3.1 Synthesis and characterization of copper(0) nanoparticles immobilized onto L-dopa grafted TiO$_2$ stabilized magnetite nanoparticles

An efficient and magnetically recoverable catalyst, Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa was designed and synthesized. The procedure for the synthesis of Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa is schematically presented in Scheme 1. Initially, Fe$_3$O$_4$ nanoparticles were synthesized by co-precipitation of Fe$^{3+}$ and Fe$^{2+}$ salts followed by the grafting of TiO$_2$ nanoparticles over magnetite nanoparticles using ultrasonication technique.

![Scheme 1](image)

**Scheme 1.** General scheme for the synthesis of Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa.

Although, Fe$_3$O$_4$ embedded TiO$_2$ spheres are relatively stable yet the aggregation and leaching of active metal species from their surface remains the drawback. Thus to get
firm anchoring of active metal nanoparticles onto the support and prevent their leaching. L-dopa was used as binding agent. \(\text{Fe}_3\text{O}_4\)-TiO\(_2\) nanoparticles were functionalized with L-dopa and finally Cu(0) nanoparticles were immobilized onto the support material via treatment with Cu(acac)\(_2\) followed by reduction with aqueous NaBH\(_4\) solution. The synthesized catalyst, Cu@Fe\(_3\)O\(_4\)-TiO\(_2\)-L-dopa was fully characterized by diverse techniques such as SEM, HR-TEM, XPS, ICP-AES, CHN analysis, EDX, XRD, FTIR, VSM and TGA studies.

**General procedure for the preparation of Cu@Fe\(_3\)O\(_4\)-TiO\(_2\)-L-dopa**

For the synthesis of core-shell particles of Fe\(_3\)O\(_4\)-TiO\(_2\), Fe\(_3\)O\(_4\) (0.960 g) was initially dispersed in 40 mL of deionized water and ultrasonicated for 30 min to get a stable ferrofluid. Subsequently, nano-TiO\(_2\) (3.43 g) was added into the ferrofluid sol and again sonicated for 30 min. Fe\(_3\)O\(_4\)-TiO\(_2\) nanoparticles so obtained were filtered, washed with deionized water (3 \(\times\) 10 mL), chloroform (3 \(\times\) 10 mL) and dried under vacuum. In order to graft L-dopa over Fe\(_3\)O\(_4\)-TiO\(_2\) nanoparticles, the mixture of Fe\(_3\)O\(_4\)-TiO\(_2\) (1 g) and L-dopa (0.2 g) was stirred in deionized water (10 mL) at 130 °C for 2 h. Black precipitates of Fe\(_3\)O\(_4\)-TiO\(_2\)-L-dopa were separated magnetically, washed with deionized water (3 \(\times\) 10 mL) and dried under vacuum. Finally, to immobilization Cu nanoparticles onto Fe\(_3\)O\(_4\)-TiO\(_2\)-L-dopa, the aqueous solution of CuCl\(_2\) (0.134 g, 1.0 mmol, 3 mL) was added into the dispersed solution of Fe\(_3\)O\(_4\)-TiO\(_2\)-L-dopa (1 g) in ethanol (10 mL), and the reaction mixture was stirred at room temperature for 3 h. Then, aqueous solution of NaBH\(_4\) (1.2 mmol, 5 mL) was added dropwise into the reaction mixture under continuous stirring over a period of 2 h. Cu@Fe\(_3\)O\(_4\)-TiO\(_2\)-L-dopa so obtained was separated magnetically and washed successively with ethanol (2 \(\times\) 20 mL) and water (2 \(\times\) 20 mL). Finally, it was dried under vacuum at room temperature to get Cu@Fe\(_3\)O\(_4\)-TiO\(_2\)-L-dopa nanoparticles as dark black powder (4.3 g).

**Characterization of Cu@Fe\(_3\)O\(_4\)-TiO\(_2\)-L-dopa**

The synthesized catalyst, Cu@Fe\(_3\)O\(_4\)-TiO\(_2\)-L-dopa was fully characterized by different techniques such as SEM, HR-TEM, XPS, ICP-AES, CHN analysis, EDX, XRD, FTIR, VSM and TGA studies.
Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) was recorded to understand the surface morphology of the synthesized catalyst. It was clearly observed from SEM images (Fig. 1) that the developed catalyst is homogeneous in nature and Cu nanoparticles were evenly spread over the surface of Fe$_3$O$_4$-TiO$_2$-L-dopa. Most of the particles of the catalyst adopts spherical shape which may be responsible for the low tendency of nanoparticles to undergo agglomeration and their enhanced catalytic efficiency.

![SEM images of Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa.](image)

**Fig. 1** SEM images of Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa.

High Resolution Transmission Electron Microscopy (HR-TEM)

The HR-TEM images (Fig. 2) of the Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa clearly demonstrate that Cu(0) nanoparticles are homogeneously spread over the Fe$_3$O$_4$-TiO$_2$-L-dopa support. Additionally, it was also observed that L-dopa forms a uniform covering over the Fe$_3$O$_4$-TiO$_2$ support and thus accountable for the better anchoring of Cu(0) nanoparticles onto the synthesized support material and avert their leaching. It has been found that size of most of the particle of the catalyst was in the range of 12 to 24 nm, and the mean particle size was about 16 nm. Further, HR-TEM image (Fig. 2d) of Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa unveiled the lattice fringes with an interplanar spacing of approximately 0.216 nm corresponding to the [111] lattice plane of metallic Cu$^1$. 

---

$^1$Cu$^1$
Fig. 2 HR-TEM images of Cu@Fe₃O₄-TiO₂-L-dopa.

X-Ray Photoelectron Spectroscopy (XPS)

X-Ray Photoelectron spectroscopy (XPS) was recorded to investigate the electron properties of the species formed on the surface of Cu@Fe₃O₄-TiO₂-L-dopa, such as the oxidation state and the binding energy of the core electron of the active copper metal. **Fig. 3a** showed the overall survey spectrum of Cu@Fe₃O₄-TiO₂-L-dopa in which peaks corresponding to carbon 1s (285.1 eV), oxygen 1s (531.9 eV) and copper 2p (932.1 eV) are clearly observed. Further, Cu 2p core level spectrum (**Fig. 3b**) showed typical Cu(0) absorptions at 932.1 and 952.7 eV for 2p₃/2 and 2p₅/2 respectively, which are consistent
with the literature values for Cu(0) nanoparticles. While a satellite shakeup near 937.5 in XPS (Fig. 3b) can be assigned to Cu(II). The presence of small amount of Cu(II) species in the catalyst may be due to the atmospheric oxidation of Cu(0) nanoparticles or incomplete reduction with NaBH₄.

![Fig. 3 XPS spectra of Cu@Fe₂O₄-TiO₂-L-dopa: a) overall survey spectrum; b) Cu 2p core level spectrum.](image-url)
Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES)

Inductively coupled plasma atomic emission spectroscopy (ICP-AES) was used to estimate the amount of Cu immobilized onto Fe₃O₄-TiO₂-L-dopa. The results revealed that the content of Cu loaded onto 0.1 g of Fe₃O₄-TiO₂-L-dopa was 2.52 wt%.

Carbon Hydrogen Nitrogen (CHN) analysis

Successful grafting of L-dopa onto Fe₃O₄-TiO₂ was further confirmed from the CHN analysis (Fig. 4) and the results are in good agreement with our proposed catalyst.

![CHN analysis of Cu@Fe₃O₄-TiO₂-L-dopa.](image)

Energy Dispersive X-ray (EDX)

The elemental composition of Cu@Fe₃O₄-TiO₂-L-dopa was also established from the energy dispersive spectrometer (EDX) (Fig. 5). The EDX analysis showed that the catalyst is composed of Fe, Ti, C, O and Cu elements, which further indicated that TiO₂ and L-dopa were successfully grafted over the magnetite nanoparticles.
Fig. 5 EDX spectrum of Cu@Fe₃O₄-TiO₂-L-dopa.

X-ray Powder Diffraction (XRD)

