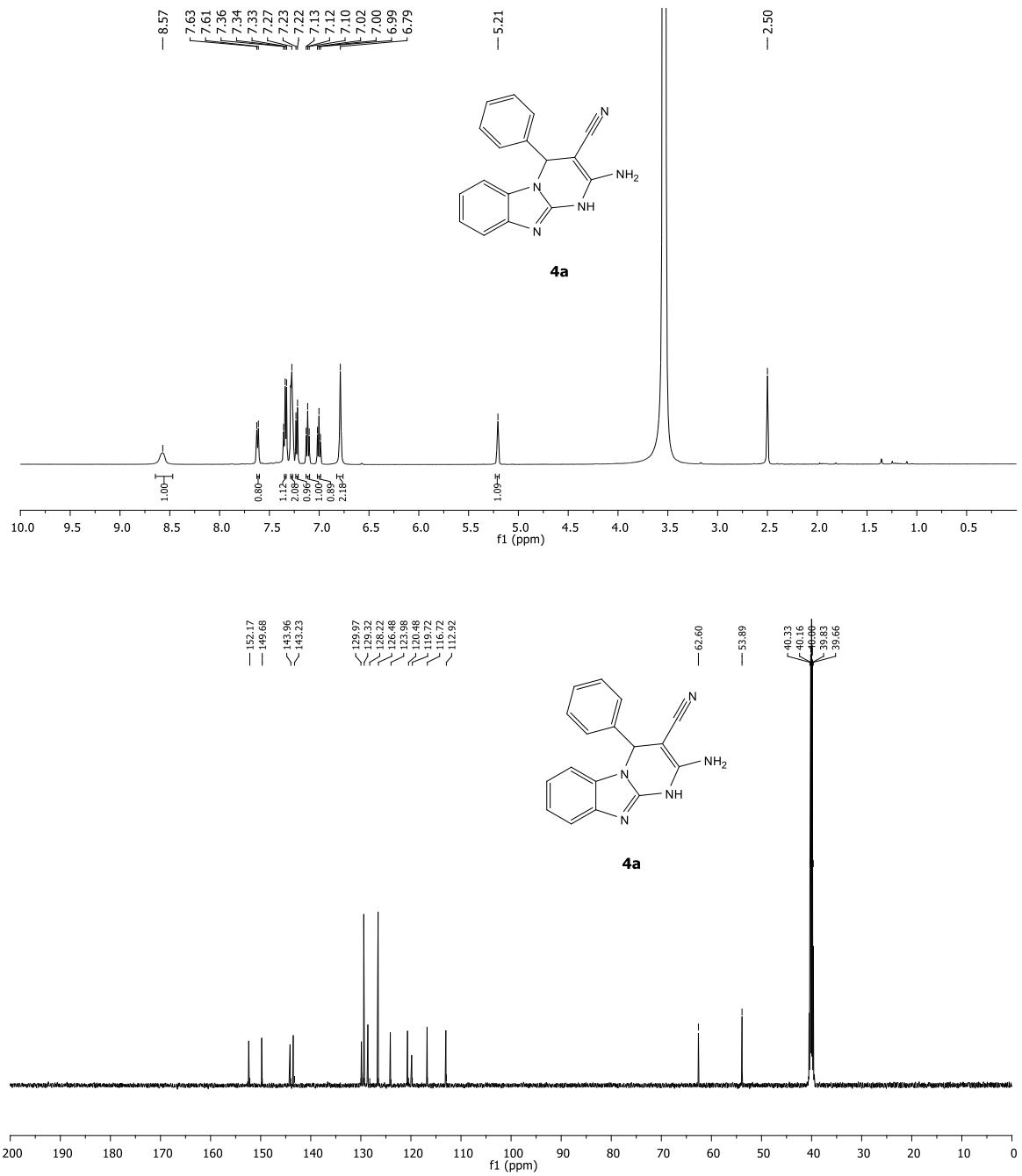


Figure 2.11 ^{1}H NMR & ^{13}C NMR of 2-Amino-4-phenyl-1,4 dihydrobenzo[4,5]imidazo [1,2-a]pyrimidine-3-carbonitrile (4a)

