CHAPTER 3

Magnetically recyclable Nano-FDP: A novel, efficient nano-organocatalyst for one-pot multi-component synthesis of pyran derivatives in water under ultrasound irradiation
3.1. Introduction:

Catalysis has appeared as an essential avenue in modern chemistry because it signifies an innovative way to meet the challenges of sustainability and energy. Existence of a catalyst is primarily obligatory in both chemical industries and in modern organic syntheses. Green catalysis is a small chapter of green chemistry but perhaps the most crucial one.\(^1\) One of the most significant characteristic that a catalyst should possess in order to become green is recyclability. Homogeneous catalysts despite possessing many benefits like: extraordinary selectivity, high TON (Turn Over Number), High TOF (Turn Over Frequency) etc. cannot fulfil this criterion because of its difficulty in isolation. However application of heterogeneous catalyst can emerge as a tremendous remedy for this problem.\(^2,3\)

Recently nanoparticles (NPs) as heterogeneous green catalysts have gained lots of attentions.\(^4,5\) However, to separate these particles with diameters less than 100 nm from reaction mixture is quite tedious, but application of magnetic nanoparticles which can be separated from reaction mixture by attaching an external magnet can solve this issue easily.\(^6,7\) Among several magnetic nanoparticles, nano-\(\text{Fe}_3\text{O}_4\) are comprehensively studied because of its simple synthetic procedure, low cost of starting materials, and relatively higher magnetic nature.\(^8\)

Since last few decades proline have received tremendous priorities in organic synthesis as homogeneous catalyst, because of its environmentally benign behaviour, high efficiency, and availability in both enantiomeric forms. But major drawbacks over application of proline as catalyst are its separation and reusability. In order to prevail over these problems, we thought of implementing L-proline on nano-\(\text{Fe}_3\text{O}_4\) which would make it a merger of homogeneous and heterogeneous catalyst and thereby will increase its greenness by resolving above mentioned complications.

Because of mounting environmental concerns on ecological safety and global warming, chemists throughout the world are developing new methodologies which are eco-friendly and efficient. So, focus on “green chemistry” by applying environmentally benign reagents and conditions are of utmost importance for synthesis of widely used organic compounds. Keeping in mind the principles of “green chemistry” it is demanding to carry out reactions in water, nature’s own reaction medium, rather than using organic solvents which are harmful. Unique structure and physiochemical properties of water lead to particular interactions like
trans-phase interaction, H-bonding, hydrophobic interaction etc. which influence the rate of reaction and shows additive outcomes. In addition to the above mentioned advantages of using water as solvent there are certain other benefits like insolubility of the desired product, easy work up procedures which simplifies their isolation. Multi-component reactions (MCRs) have emerged as an important chemical processes that involve the well defined condensation of more than two reactants to form desired products, and most of the atoms present in reactants are retained in products (high atom economy). In true sense this strategy of MCR offers significant environment friendly features like reduction in number of steps, energy consumption and waste production.

Ultrasonication activates organic reactions because of cavitation collapse. Cavitation produces high pressure and temperature inside the bubbles, which causes blustery flow of liquids and improved mass transfer. Compared to traditional methods, this method, provides higher yield and selectivity, with gentle reaction conditions and shorter reaction time.

Pyran, an important class of heterocyclic compound signifies lots of importance in pharmaceutical industry as well as in medical world owing to its promising medicinal and biological activities like anti-cancer, anti-tumour, anti-oxidant, anti-microbial, anti-inflammatory, anti-HIV, anti-proliferative, anti-tumour etc. Structures of some biologically active pyran derivatives are shown in Fig.1. On continuation of our exploration towards synthesis and application 1 different nanoparticles in multi-component reactions, we herein report a novel nano-Fe$_3$O$_4$-DOPA-L-proline (nano-FDP) catalyst, which shows extraordinary catalytic activity in one-pot multi-component synthesis of pyran derivatives under ultrasonic irradiation.