Unambiguous evidence of copper nanoparticles onto Fe₃O₄-TiO₂-L-dopa is also provided via X-ray powder diffraction analysis (XRD). XRD pattern of Fe₃O₄-TiO₂-L-dopa (Fig. 6a) unveiled diffraction patterns at 2θ = 30.2, 35.4, 42.3, 57.3 and 62.3°, which corresponds to [111], [220], [311], [440] and [511] planes of cubic phase of Fe₃O₄ lattice. Further, peaks at 25.2, 48.1 and 53.8° corresponds to [101], [200] and [105] planes of cubic phase of TiO₂ lattice. Whereas XRD spectrum of Cu@Fe₃O₄-TiO₂-L-dopa (Fig. 6b) showed three new peaks at 43.1, 50.2 and 74.06° corresponding to [111], [200] and [220] crystal faces of metallic Cu. The sharp and strong peaks suggest that the synthesized catalyst is crystalline in nature. Thus, HR-TEM, XPS and XRD spectra inclusively implicit the presence of Cu(0) nanoparticles onto the L-dopa functionalized and TiO₂ stabilized magnetite nanoparticles.
Fig. 6 XRD spectra: a) Fe$_3$O$_4$-TiO$_2$-L-dopa; b) Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa.
Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR spectroscopy was used to investigate the existence of various functional groups in the synthesized catalyst, Cu@Fe₃O₄-TiO₂-L-dopa and its precursors. The FT-IR spectra of Fe₃O₄, Fe₃O₄-TiO₂-L-dopa and Cu@Fe₃O₄-TiO₂-L-dopa are shown in Fig. 7a-c respectively. FT-IR spectrum of Fe₃O₄ showed broad band at 595 cm⁻¹ due to Fe-O stretching vibration of Fe₃O₄. FT-IR spectrum of Fe₃O₄-TiO₂-L-dopa showed bands at 3441.01, 2926, 2856, 2360, 2335, 1625, 1489, 1415, 1286, 638 and 580 cm⁻¹. The bands appearing at about 3441 and 638 cm⁻¹ corresponds to N-H stretching vibration of L-dopa and absorption bands of O–Ti–O, respectively. It has been observed that stretching vibrations of the C-H of CH₂ group of L-dopa appeared at 2926, 2856, 2360 and 2353 cm⁻¹, while band at 1489 cm⁻¹ corresponds to the bending vibration of C-H of CH₂ group of L-dopa. Moreover, bands at 1625 and 1415 cm⁻¹ ascribed to carboxylate group of L-dopa, whereas band at 1286 cm⁻¹ signifies C-O stretching vibration of carboxylate group. This shows that plenty of L-dopa molecules are grafted over the support (Fe₃O₄-TiO₂). However, no considerable change prevailed in FT-IR spectrum of Cu@Fe₃O₄-TiO₂-L-dopa (Fig. 7c), although minor decrease in the intensity
of bands observed due to the immobilization of Cu nanoparticles over the support. Thus, FTIR spectrum gives valuable information about the formation of protective layer of TiO$_2$ nanoparticles over the Fe$_3$O$_4$ nanoparticles and successful grafting of L-dopa onto Fe$_3$O$_4$-TiO$_2$.

**Vibrating Sample Magnetometer (VSM)**

The magnetic property of the proposed catalyst was investigated with vibrating sample magnetometry (VSM) at room temperature. VSM of Fe$_3$O$_4$ and Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa are shown in **Fig. 8a** and **8b** respectively. The magnetization curve of Fe$_3$O$_4$ revealed super paramagnetic property with saturation magnetization of about 59 emu/g. After coating of Fe$_3$O$_4$ nanoparticles with TiO$_2$, L-dopa and Cu nanoparticles, the superparamagnetic property of Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa was found to be about 46.7 emu/g. The small decrease in the saturation values as shown in **Fig. 8a** and **8b** was due to the amalgamation of non-magnetic material onto the surface of magnetic material, but still the proposed catalyst is magnetic enough to be separated via magnet. The TiO$_2$ coating on Fe$_3$O$_4$ relatively well defends them from oxidation, reinforces the magnetic stability and enables it to disperse fast when the magnetic field is removed.

![VSM spectra](image)

**Fig. 8** VSM spectra: a) Fe$_3$O$_4$; b) Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa.
Thermogravimetric Analysis (TGA)

The thermal stability of the catalyst was investigated by carrying out thermal gravimetric analysis in the temperature range of 25-800 °C at a heating rate of 10 °C/min under nitrogen atmosphere. The TGA profile of Cu@Fe₃O₄-TiO₂-L-dopa (Fig. 9) showed reasonable stability up to 350 °C, after which there was a sharp weight loss. The slight weight loss of 1.5% has been occurred at 130 °C which may be owing to the absorbed water molecules and no appreciable weight loss up to 350 °C was noticed. The major weight loss occurred after 350 °C was due to the decomposition of chemisorbed material i.e., L-dopa from the Cu@Fe₃O₄-TiO₂-L-dopa. This confirms that the reported catalyst is thermally stable below 350 °C and can easily be applied in any reaction below this temperature.

![TGA spectrum of Cu@Fe₃O₄-TiO₂-L-dopa.](image)
REFERENCES


3.2 Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa as a novel and efficient catalyst for the Chan-Lam cross-coupling reaction in ligand-free conditions

Amines being pivotal chemical intermediates, play a crucial role in different fields of chemistry, such as agrochemicals, pharmaceuticals, pigments, dyes, etc.\(^1\) The aromatic C-N bond containing organic motifs possesses indispensable importance in the field of synthetic organic chemistry due to the ubiquity of $N$-arylamine derivatives in numerous molecules of biological importance\(^2\).\(^3\). In general, the $N$-aryl bond formation is vital that can decide the biological activity of a molecule in a strategic position during structure activity relationship (SAR) studies\(^4\). Transition metal catalyzed C-N bond formation is presently a subject of immense interest, and intensive research is being carried out in this field to synthesize useful organic compounds\(^5\). $N$-arylated compounds constitute a common structural motif in various potentially useful therapeutic agents and drugs\(^6\) (Fig. 1).

![Chemical structures](image)

**Fig. 1** Some biologically important C–N bond containing organic compounds.
**Earlier approaches for C-N cross-coupling reaction**

The preparation of diversely functionalized amines via amination of aryl halides using transition metals as catalysts has been extensively reported by various researchers\(^7\).

Ullmann\(^8\) and Goldberg\(^9\) employed copper for the construction of the C-N bond and were the first to introduce amino group in a controlled manner a century ago. Copper salts in stoichiometric amounts were used to activate aryl halides which react with amine nucleophiles resulting in the formation of C-N bond. The synthetic utility of this procedure is, however, subjected to limitations by the generation of stoichiometric amounts of copper salts as waste and harsh reaction conditions.

Migita and co-workers\(^10\) have submitted the first report of palladium catalyzed C-N cross-coupling reaction. Here, the cross-coupling between several aryl bromides and \(N,N\)-diethylamino-tributyltin were carried out using 1 mol% \(\text{PdCl}_2[\text{P(}\text{o-}\text{Toly})_3]_2\) (Scheme 1). It was reported that only electronically neutral and sterically unencumbered substrates gave good yields.

**Scheme 1**

\[
\text{Br} \quad \begin{array}{c}
\text{R}\text{R}^+ \quad \text{Bu}_3\text{Sn-N} \quad \text{PdCl}_2[\text{P(}\text{o-}\text{Toly})_3]_2 \quad \text{C}_6\text{H}_5\text{CH}_3, 100 ^\circ\text{C} \quad \text{R} \quad \text{N} \\
\end{array} \quad 16-81\% \text{ yield}
\]

In 1995, Buchwald and Hartwig have independently reported organotin-free cross-couplings between aryl halides and free amines in the presence of a bulky base i.e. \(\text{NaO}^+\text{Bu}\) or \(\text{LiHMDS}\) (Scheme 2). But the substrate scope was limited only to secondary amines\(^11,12\).

**Scheme 2**

\[
\text{Br} \quad \begin{array}{c}
\text{R}^1 \text{R}^+ \quad \text{R}_2\text{NH} \quad \text{PdCl}_2[\text{P(}\text{o-}\text{Toly})_3]_2 \quad \text{or} \quad \text{Pd}[\text{P(}\text{o-}\text{Toly})_3]_2 \quad \text{or} \quad \text{Pd(dba)}_2[\text{P(}\text{o-}\text{Toly})_3]_2 \\
\quad \text{NaO}^+\text{Bu} \quad \text{or} \quad \text{LiHMDS} \quad \text{Toulene or THF} \quad 55-100 ^\circ\text{C} \\
\end{array} \quad \text{R}^1 \quad \text{NR}_2
\]
Still, this synthetic route has numerous limitations such as the use of expensive, moisture and air sensitive ligands, harsh reaction conditions, formation of side products, long reaction time, tedious workup and low yields.

Chan, Evans and Lam\textsuperscript{13-15}, individually attempted and developed a mild procedure for Cu-mediated oxidative amination of aryl boronic acid. This coupling reaction is also known as Chan-Lam coupling reaction. Chan-Lam coupling reaction is a copper (II) species catalyzed cross-coupling reaction between an aryl boronic acid and an amine or an alcohol to yield the corresponding secondary aryl amines or aryl ethers, respectively.

However, the use of excess of Cu(OAc)$_2$, aryl boronic acid, additives such as pyridine-$N$-oxide, TEMPO, molecular oxygen etc., harsh reaction conditions and the long reaction time are considered as major limitations associated with this cross-coupling method; regardless of the quite stable and non-toxic nature of aryl boronic acid\textsuperscript{16}. Thereafter, several modifications were employed to improve the yield and efficiency of Chan-Lam reaction using various copper salts in the presence of different ligands. Some of these are cited below:

Gogoi et al.\textsuperscript{17} have reported significant catalytic activity of a unique Cu–salen type complex for the $N$-arylation of anilines with arylboronic acids. This method was found to be applicable for a wide range of electronically diversified arylboronic acids and anilines, and afforded products in good to excellent yields (\textbf{Scheme 3}).