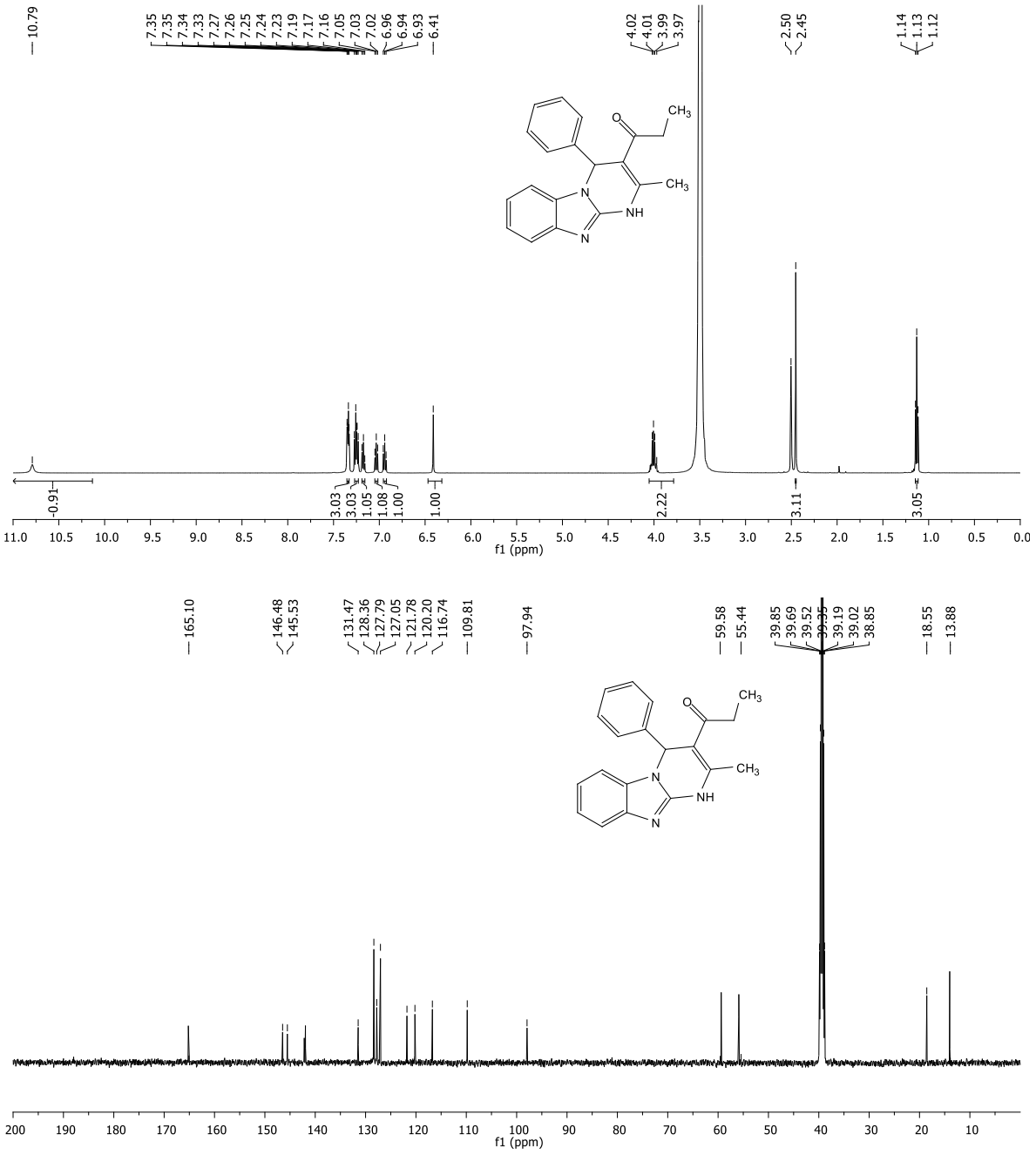


Figure 2.12 ^{1}H NMR & ^{13}C NMR of 2-Amino-4-phenyl-1,4 dihydrobenzo[4,5]imidazo [1,2-a]pyrimidine-3-carbonitrile (4m)

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