![Image of structures of biologically active pyran derivatives]

Fig. 1: Structures of few biologically active pyran derivatives
3.2. Results and discussion:

Organocatalysts have been extensively used in organic synthesis, but still there is a lack of using it under sustainable conditions. Even though proline is an efficient catalyst for many organic transformations but its recovery from reaction mixture is very difficult. So we planned to attach proline with magnetic nanoparticles for making it easily recyclable. Dopamine, a stable and easily available starting material contains phenolic –OH and aliphatic amine group. The phenolic –OH group strongly co-ordinates to ferrite molecule by chelating effect and the L-proline binds via amide bond with amine functionality of dopamine thereby keeping the secondary amine site of L-proline free for catalysis. Nano-FDP was synthesized by a simple, efficient and cost effective procedure as shown in **Scheme1**.

![Scheme 1: Synthesis of nano-FDP](image)

Comparative FT-IR spectra of nano-FDP, nano-Fe₃O₄-DOPA (nano-FD) and nano-Fe₃O₄ are shown in Fig. 2. Fe-O vibration is observed as prominent peak at around 591-611 cm⁻¹ and appears in all the three spectra. Peaks at 1630 and 1400 cm⁻¹ in the spectrum of nano-Fe₃O₄-DOPA are due to primary -NH₂ bending, and -C-N stretching of dopamine moiety, indicating the successful attachment of dopamine molecule on
nano-Fe$_3$O$_4$. These peaks are also present in the spectrum of nano-FDP in almost the same region. Prominent sharp peak at around 1465 cm$^{-1}$ in nano-FDP’s spectrum indicates the secondary –N-H stretching of amide linkage. Prominent peak at 1685 cm$^{-1}$ in the spectrum of nano-FDP is the characteristic peak of carbonyl group which arises due to the stretching of amide carbonyl bond indicating the successful attachment of L-proline with dopamine via amide bond formation. The peak at around 3430 cm$^{-1}$ in the spectrum of nano-Fe$_3$O$_4$ is because of -OH stretching vibration of nano-Fe$_3$O$_4$. This is also present in the other two spectra at 3415 and 3465 cm$^{-1}$. If we observe carefully, peak at around 3465 cm$^{-1}$ in the spectrum of nano-FDP is very sharp indicating the –N-H stretching of L-proline moiety.

EDX analysis was carried out in order to determine elemental composition of nano-FDP. This analysis confirmed the presence of iron, carbon, nitrogen and oxygen (shown in Fig. 3A). SEM images of nano-Fe$_3$O$_4$, and nano-FDP are shown in Fig. 3B and 3C respectively. From SEM images it was confirmed that nano-FDP possess spherical shape.

Particle size of nano-FDP was examined by TEM analysis. The typical TEM images of nano-FDP (Fig. 4) revealed that, the size of the nanoparticles are in the range of 5-20 nm which is same as that of typical diameter of nano-Fe$_3$O$_4$. From TEM images, it is also evident that, black spots are consistently scattered throughout the sample and this can be attributed to the presence of nano-Fe$_3$O$_4$. The corresponding SAED (Selected Area Electron Diffraction) pattern showed spotty diffraction proving the crystalline behaviour of the sample. The width of the L-proline attached dopamine coating is around 4 nm which is clearly visible in the TEM image of freshly prepared nano-FDP (Fig. 4A, B and C).
Fig. 2: Comparative FT-IR spectra of nano-FDP, nano-Fe₃O₄ and nano-Fe₃O₄-DOPA (FD)

Fig. 3: (A) EDX of nano-FDP, (B) SEM of nano-Fe₃O₄ and (C) SEM nano-FDP
**Fig. 4:** TEM of images of nano-FDP (A) at 200 nm, (B) at 10 nm and (C) SAED pattern of nano-FDP

XRD-diffraction patterns of the prepared nano-Fe$_3$O$_4$ and nano-FDP is shown in Fig. 5A and Fig. 5B respectively. Spectra of nano-Fe$_3$O$_4$ MNPs and nano-FDP show prominent peaks at almost same region. This indicates that crystalline spinal ferrite core structure is preserved in the final catalyst. PXRD patterns shows six characteristic peaks at $2\theta = 30.29^0$, $35.59^0$, $43.25^0$, $53.84^0$, $57.16^0$, $62.79^0$ which corresponds to the indices (2 2 0), (3 1 1), (4 0 0), (4 2 2), (5 1 1) and (4 4 0) respectively.\(^{33}\)