\textbf{Scheme 3}

\[
\text{R}-\text{NH}_2 + (\text{HO})_2\text{B-R'} \xrightarrow{\text{Cu-complex (20 mol\%)}} \text{K}_2\text{CO}_3 (3 \text{ eq.}), \text{H}_2\text{O} (3 \text{ mL}), \text{r.t., air} \xrightarrow{} \text{R}-\text{N-R'}
\]

Selective $N$-arylation of 3-aminophenol has been achieved successfully with Cu(OAc)$_2$/AgOAc by Reddy et al., whereas the chemoselective $N$-arylated products of 4-aminophenols were obtained with Cu(OAc)$_2$/Cs$_2$CO$_3$ system in the presence of benzoic acid as an additive. Both the catalytic systems are compatible with various functional groups, particularly with halo-substrates (\textbf{Scheme 4}).\textsuperscript{18}
Baruah et al.\textsuperscript{19} have reported catalytic activity of three N,S-donor ligands, i.e. L1 [2-(4-methoxy benzylidene)-N-phenylhydrazinecarbothioamide], L2 [2,2\textprime{}-(1,2-diphenylethane-1,2-diylidene)bis (hydrazinecarbothioamide)] and L3 [2-(4-methoxybenzylidene) hydrazine carbothioamide] for the N-arylation of imidazoles with arylboronic acids at room temperature. The method was applicable for N-arylation of a wide range of electronically diverse arylboronic acids with imidazoles and gave modest to excellent isolated yields. Out of three ligands, \textit{in situ} generated copper(II) complex of the ligand namely, 2-(4-methoxybenzylidene)-N-phenylhydrazinecarbothioamide (L1) was found to be highly efficient homogeneous catalyst for the N-arylation reaction (Scheme 5).

Scheme 5

\[
\begin{array}{cccc}
\text{R}^1 & \text{N} & \text{NH} & + \\
\text{N} & \text{NH} & \text{HO} & \text{B} & \text{HO} & \text{R}^2 \\
\end{array}
\xrightarrow{\text{Cu(OAc)}_2/L_1 (1 \text{ mol} \%) / \text{K}_2\text{CO}_3 (2 \text{ eq}) / \text{ethanol (5 mL)}}
\text{Cu(OAc)}_2 / \text{L}_1 (1 \text{ mol} \%)
\text{K}_2\text{CO}_3 (2 \text{ eq.})/ \text{ethanol (5 mL)}
\text{r.t.}
\end{array}
\]

Ni- and Cu-based catalytic systems have been developed for the selective N-arylation of 2-aminobenzimidazoles by Kumar et al.\textsuperscript{20} Here, selective N-arylation of primary amine was achieved successfully by Ni-catalyzed boronic acid promoted cross-coupling reaction, whereas, selective N-arylation of the azole nitrogen was done with aryl halides under Cu catalysis conditions (Scheme 6).

Scheme 6

\[
\begin{array}{c}
\text{I} \\
\text{Cu}_2\text{O}, \text{KOH} \\
\text{DMSO}, 120 \text{ }{^\circ}\text{C} \\
\text{N}_2, 14-18 \text{ h}
\end{array}
\xrightarrow{\text{Cu}_2\text{O}, \text{KOH}}
\text{I}
\text{Cu}_2\text{O}, \text{KOH}
\text{DMSO}, 120 \text{ }{^\circ}\text{C}
\text{N}_2, 14-18 \text{ h}
\end{array}
\]

\[
\begin{array}{c}
\text{(HO)}_2\text{B} \\
\text{Ni(OAc)}_2 \\
\text{DBU}, \text{DMSO} \\
\text{50 }{^\circ}\text{C}, 10-15 \text{ h}
\end{array}
\xrightarrow{\text{(HO)}_2\text{B}}
\text{(HO)}_2\text{B}
\text{Ni(OAc)}_2
\text{DBU}, \text{DMSO}
\text{50 }{^\circ}\text{C}, 10-15 \text{ h}
\end{array}
\]

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An efficient copper promoted method for the synthesis of aryloxime ethers from aryloximes and arylboronic acids under mild reaction conditions has been reported by Mondal et al.\textsuperscript{21} (Scheme 7).

**Scheme 7**

An efficient route for the Chan-Lam cross-coupling of different aryl amines with various arylboronic acids was reported by Keesara et al.\textsuperscript{22} using Ni(OAc)\textsubscript{2}.4H\textsubscript{2}O as catalyst along with N-(pyridine-2-yl)benzamide ligand. The reported method showed applicability on broad range of substrates and afforded products in moderate to good yields with low catalytic loadings (Scheme 8).

**Scheme 8**

Guan et al. have reported an efficient method for the \(N\)-arylation of (benz)imidazoles or amines with diarylboronic acids using Cu(OAc)\textsubscript{2} (5 mol\%) (Scheme 9).\textsuperscript{23} Moreover, it has been observed that higher loadings of Cu(OAc)\textsubscript{2} (20 mol\%) and boronic acids were required for the cross-coupling reaction of less reactive substrates such as anilines and aliphatic amines.

**Scheme 9**
Xu et al.\textsuperscript{24} have reported the synthesis of $N$-aryl phosphinamides and phosphonamides via Chan-Evans-Lam reaction mediated by copper(II) species. The products were obtained in higher yields (up to 88\%), and the reported protocol showed good functional group tolerance in ligands and co-catalyst free conditions (Scheme 10).

\textbf{Scheme 10}

\[
\begin{array}{c}
\text{Ph} \text{P} \text{NH}_2 + \text{R}_2 \text{C} \text{C} \text{B(OH)}_2 \xrightarrow{\text{Cu(OAc)}_2, \text{Cs}_2\text{CO}_3} \text{Ph} \text{P} \text{N} \text{R}_1 \text{R}_2 \\
toluene, 80 \, ^\circ\text{C}, 10 \, \text{h}
\end{array}
\]

Janikova \textit{et al.}\textsuperscript{25} have reported Cu$_2$S/TMEDA catalyzed Chan-Lam cross-coupling of several imidazole-based heterocycles with aryl boronic acids. It has been shown that both the reactive sites of benzimidazolone underwent $N$-arylation at similar rates, leading to the formation of mono- and di-arylated benzimidazolones. Further, the Cu$_2$S/ TMEDA also catalyzed the $N$-arylation of primary aliphatic amines with boronic acid in good yields (Scheme 11).

\textbf{Scheme 11}

\[
\begin{array}{c}
\text{R}_2 \text{C} \text{N} \text{H}_2 + \text{R}_2 \text{C} \text{C} \text{B(OH)}_2 \xrightarrow{\text{Cu}_2\text{S} (5 \, \text{mol\%}), \text{TMEDA} (1 \, \text{eq.})} \text{R}_2 \text{C} \text{N} \text{R}_1 \text{R}_2 + \text{R}_2 \text{C} \text{N} \text{R}_1 \text{R}_2 \\
\text{DMF, 8 h, r.t., air}
\end{array}
\]

Chan-Lam cross-coupling was successfully reported for the functionalization of the surface of mesoporous silica gel in base-free conditions by Kubi \textit{et al.} Different aliphatic, aromatic and heterocyclic compounds were effectively immobilized onto the surface of silica gel by a copper-catalyzed reaction of corresponding boronic acids under mild conditions. The catalysts showed increased reactivity in the characteristic reactions. However, the disadvantage associated with this method is that it cannot be used for the introduction of functional groups that are reactive to boronic acids (OH, NH$_2$ or COOH) under the reaction conditions (Scheme 12).\textsuperscript{26}
Bodhak et al.\textsuperscript{27} have reported highly efficient heterogeneous chitosan supported copper(II) catalyst for the C-N cross coupling between aryl halides and aliphatic diamines/amino alcohols. The key advantages of this reaction are reduced reaction time, high yield of the products, convenient work up procedure, recyclability of the catalyst and less metal contamination of the products (Scheme 13).

Scheme 13

A new hybrid catalyst was developed by the immobilization of copper acetate onto the surface of cobalt ferrite magnetic nanoparticles functionalized with N-O chelating ligand. The reported catalyst showed excellent activity for C-N bond formation in the presence of triethylamine at room temperature and afforded products in good yield. Moreover, catalyst could be easily recovered via external magnet and reused for consecutive catalytic cycles without significant decrease in the catalytic activity (Scheme 14).\textsuperscript{28}

Scheme 14
Khosravi et al.\textsuperscript{20} have reported an efficient method for the cross-coupling of aromatic amines with phenyl boronic acid using Cu\textsubscript{2}(BDC\textsubscript{2})(BPY)–MOF as an reusable heterogeneous catalyst. Here, green and energy-efficient method i.e. ball-milling strategy was used for the synthesis of nanoporous metal–organic framework. The key advantages of this procedure were short reaction times, solvent-free conditions, high yield and easy work up procedure (Scheme 15).

Scheme 15

\[
\text{Ar-NH}_2 + \text{Ar-B(OH)OH} \xrightarrow{\text{Cu-MOFs, MeOH/H}_2\text{O, r.t.}} \text{Ar-NH}_2
\]

The most commonly reported catalysts for the C-N cross-coupling reactions include Cu(II) complexes, [Cu(DMAP)_4]I, Cu–salen type complex, copper-exchanged fluorapatite, Ni- and Cu-based catalyst etc. But, all these catalysts were homogeneous in nature and cannot be recovered from the reaction mixture. As a result, these processes became very expensive and moreover, separation of the products from catalyst was also a tedious process. These problems can be overcome by immobilizing the active metal species on heterogeneous supports. Very few reports of heterogeneous catalyst catalyzed C-N cross-couplings have been reported in the literature. Still, the high reaction temperature and long reaction time are some of the limitation associated with the reported heterogeneous catalysts. Thus, endeavouring efforts for finding better methods for Chan-Lam coupling are gaining much impetus recently.

Thus, the development of simple, efficient and environment-benign procedure for the C-N cross-coupling reaction in ligand-free conditions has been the main focus of our research (Scheme 16). Herein, we report the C-N cross-coupling reaction between diversely substituted anilines and phenyl boronic acid using water as the reaction medium, K\textsubscript{2}CO\textsubscript{3} (1.2 eq, 0.165 g) as base and Cu@Fe\textsubscript{3}O\textsubscript{4}-TiO\textsubscript{2}-L-dopa (1.9 mol\% Cu, 0.05 g) as catalyst. The substituted diarylamines were obtained in good yields.
Results and discussion

Substituted diarylamines have drawn considerable attention due to their diverse applications in various medicinal and natural products. The catalytic activity of the developed catalyst has been tested for the Chan-Lam cross-coupling reaction using aniline and phenyl boronic acid as the test substrates. Firstly, catalytic activity of different copper sources for Chan-Lam cross-coupling was examined. The model reaction was attempted with different copper sources such as CuSO₄·5H₂O, Cu(OAc)₂·H₂O, CuCl₂·2H₂O and the synthesized catalyst Cu@Fe₃O₄-TiO₂-L-dopa using K₂CO₃ as base and H₂O as solvent (entries 1-3, 11, Table 1). It has been found that poor yield of diphenylamine were obtained with copper salts such as CuSO₄·5H₂O, Cu(OAc)₂·H₂O and CuCl₂·2H₂O (25-35%) (entries 1-3, Table 1), whereas Cu@Fe₃O₄-TiO₂-L-dopa gave excellent results both in terms of time and yield i.e. 92% of diphenylamine was obtained in 3h (entry 11, Table 1).

In order to obtain best optimize reaction conditions for the C-N cross-coupling, different experiments were performed on the model reaction with respect to various solvents (CH₃CN, H₂O, EtOH and DMF), bases (NaHCO₃, Na₂CO₃, and K₂CO₃) and mole% Cu composition (0.95, 1.9 and 3.8) of the synthesized catalyst. To evaluate the importance of base, the test reaction was also attempted without base, poor yield of the product was obtained (entry 4, Table 1). This unveils that base plays a significant role in the Chan-Lam cross coupling reaction as it activates the phenyl boronic acid during the progress of the reaction. Then, effect of different bases (organic and inorganic) was investigated on the C-N cross-coupling reaction and observed that organic base (triethyl amine) gave poor yield, whereas inorganic bases gave relatively satisfactory results. It has been observed that out of the various inorganic bases tested (NaHCO₃, Na₂CO₃ and K₂CO₃), K₂CO₃ gave excellent results in terms of yield and reaction time (entry 5-6, 11, Table 1).
Further, in order to evaluate the appropriate amount of K$_2$CO$_3$ required to carry out C-N coupling smoothly, the model reaction was performed with different amounts of K$_2$CO$_3$. It was found that 1.2 eq of K$_2$CO$_3$ was the appropriate amount to catalyse the C-N cross-coupling reaction. Effect of different solvents such as CH$_3$CN, H$_2$O, EtOH and DMF was also investigated and results revealed that water was the best solvent for this cross-coupling reaction owing to the excellent stability of phenyl boronic acid in aqueous medium (entries 7-9, 11, Table 1).

Lastly, the amount of catalyst necessary to carry out the C-N coupling reaction effectively was also optimized. In order to attain maximum conversion, cross-coupling reaction between aniline and phenyl boronic acid was carried out in the presence of K$_2$CO$_3$ as base and water as solvent at 80 °C under different catalyst loadings (entries 10-12, Table 1). It was found that good yield of the product was obtained when 0.05 g (1.9 mol% Cu) of the catalyst was used (entry 11, Table 2). Thus, after performing various experiments, it was concluded that the reported catalyst gave best results for Chan-Lam cross-coupling reaction in the presence of K$_2$CO$_3$ (1.2 eq, 0.165 g) as base, water as reaction medium and a catalyst consisting of 1.9 mol% Cu (0.05 g).

Table 1. Effect of different copper sources, bases and solvents towards the C-N cross-coupling reaction of aniline with phenylboronic acid$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu source (mol%)</th>
<th>Base</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuSO$_4$.5H$_2$O (2)</td>
<td>K$_2$CO$_3$</td>
<td>H$_2$O</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)$_2$.H$_2$O (2)</td>
<td>K$_2$CO$_3$</td>
<td>H$_2$O</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>CuCl$_2$.2H$_2$O (2)</td>
<td>K$_2$CO$_3$</td>
<td>H$_2$O</td>
<td>24</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa (1.9)</td>
<td>No base</td>
<td>H$_2$O</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa (1.9)</td>
<td>Na$_2$CO$_3$</td>
<td>H$_2$O</td>
<td>3</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa (1.9)</td>
<td>NaHCO$_3$</td>
<td>H$_2$O</td>
<td>3</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>Catalyst and solvent (5 mL) at 80 °C.</td>
<td>Isolated yield.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>-------------------------------------</td>
<td>-----------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Cu@Fe₃O₄-TiO₂-L-dopa (1.9) K₂CO₃ EtOH 3 78</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Cu@Fe₃O₄-TiO₂-L-dopa (1.9) K₂CO₃ CH₃CN 3 60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Cu@Fe₃O₄-TiO₂-L-dopa (1.9) K₂CO₃ DMF 3 56</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Cu@Fe₃O₄-TiO₂-L-dopa (0.95) K₂CO₃ H₂O 3 80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Cu@Fe₃O₄-TiO₂-L-dopa (1.9) K₂CO₃ H₂O 3 92</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Cu@Fe₃O₄-TiO₂-L-dopa (3.8) K₂CO₃ H₂O 3 91</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Reaction conditions: aniline (1 mmol), phenyl boronic acid (1.2 mmol), base (1.2 mmol), Catalyst and solvent (5 mL) at 80 °C.

Impressed from the above results, the catalytic activity of Cu@Fe₃O₄-TiO₂-L-dopa was further explored for the Chan-Lam cross-coupling reaction with electronically diverse anilines, and results are summarized in Table 2. The cross-coupling was found to proceed with high regiospecificity and substituted diarylamines were obtained as a single regioisomer in good to excellent yields. As shown in Table 2, when C-N cross-coupling reaction performed with non-halide substituted aryl amines (entries 1-3, 9-10, Table 2), substituted diarylamines were obtained as single regioisomers in good to excellent yields. Whereas, with aliphatic amine such as diethylamine (entry 11, Table 2), only 60% yield of the desired product was obtained. Thus, it was concluded that Chan-Lam cross-coupling reaction worked slowly with aliphatic amines. An interesting observation was noticed when C-N cross-coupling reaction was performed with halide substituted arylamines. It was found that when Chan-Lam cross-coupling reaction was attempted with 4-fluoroaniline (entry 4, Table 2) and 2-fluoroaniline (entry 5, Table 2), C-N cross-coupling products were formed in good yields i.e. 90% and 92%, respectively, without the formation of any side products. However, when the same coupling reaction was tested with 4-chloroaniline (entry 6, Table 2), 4-bromoaniline (entry 7, Table 2) and 2-iodoaniline (entry 8, Table 2), desired products were obtained in low yields. It was found that the low yields of C-N cross-coupling products in case of entries 6-8 (Table 2) were due to the formation of C-C coupling products as side products. When C-N cross-
coupling was tested with 2-iodo aniline, isolated yields of C-N cross-coupling and C-C cross-coupling products were found to be 55% and 40% respectively. But in case of 4-chloroaniline and 4-bromoaniline, only 15% and 26% C-C coupling products were formed respectively. It was proposed that increased yield of C-C coupling product in iodo substituted aniline than the bromo and chloro substituted counterparts is due to the good leaving nature of iodo group compared with that of bromo and chloro groups. Besides, pure C-N cross-coupling in the case of fluoro substituted aniline might occur owing to the the poor leaving nature of fluoro group.

Table 2. C-N cross-coupling reaction of different anilines with phenyl boronic acid in the presence of Cu@Fe₃O₄-TiO₂-L-dopa using water at 80 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Product 1" /></td>
<td>3</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Product 2" /></td>
<td>3</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Product 3" /></td>
<td>2.5</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Product 4" /></td>
<td>2.5</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Product 5" /></td>
<td>2.5</td>
<td>92</td>
</tr>
</tbody>
</table>
Reaction conditions: aniline (1 mmol), phenylboronic acid (1.2 mmol), Cu@Fe₃O₄-TiO₂-L-dopa (1.9 mol% Cu, 0.05 g), K₂CO₃ (1.2 mmol, 0.165 g), H₂O (5 mL) at 80 °C.

Isolated yield.

Along with C-N cross-coupling, C-C coupling also takes place.

Recyclability and heterogeneity

The cross-coupling between aniline and phenyl boronic acid was selected as the model reaction to check the recyclability of Cu@Fe₃O₄-TiO₂-L-dopa for the Chan-Lam coupling reaction (entry 1, Table 2). After completion of the reaction as monitored by TLC, the catalyst was separated using external magnet, washed with chloroform (3 × 10 mL), deionized water (3 × 10 mL) and dried under vacuum. Then, the same reaction
under the same reaction conditions was performed with the used catalyst. It is pertinent to mention that amount of reactants taken for further run were adjusted according to the amount of catalyst recovered from the previous run. No notable decrease in the catalytic activity of the catalyst was observed up to six runs (Fig. 2).

Furthermore, to check the heterogeneity of the catalyst, a fresh reaction (entry 1, Table 2) was performed until the conversion was 50% (1.5 h), and at that point, the catalyst was filtered off from the reaction mixture while hot. The liquid phase so obtained was then shifted to another flask and again allowed to react. It was observed that supernatant showed no further increase in the conversion of the reactants, therefore excluding the possibility of leaching of Cu(0) nanoparticles. This strongly suggests that the catalyst is heterogeneous in nature. The ICP-AES analysis of the reused Cu@Fe₃O₄-TiO₂-L-dopa after the 6th run was also carried out to estimate the Cu concentration. It was found that the concentration of Cu(0) in the reused catalyst was reduced from 2.52 wt% to 2.39 wt%. The small amount of Cu(0) leaching from the support might be due to some changes that occurred on the surface of the magnetic catalyst during the reaction.

![Graph showing recyclability of Cu@Fe₃O₄-TiO₂-L-dopa.](image)

**Fig. 2** Recyclability of Cu@Fe₃O₄-TiO₂-L-dopa. Reaction conditions: aniline (1 mmol), phenylboronic acid (1.2 mmol), Cu@Fe₃O₄-TiO₂-L-dopa (1.9 mol% Cu, 0.05 g), K₂CO₃ (1.2 mmol, 0.165 g), H₂O (5 mL) at 80 °C.
Proposed mechanism

The plausible mechanism for the Cu@Fe₃O₄-TiO₂-L-dopa catalyzed C-N cross-coupling reaction has been proposed (Fig. 3). It involves oxidative addition followed by transmetallation and reductive elimination. In the first step, Cu(0) species activates the N-H bond by an oxidative addition, which provides an organo Cu (II) complex prone to react with nucleophiles. This step is followed by transmetallation and finally, reductive elimination to afford the corresponding product along with the regeneration of the catalyst.

![Proposed mechanism for the C-N cross-coupling reaction](image)

**Fig. 3** Proposed mechanism for the C-N cross-coupling reaction in the presence of Cu@Fe₃O₄-TiO₂-L-dopa.

Conclusions

We have developed a novel and efficient magnetic Cu(0) catalytic system (Cu@Fe₃O₄-TiO₂-L-dopa). Here, TiO₂ nanoparticles were grafted over the Fe₃O₄ nanoparticles in order to stabilize them and to prevent their agglomeration. L-dopa has emerged as an excellent interparticle linker which reduces the leaching of Cu(0) nanoparticles. The catalytic efficiency of the Cu@Fe₃O₄-TiO₂-L-dopa was tested for the Chan-Lam cross-coupling reaction with electronically diverse anilines. The cross-coupling was found to
proceed with high regiospecificity and substituted diarylamines were obtained as a single
regioisomer in good to excellent yields. Moreover, it has been observed that with halide
substituted arylamines, along with C-N cross-coupling, C-C coupling also takes place as
side reaction. Thus, simple, efficient and environmentally-benign procedure has been
developed for the C-N cross-coupling reaction in ligand-free conditions.
Experimental

General procedure for the Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa catalyzed Chan-Lam coupling reaction

Aryl amine (1 mmol), phenyl boronic acid (1.2 mmol), K$_2$CO$_3$ (1.2 mmol), Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa (1.9 mol% Cu, 0.05 g) and water (5 mL) were taken in a round bottom flask (25 mL), and the reaction mixture was stirred at 80 °C for the appropriate time. After completion of the reaction as monitored by TLC, catalyst was separated from the reaction mixture via magnet, washed with ethanol (2 × 5 mL) followed by deionized water (2 × 10 mL) and dried under vacuum. The supernatant was diluted with ethyl acetate, washed with deionized water (3 × 20 mL) and dried over anhyd. Na$_2$SO$_4$. Finally, the product was obtained after removal of the solvent under reduced pressure followed by crystallization from a suitable solvent or passing through column of silica gel and elution with EtOAc-pet. ether (1:99).

The structures of the products were confirmed by $^1$H NMR, $^{13}$C NMR and mass spectral data and comparison with authentic samples prepared according to the literature methods.
Spectral data of the compounds listed in Table 2

Diphenylamine (entry 1)

Pale yellow liquid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.75 (bs, 1H, NH, exchangeable with D$_2$O), 7.37-7.41 (t, 2H, J=8 Hz, Ar-H), 7.47-7.51 (t, 4H, J=8 Hz, Ar-H), 7.63-7.65 (d, 4H, J=8 Hz, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 112.83, 117.61, 129.35, 130.92, 145.21; MS (ESI): 168 (M-1), 170 (M+1).

N-(4-Methylphenyl) benzenamine (entry 2)

Pale yellow liquid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.51 (s, 3H, CH$_3$), 5.84 (bs, 1H, NH, exchangeable with D$_2$O), 7.36-7.39 (t, 2H, J=8 Hz, Ar-H), 7.45-7.49 (t, 3H, J=8 Hz, Ar-H), 7.61-7.63 (d, 4H, J=8 Hz, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 23.0, 109.96, 115.69, 127.15, 129.35, 132.87, 143.66; MS (ESI): 183 (M$^+$).

N-(4-Methoxyphenyl)benzenamine (entry 3)

Pale yellow liquid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.86 (s, 3H, OCH$_3$), 5.86 (bs, 1H, NH, exchangeable with D$_2$O), 6.96-7.02 (m, 5H, Ar-H), 7.35-7.37 (d, 2H, J=8 Hz, Ar-H), 7.53-7.59 (m, 2H, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 56.76, 112.78, 114.78, 126.42, 129.69, 145.62; MS (ESI): 199 (M$^+$).
N-(4-Fluorophenyl)benzenamine (entry 4)

Brown liquid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.49 (bs, 1H, NH, exchangeable with D$_2$O), 7.37-7.41 (t, 2H, J=8 Hz, Ar-H), 7.47-7.51 (t, 3H, J=8 Hz, Ar-H), 7.63-7.65 (d, 4H, J=8 Hz, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 116.62, 122.05, 127.13, 128.70 (J= 157 Hz), 130.28, 140.79; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -121.99 (m, 1F); MS (ESI):187 (M$^+$).

N-(2-Fluorophenyl)benzenamine (entry 5)

Brown liquid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.40 (bs, 1H, NH, exchangeable with D$_2$O), 7.14-7.16 (dd, 3H, J=8 Hz, Ar-H), 7.33-7.38 (m, 3H, Ar-H), 7.55-7.57 (d, 3H, J=8 Hz, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 111.14, 113.99, 119.10, 124.09, 124.46 (d, J= 37 Hz), 128.78, 133.26, 147.11; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -131.67 (m, 1F), MS (ESI): 187 (M$^+$).

N-(4-Chlorophenyl)benzenamine (entry 6)

Yellow liquid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.85 (bs, 1H, NH, exchangeable with D$_2$O), 6.48-6.52 (m, 5H, Ar-H), 7.05-7.07 (d, 2H, J=8 Hz, Ar-H), 7.37-7.39 (d, 2H, J=8 Hz, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 113.83, 116.94, 130.08, 142.54; MS (ESI): 203 (M$^+$), 205 (M+2)
N-(4-Bromophenyl)benzenamine (entry 7)

![Chemical structure](image)

Brown liquid. $^1$H NMR (400 MHz, CDCl$_3$): δ 5.45 (bs, 1H, NH, exchangeable with D$_2$O), 6.76-6.81 (m, 5H, Ar-H), 7.25-7.27 (d, 2H, J=8 Hz, Ar-H), 7.44-7.46 (d, 2H, J=8 Hz, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 116.78, 118.45, 128.90, 129.87, 131.98, 143.65; MS (ESI): 248 (M$^+$), 250 (M+2).

N-(2-Iodophenyl)benzenamine (entry 8)

![Chemical structure](image)

Brown liquid. $^1$H NMR (400 MHz, CDCl$_3$): δ 4.81 (bs, 1H, NH, exchangeable with D$_2$O), 6.79-6.81 (d, 1H, J=8 Hz, Ar-H), 6.84-6.88 (t, 1H, J=8 Hz, Ar-H), 7.15-7.21 (m, 2H, Ar-H), 7.28-7.38 (m, 1H, Ar-H), 7.45-7.48 (m, 4H, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 115.96, 118.82, 127.16, 128.53, 128.84, 129.08, 130.43, 139.71, 143.90; MS (ESI): 295 (M$^+$).

N-Phenylpyridin-2-amine (entry 9)

![Chemical structure](image)

Yellow liquid. $^1$H NMR (400 MHz, CDCl$_3$): δ 4.69 (bs, 1H, NH, exchangeable with D$_2$O), 7.03-7.09 (m, 5H, Ar-H), 7.18-7.20 (d, 1H, J=8 Hz, Ar-H), 7.28-7.31 (m, 3H, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 112.69, 114.52, 125.06, 129.05, 130.43, 138.41, 139.89, 145.85; MS (ESI): 170 (M$^+$).
N-(4-Nitrophenyl)benzenamine (entry 10)

Yellow liquid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.78 (bs, 1H, NH, exchangeable with D$_2$O), 6.52-6.54 (d, 2H, J=8 Hz, Ar-H), 6.79-6.81 (d, 3H, J=8 Hz, Ar-H), 7.15-7.17 (d, 2H, J=8 Hz, Ar-H), 7.56-7.58 (d, 2H, J=8 Hz, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 112.78, 113.98, 114.89, 117.98, 128.78, 137.76, 147.89, MS (ESI): 214 (M$^+$).

N,N-Diethylbenzenamine (entry 11)

Yellow liquid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.20-1.23 (t, 6H, J=4 Hz, 2 $\times$ CH$_3$), 3.59-3.64 (m, 4H, 2 $\times$ CH$_2$), 6.78-6.63 (m, 3H, Ar-H), 7.04-7.09 (m, 2H, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 13.56, 46.8, 114.78, 119.89, 127.89, 136.42, 143.89; MS (ESI): 149 (M$^+$).

4-Aminobiphenyl (entry 6,7)

Yellow solid, M. pt. 51-52 °C (Lit. M.pt. 52-53 °C)$^{30}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.95 (bs, 2H, NH$_2$, exchangeable with D$_2$O), 6.80-6.82 (d, 2H, J = 8 Hz, Ar-H), 7.46-7.49 (m, 3H, Ar-H), 7.64-7.72 (m, 4H, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 116.8, 126.5, 127.7, 127.9, 128.5, 128.7, 136.5, 147.2; MS (ESI): 169 (M$^+$).
2-Aminodiphenyl (entry 8)

Black semi-solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.18 (bs, 2H, NH$_2$, exchangeable with D$_2$O), 6.80-6.82 (d, 1H, J = 8 Hz, Ar-H), 6.85-6.89 (t, 1H, J=8 Hz, Ar-H), 7.15-7.21 (m, 1H, Ar-H), 7.37-7.39 (m, 1H, Ar-H), 7.44-7.48 (m, 3H, Ar-H), 7.62-7.64 (d, 2H, J=8 Hz, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 115.4, 119.1, 127.1, 128.0, 129.3, 130.6, 139.4, 143.2; MS (ESI): 169 (M$^+$).
REFERENCES


3.3 One-pot synthesis of dehydroacridine-1,8-diones using Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa in aqueous medium

Acridine and acridine-1,8-dione derivatives are polyfunctionalized 1,4-dihydropyridine derivatives. These are essential structural motifs possessing antiviral, antimalarial and antiallergic properties$^{1-3}$. Besides, acridines are also used as potent drugs for antitumor activity both \textit{in vitro} and \textit{in vivo} against a series of murine and human tumors$^4$. They are also used in $n$-type semiconductors, electroluminescent devices and acts as fluorescent molecular probes for monitoring polymerization processes$^5$. Moreover, fluorinated acridones possessed anticancer activity$^6$-$^9$. Besides, they showed potential applications in the field of laser technologies$^{10}$. Further, a wide range of acridine derivatives serve as potent antimicrobial agents (Fig. 1)$^{11}$-$^{12}$ such as Amsacrine, an antineoplastic agent, used against acute leukemia, whereas Ledakrin is an antitumor agent. Rivanol is used as abortifacient and as antiseptic, whereas Quinacrine is used for therapy and prophylaxis of malaria. In addition, Acriflavine is one of the milestones in the history of acridines and is the name of a mixture of 3,6-diaminoacridinium hydrochloride and 3,6-diamino-10-methylacridinium chloride. It has been found to possess antibacterial, antiseptic, anticancer and antimalarial activities \textit{in vitro} and \textit{in vivo}.

![Chemical Structures](image)

\textbf{Fig. 1} Some biologically active acridine derivatives.
Earlier methods reported for the synthesis of decahydroacridine-1,8-diones

It is well renowned that the acridine and its derivatives are of immense significance both in organic synthesis and in biological chemistry. A straightforward method for the synthesis of these compounds involves a condensation between arylaldehydes, cyclic 1,3-dicarboxyls, and ammonium acetate or anilines, catalyzed by various compounds such as poly-phosphoric acid\(^{13}\), Amberlyst-15\(^{14}\), organic solvents\(^{15}\), ionic liquids\(^{16}\), \(p\)-dodecylbenzenesulfonic acid\(^{17}\) etc. This synthesis was also reported under microwave irradiation\(^{18}\). Some of the recent methods reported for the synthesis of decahydroacridine-1,8-diones are presented below:

Rahmani \textit{et al.}\(^ {19}\) have reported an efficient and heterogeneous catalytic system i.e. nano titanium dioxide for the one-pot multicomponent synthesis of \(3,3,6,6\)-tetramethyl-9-substituted phenyl-decahydroacridine-1,8-dione derivatives from dimesone, aromatic aldehydes and ammonium acetate under mild reaction conditions (Scheme 1).

\textbf{Scheme 1}

\begin{center}
\begin{tikzpicture}
\path[use as bounding box] (-2.5,-2.5) rectangle (2.5,2.5);
\node (CHO) at (0,0) {CHO};
\node (2O2C) at (1,1) {\(\text{O} \text{O} \text{R}_1 \text{R}_2\)};
\node (NH4OAc) at (2,0) {\(\text{NH}_4\text{OAc}\)};
\node (nano-TiO2) at (3,0) {\text{nano-TiO}_2 (10 mol\%)};
\node (EtOH, reflux) at (4,0) {\text{EtOH, reflux}};
\node (Z) at (5.5,0) {Z};
\node (R1) at (6.5,0) {R_1};
\node (R2) at (7.5,0) {R_2};
\draw[->] (CHO) -- (2O2C);
\draw[->] (2O2C) -- (NH4OAc);
\draw[->] (NH4OAc) -- (nano-TiO2);
\draw[->] (nano-TiO2) -- (EtOH, reflux);
\draw[->] (EtOH, reflux) -- (Z);
\draw[->] (Z) -- (R1);
\draw[->] (R1) -- (R2);
\end{tikzpicture}
\end{center}

One-pot synthesis of biologically significant acridinediones from \(\beta\)-enaminones, aldehydes and cyclic 1,3-diketones in dimethyl formamide using indium(III) triflate as a catalyst has been reported by To \textit{et al.}\(^ {20}\) The main disadvantages associated with this method are the use of expensive indium(III) triflate as a catalyst and dimethyl formamide as a highly polar solvent (Scheme 2).
Silica iodide (SiO$_2$-I) has been utilized as an efficient catalyst for the one-pot three component condensation of aromatic aldehydes, dimedone and ammonium acetate in ethanol at 80°C. The synthesized compounds also showed anti-cancer activity against MCF-7 and HepG2 cell lines$^{21}$ (Scheme 3).

One-pot multi-component synthesis of structurally important NH- and N-substituted acridine-1,8-diones from corresponding electron-deficient and electron-rich aromatic aldehydes, aromatic amines or ammonium acetate and dimedone or cyclohexyl-1,3-diones in the presence of CAN (ceric ammonium nitrate) under ultrasonic conditions has been reported by Sudha et al.$^{22}$ (Scheme 4).
A simple and efficient one-step method for the synthesis of acridine and its derivatives from aromatic aldehydes, cyclic diketones and aryl amines in the presence of Cu-doped ZnO nanocrystalline powder has been reported by Alinezhad et al.\textsuperscript{23} The reported method possesses several advantages such as short reaction time, good yields and operational simplicity.

An economical, eco-friendly, non-corrosive and recoverable ionic liquid, $\text{[Et}_3\text{N}]^+\text{[HSO}_4^-]$ has been successfully utilized for the multi-component one-pot synthesis of phenyl polyhydro acridine diones by Rajendran et al.\textsuperscript{24}

The acidic ionic liquids, $\text{[DISM][CCl}_3\text{COO]}$ and $\text{[DSIM][CF}_3\text{COO]}$ have been successfully utilized as recyclable catalysts for the preparation of 1,8-dioxo-decahydroacridine derivatives under solvent-free conditions at 80-100 °C (\textbf{Scheme 5}).\textsuperscript{25}

\textbf{Scheme 5}

![Scheme 5](image)

Green and efficient ionic liquid catalysts such as $\text{[MIMPS]}_3\text{PW}_{12}\text{O}_{40}$ and $\text{[TEAPS]}_3\text{PW}_{12}\text{O}_{40}$ have been reported for the synthesis of 1,8-dioxo-decahydroacridine derivatives via one-pot three component reaction of 1,3-cyclohexanediones, aromatic aldehydes and aromatic amines or ammonium acetate.\textsuperscript{26}

Vaghei \textit{et al.} have reported $\text{N,N'}$-dibromo-$\text{N,N'}$-1,2-ethanediylbis(p-toluenesulfonamide) [BNBTS] as an efficient and reusable catalyst for the one-pot synthesis of benzo[c]acridines from aldehydes, anilines, and cyclic 1,3-dicarbonyl compounds in good to excellent yields under solvent-free conditions (\textbf{Scheme 6}).\textsuperscript{27}
Scheme 6

Wang et al.\textsuperscript{28} have reported a facile approach for the synthesis of diversely substituted acridines via the tandem coupling/cyclization of substituted 2-bromobenzaldehydes with different anilines. The reported method was catalyzed by Pd\textsubscript{2}(dba)\textsubscript{3} in the presence of diphosphine ligand (dppf) and afforded a broad range of substituted acridines in good to excellent yields. Further, Lewis acid, AlCl\textsubscript{3}, was required to promote the cyclization in case of electron deficient anilines.

Kumar and his coworkers\textsuperscript{29} have synthesized a variety of 2-methyl-9-substituted acridines via nucleophilic substitution of 2-methyl-9-chloroacridine with aromatic amines. Most of the synthesized compounds have showed higher \emph{in vitro} cytotoxic activity against A-549 and MCF-7 cancer cell lines.

Various methods have been reported in the literature for the synthesis of decahydroacridine-1,8-diones, possessing several advantages. But on the other hand, also suffers from numerous disadvantages such as, the use of corrosive acid catalysts or expensive ionic liquids, nano-TiO\textsubscript{2} and In(OTf)\textsubscript{3}, platinum nanoparticles, use of polar organic solvents, harsh reaction conditions, long reaction times, unsatisfactory yields and tedious workup procedures. To overcome these problems, herein we have reported an efficient and green method for the synthesis of decahydroacridine-1,8-diones by the one-pot condensation of aromatic aldehydes, dimedone and aromatic amines or ammonium acetate in water at 80 °C using Cu@Fe\textsubscript{3}O\textsubscript{4}-TiO\textsubscript{2}-L-dopa as magnetically recoverable catalyst (Scheme 7).
Scheme 7

\[
\begin{align*}
2 \text{O} & \text{C} = \text{O} \quad + \quad \text{R}^1\text{CHO} \quad + \quad \text{NH}_4\text{OAc} \quad \xrightarrow{\text{Cu@Fe}_3\text{O}_4\text{-TiO}_2\text{-L-dopa (0.1 g)}} \quad \text{H}_2\text{O}, 80 \degree \text{C} \\
2 \text{O} & \text{C} = \text{O} \quad + \quad \text{R}^1\text{CHO} \quad + \quad \text{R}^2\text{NH}_2 \quad \xrightarrow{\text{Cu@Fe}_3\text{O}_4\text{-TiO}_2\text{-L-dopa (0.1 g)}} \quad \text{H}_2\text{O}, 80 \degree \text{C}
\end{align*}
\]

Results and discussion

Optimization of the reaction conditions

The reaction between benzaldehyde (1 mmol), aniline (1 mmol) and dimeredone (2 mmol) was chosen as model reaction in order to obtained best optimized conditions for the synthesis of decahydroacridine-1,8-diones. Initially, effect of different solvents, such as ethanol, acetonitrile and water was investigated taking the model reaction (Table 1). From Table 1, it was clearly depicted that among different solvents, water has appeared as an appropriate solvent in terms of yield and mild reaction conditions. Temperature also plays a vital role in determining the course of the reaction. The model reaction was carried out at different temperatures, such as 60, 80 and 100 °C in an aqueous medium and it was observed that the best results were obtained at 80 °C (entries 3-5, Table 1). After the optimization of the reaction conditions for the synthesis of decahydroacridine-1,8-diones, a series of decahydroacridine-1,8-dione derivatives were synthesized from dimeredone, arylaldehydes and ammonium acetate or anilines using Cu@Fe\textsubscript{3}O\textsubscript{4}-TiO\textsubscript{2}-L-dopa as the catalyst, and good to excellent yields were obtained (Table 2).
Table 1. Effect of different solvents and temperature on the Cu@Fe₃O₄-TiO₂-L-dopa catalyzed one-pot synthesis of decahydroacridine-1,8-diones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (min)</th>
<th>Yield (^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetonitrile</td>
<td>80</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>80</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>Water</td>
<td>80</td>
<td>30</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>Water</td>
<td>60</td>
<td>30</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>Water</td>
<td>100</td>
<td>30</td>
<td>92</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: aniline (0.09 g, 1 mmol), dimedone (0.280 g, 2 mmol), benzaldehyde (0.106 g, 1 mmol) and Cu@Fe₃O₄-TiO₂-L-dopa (0.1 g), water (5 mL) at 80 °C.

\(^b\)Isolated yield.

Table 2. Cu@Fe₃O₄-TiO₂-L-dopa catalyzed one-pot multicomponent synthesis of decahydroacridine-1,8-diones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Time (min.)</th>
<th>Yield (^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHO</td>
<td><img src="image1.png" alt="Product 1" /></td>
<td>15</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>CHO</td>
<td><img src="image2.png" alt="Product 2" /></td>
<td>20</td>
<td>92</td>
</tr>
</tbody>
</table>
3

4

5

6

7
Reaction conditions: ammonium acetate (1 mmol, entries 1-5) or aromatic amine (1 mmol, entries 6-10), dimedone (2 mmol), aldehyde (1 mmol) and Cu@Fe$_3$O$_4$-TiO$_2$-L-dopa (0.1 g, 3.8 mol% Cu), water (5 mL) at 80 °C.

Isolated yield.

Recyclability

To test the recyclability of the catalyst for the one-pot synthesis of decahydroacridine-1,8-diones, a series of five consecutive runs were carried out in case of ammonium acetate, dimedone and 4-\(N,N\)-dimethylbenzaldehyde for the synthesis of corresponding
decahydroacridine-1,8-diones (entry 3, Table 2) and the results are presented in Fig. 2. It was found that there was no considerable loss in catalytic activity of the Cu@Fe₃O₄-TiO₂-L-dopa upto the fifth run, which made the process more cost-effective.

Fig. 2  Recyclability of Cu@Fe₃O₄-TiO₂-L-dopa. Reaction conditions: ammonium acetate (1 mmol), dimedone (2 mmol), 4-N,N-dimethylbenzaldehyde (1 mmol) and Cu@Fe₃O₄-TiO₂-L-dopa (0.1 g, 3.8 mol% Cu), water (5 mL) at 80 °C.

**Proposed mechanism**

The plausible mechanism for the Cu@Fe₃O₄-TiO₂-L-dopa catalyzed one-pot synthesis of decahydroacridine-1,8-diones has been proposed and presented in Fig. 3. Here, Cu(0) NPs immobilized onto Fe₃O₄-TiO₂-L-dopa catalyzes the reaction by electrophilic activation of the carbonyl groups of aldehyde and dimedone; thereby makes it susceptible to nucleophilic attack. The first step involves the Knoevenagel condensation between 5,5-dimethyl-1,3-cyclohexanenedione and benzaldehyde (both activated by Fe₃O₄-TiO₂-L-dopa) to give intermediate I. The intermediate I reacts with another molecule of 5,5-dimethyl-1,3-cyclohexanenedione activated by Cu NPs to form another intermediate II via Michael addition reaction. Finally, intermediate II on reaction with aniline gives intermediate III, which undergoes cyclization followed by dehydration, leading to the formation of the desired product IV and catalyst is regenerated back.
Conclusion

In conclusion, an efficient, sustainable and magnetically separable catalyst, Cu@Fe₃O₄-TiO₂-L-dopa was developed. The synthesized catalyst showed excellent catalytic activity for the one-pot synthesis of decahydroacridine-1,8-diones under mild reaction conditions. The method offers numerous advantages such as short reaction time, mild reaction conditions, use of water as green solvent, simple work-up procedure, good yield of products and recyclability of Cu@Fe₃O₄-TiO₂-L-dopa upto five reaction cycles.
Experimental

**General procedure for the Cu@Fe₃O₄-TiO₂-L-dopa catalyzed one-pot synthesis of decahydroacridine-1,8-diones**

To a mixture of aromatic aldehyde (1 mmol), dimedone (2 mmol), aromatic amines (1 mmol) or NH₄OAc (1 mmol) and Cu@Fe₃O₄-TiO₂-L-dopa (0.1 g, 3.8 mol% Cu) in a round bottom flask (25 mL), water (5 mL) was added and the reaction mixture was stirred at 80 °C for an appropriate time (Table 2). The progress of the reaction was monitored through TLC. On completion, the reaction mixture was cooled, ethyl acetate (30 mL) was added and the catalyst was separated via external magnet. The catalyst obtained was washed with ethyl acetate and distilled water, dried in an oven. The organic layer was washed with water (3 × 15 mL) and dried over anhyd. Na₂SO₄. The product was obtained after removal of the solvent under reduced pressure, followed by crystallization from ethyl acetate.

The structures of the products were confirmed by ¹H NMR, ¹³C NMR and mass spectral data and comparison with authentic samples prepared according to the literature methods.
Spectral data of products listed in Table 2

3,3,6,6-Tetramethyl-9-phenyl-1,8-dioxodecahydroacridine (entry 1)

White coloured solid, M. pt. 272-275 °C (Lit. M.pt. 277-278 °C)\textsuperscript{30}. \textsuperscript{1}H NMR (400MHz, DMSO-\textit{d}_6): δ 1.05 (s, 6H, 2 × CH\textsubscript{3}), 1.19 (s, 6H, 2 × CH\textsubscript{3}), 2.23-2.56 (m, 8H, 4 × CH\textsubscript{2}), 5.07 (s, 1H, CH), 7.27-7.59 (m, 5H, ArH), 10.46 (bs, 1H, NH, exchangeable with D\textsubscript{2}O); \textsuperscript{13}C NMR (100 MHz, DMSO-\textit{d}_6): δ 27.6, 28.9, 30.9, 31.7, 46.1, 46.7, 114.9, 127.8, 131.2, 135.4, 149.5, 190.0; MS (ESI): 349.2 [M\textsuperscript{+}].

3,3,6,6-Tetramethyl-9-(4-methoxyphenyl)-1,8-dioxodecahydroacridine (entry 2)

Yellow coloured crystals, M. pt. 267-270 °C (Lit. M.pt. 272-273 °C)\textsuperscript{30}. \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6): δ 0.87 (s, 6H, 2 × CH\textsubscript{3}), 1.01 (s, 6H, 2 × CH\textsubscript{3}), 1.96-2.00 (d, 2H, J= 16Hz, CH\textsubscript{2}), 2.15-2.19 (d, 2H, J= 16 Hz, CH\textsubscript{2}), 2.29-2.33 (d, 2H, J= 16 Hz, CH\textsubscript{2}), 2.42-2.46 (d, 2H, J= 16 Hz, CH\textsubscript{2}), 3.66 (s, 3H, OCH\textsubscript{3}), 4.74 (s, 1H, CH), 6.70-6.72 (d, 2H, J= 8Hz, ArH), 7.04-7.06 (d, 2H, J= 8Hz, ArH), 9.28 (bs, 1H, NH, exchangeable with D\textsubscript{2}O); \textsuperscript{13}C NMR (100 MHz, DMSO-\textit{d}_6): δ 27.1, 29.4, 32.4, 40.0, 50.7, 55.4, 112.5, 113.5, 129.2, 139.8, 149.8, 157.5, 195.2; MS (ESI): 380.2 [M+1].
3,3,6,6-Tetramethyl-9-(4-N,N-dimethylphenyl)-1,8-dioxodecahydroacridine (entry 3)

Orange coloured crystals, M. pt. 261-263 °C (Lit. M.pt. 265-267 °C)\(^3\). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 0.88 (s, 6H, 2 \times CH\(_3\)), 1.01 (s, 6H, 2 \times CH\(_3\)), 1.95-1.99 (d, 2H, J= 16Hz, CH\(_2\)), 2.14-2.18 (d, 2H, J= 16 Hz, CH\(_2\)), 2.28-2.32 (d, 2H, J= 16 Hz, CH\(_2\)), 2.41-2.45 (d, 2H, J= 16 Hz, CH\(_2\)), 2.79 (s, 6H, 2 \times CH\(_3\)), 4.68 (s, 1H, CH), 6.51-6.53 (d, 2H, J= 8Hz, ArH), 6.94-6.97 (d, 2H, J= 12Hz, ArH), 9.22 (bs, 1H, NH, exchangeable with D\(_2\)O); \(^1\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 29.3, 28.2, 33.5, 35.6, 46.0, 47.8, 114.0, 126.7, 133.5, 136.7, 146.6, 150.5, 191.8; MS (ESI): 392.25 [M\(^+\)].

3,3,6,6-Tetramethyl-9-(4-chlorophenyl)-1,8-dioxodecahydroacridine (entry 4)

White coloured solid, M. pt. 292-294 °C (Lit. M.pt. 294-296 °C)\(^3\). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 0.90 (s, 6H, 2 \times CH\(_3\)), 1.04 (s, 6H, 2 \times CH\(_3\)), 2.06-2.10 (d, 2H, J= 16Hz, CH\(_2\)), 2.25-2.29 (d, 2H, J= 16 Hz, CH\(_2\)), 2.49-2.60 (m, 4H, CH\(_2\)), 4.49 (s, 1H, CH), 7.17-7.19 (d, 2H, J= 8Hz, ArH), 7.27-7.29 (d, 2H, J= 8Hz, ArH), 9.35 (bs, 1H, NH, exchangeable with D\(_2\)O); \(^1\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 27.1, 29.1, 31.4, 32.1, 50.4, 114.4, 128.5, 130.4, 131.1, 143.5, 163.8, 196.8; MS (ESI): 383.17 [M\(^+\)], 385.16 [M+2].
3,3,6,6-Tetramethyl-9-(3-nitrophenyl)-1,8-dioxodecahydroacridne (entry 5)

Yellow coloured crystals, M. pt. 281-283 °C (Lit. M.pt. 287-289 °C)\textsuperscript{30}. \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6): \(\delta 1.15\) (s, 6H, 2 \(\times\) CH\(_3\)), 1.30 (s, 6H, 2 \(\times\) CH\(_3\)), 2.38-2.50 (m, 8H, 4 \(\times\) CH\(_2\)), 5.57 (s, 1H, CH), 7.29-8.08 (m, 4H, ArH), 11.89 (bs, 1H, NH, exchangeable with D\(_2\)O); \textsuperscript{13}C NMR (100 MHz, DMSO-\textit{d}_6): \(\delta 27.0, 29.3, 31.3, 32.8, 42.9, 46.4, 114.8, 119.5, 121.06, 122.2, 129.1, 133.0, 140.3, 148.5, 191.0\); \textbf{MS (ESI)}: 394.19 [M\textsuperscript{+}].

3,3,6,6-Tetramethyl-9,10-diphenyl-1,8-dioxodecahydroacridine (entry 6)

Yellow solid, M. pt. 249-251 °C (Lit. M.pt. 253-255 °C)\textsuperscript{14a}. \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6): \(\delta 0.85\) (s, 6H, 2 \(\times\) CH\(_3\)), 1.01 (s, 6H, 2 \(\times\) CH\(_3\)), 1.83-2.49 (m, 8H, 4 \(\times\) CH\(_2\)), 4.83 (s, 1H, CH), 7.02-7.16 (m, 5H, ArH), 7.27-7.32 (m, 5H, ArH); \textsuperscript{13}C NMR (100 MHz, DMSO-\textit{d}_6): \(\delta 27.2, 28.3, 40.5, 40.9, 51.3, 111.9, 116.3, 118.8, 125.8, 128.7, 129.1, 129.6, 141.3, 142.2, 153.3, 198.9\); \textbf{MS (ESI)}: 425.24 [M\textsuperscript{+}].
3,3,6,6-Tetramethyl-9-(4-methoxyphenyl)-10-(4-chlorophenyl)-1,8-dioxodecahydroacridine (entry 7)

Yellow coloured crystals, M. pt. 252-254 °C (Lit. M.pt. 255-257 °C).\(^1\)\(^{1}\)H NMR (400 MHz, DMSO-\textit{d}_6): \(\delta\) 0.72 (s, 6H, 2 × CH\(_3\)), 0.89 (s, 6H, 2 × CH\(_3\)), 1.74-1.78 (d, 2H, J= 16Hz, CH\(_2\)), 1.98-2.02 (d, 2H, J= 16 Hz, CH\(_2\)), 2.16-2.21 (m, 4H, 2 × CH\(_2\)), 3.69 (s, 3H, OCH\(_3\)), 4.96 (s, 1H, CH), 6.79-6.81 (d, 3H, J= 8 Hz, ArH), 7.19-7.21 (d, 3H, J= 8Hz, ArH), 7.67-7.69 (d, 2H, J= 8Hz, ArH); \(^{13}\)C NMR (100 MHz, DMSO-\textit{d}_6): \(\delta\) 26.4, 29.8, 32.1, 32.4, 41.4, 50.1, 113.1, 117.4, 128.5, 130.1, 130.8, 139.1, 145.8, 151.1, 156.8, 195.9; MS (ESI): 489.10 [M\(^+\)], 491.24 [M+2].

3,3,6,6-Tetramethyl-9-(4-chlorophenyl)-10-(4-fluorophenyl)-1,8-dioxodecahydroacridine (entry 8)
Yellow coloured crystals, M.pt. 280-282 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 0.72 (s, 6H, 2 $\times$ CH$_3$), 0.89 (s, 6H, 2 $\times$ CH$_3$), 1.75-1.79 (d, 2H, J= 16Hz, CH$_2$), 1.99-2.03 (d, 2H, J= 16 Hz, CH$_2$), 2.17 (s, 2H, CH$_2$), 2.21-2.22 (d, 2H, J= 4Hz, CH$_2$), 5.01 (s, 1H, CH), 7.29-7.33 (m, 4H, ArH), 7.43-7.47 (m, 4H, ArH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 26.4, 29.1, 31.4, 32.4, 41.4, 50.0, 55.1, 113.5, 113.8, 128.8, 130.4, 134.5, 137.5, 138.8, 150.8, 157.8, 196.2; MS (ESI): 476.18 [M-1], 478.19 [M+1].

3,3,6,6-Tetramethyl-9-(4-chlorophenyl)-10-phenyl-1,8-dioxodecahydro-acridine (entry 9)

White coloured solid, M. pt. 242-244 °C (Lit. M.pt. 244-246 °C$^{26}$). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 0.83 (s, 6H, 2 $\times$ CH$_3$), 0.95 (s, 6H, 2 $\times$ CH$_3$), 1.80-2.23 (m, 8H, 4 $\times$ CH$_2$), 5.21 (s, 1H, CH), 7.22-7.27 (m, 4H, ArH), 7.38-7.58 (m, 5H, ArH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 26.7, 29.5, 32.3, 38.1, 41.8, 50.1, 114.1, 115.3, 119.3, 128.1, 129.4, 129.7, 131.3, 138.8, 144.6, 149.8, 195.5; MS (ESI): 459.2 [M$^+$], 461.2 [M+2].

3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-10-(4-chlorophenyl)-1,8-dioxodecahydro-acridine (entry 10)
Yellow coloured solid, M. pt. 290-292 °C (Lit. M.pt. 315-316 °C)\(^{31}\). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 0.71 (s, 6H, \(2 \times \text{CH}_3\)), 0.90 (s, 6H, \(2 \times \text{CH}_3\)), 1.78-1.82 (d, 2H, J= 16 Hz, \(\text{CH}_2\)), 1.99-2.03 (d, 2H, J= 16 Hz, \(\text{CH}_2\)), 2.19 (s, 2H, \(\text{CH}_2\)), 2.23-2.24 (d, 2H, J= 4Hz, \(\text{CH}_2\)), 5.15 (s, 1H, CH), 7.55-7.60 (m, 4H, ArH), 7.69-7.71 (d, 2H, J= 8Hz, ArH), 8.14-8.16 (d, 2H, J= 8Hz, ArH); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 26.8, 29.5, 32.7, 33.8, 41.5, 50.3, 112.4, 116.0, 124.1, 129.7, 137.7, 146.5, 151.7, 153.9, 164.8, 196.0; MS (ESI): 504.18 [M\(^+\)], 506.18 [M+2].
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153-160, 163-172