**Fig. 5:** (A) PXRD of nano-Fe$_3$O$_4$ and (B) PXRD of nano-FDP

Vibrating Sample Magnetometer (VSM) analysis was carried out to study the magnetic behaviour of synthesized nano-FDP. Fig. 6 shows the magnetization curve for nano-FDP. Saturation magnetization value of nano-FDP was found to be 59.89 emu/g, which is slightly lower than that of bare nano-Fe$_3$O$_4$ (67.22 emu/g)\(^{34}\) because of coating.
In order to scrutinize the catalytic activity of nano-FDP, we employed it in four component reaction of ethylacetoacetate (11), hydrazine hydrate (10), 4-chlorobenzaldehyde (8a) and malononitrile (9) for synthesizing pyran derivatives (12a). Firstly, ethylacetoacetate (1 mmol) and hydrazine hydrate (1.5 mmol) were mixed together, which immediately leads to the formation of white precipitate of 3-methyl-1Hpyrazol-5(4H)-one (15a) to that 4-chlorobenzaldehyde (1 mmol), and malononitrile (1 mmol) with nano-FDP were added and ultrasonicated in presence of various solvents like DCM, chloroform, THF, ethanol (EtOH) and water (Fig. 7). It was found that polar protic solvents like water and ethanol producing better results than polar aprotic solvents like DCM, chloroform and THF. The reaction was also tested under solvent-free condition but it offered unsatisfactory result. So, water was chosen as desired solvent because it is cheap, easily available, was giving excellent yield and it is nature’s own medium for reaction.

**Fig. 6: VSM of nano-FDP**

After selection of solvent, we shifted our focus towards comparison of catalytic
activity of nano-FDP with other catalysts. Model reaction was then refluxed, as well as ultrasonicated in water (10 ml) in presence of various homogeneous and heterogeneous catalysts like Et$_3$N, morpholine, Fe$_2$SO$_4$, FeCl$_3$, glutathione, L-proline, Ni NPs, Pd NPs, nano-Fe$_3$O$_4$, nano-Fe$_3$O$_4$@DOPA (nano-FD), SiO$_2$ NPs, and nano-Fe$_3$O$_4$-DOPA- L-proline (nano- FDP) (Table 1). After 3h in absence of catalyst, very less amount of product was formed (Table 1). From Table 1, it is evident that all the catalysts successfully promoted the reaction. Even though reaction went smoothly under reflux as well as ultrasonication, but we decided to report the reaction under ultrasonic irradiation because it was found that the desired product was forming within very short interval of time under ultrasonication and most importantly without supply of any external thermal energy, i.e. at room temperature.

Table 1: Catalyst standardization $^a$

<table>
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<tr>
<th>Sl. No</th>
<th>Catalyst $^b$</th>
<th>Conventional heating(100 $^\circ$C)</th>
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<td></td>
<td></td>
<td>Time (min) $^c$</td>
<td>Yield (%) $^d$</td>
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<td>Time (min) $^c$</td>
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<td></td>
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<td>11</td>
<td>Nano-FDP</td>
<td><strong>30</strong></td>
<td><strong>91</strong></td>
<td><strong>10</strong></td>
<td><strong>98</strong></td>
<td></td>
</tr>
</tbody>
</table>

$^a$Reaction condition: Ethylacetoacetate (11, 1 mmol), hydrazine hydradate (10, 1.5 mmol), 4-Cl C$_6$H$_5$ (8a, 1 mmol), malononitrile (9, 1 mmol), 5ml water; $^b$amount taken for all the solid catalyst was 0.006 g and Et$_3$N taken 0.01m l; $^c$time is in minutes; $^d$isolated yield.

On discovering this fact, we carried a detailed observation of the model reaction under various time scale, and it was found that the complete conversion of reactants into desired product took place after 10 min of continuous irradiation (Fig. 8).
Amount of catalyst used also had significant effect on reaction and 0.006 g of Nano-FDP was found to be sufficient enough to carry out the reaction. Further increase in the catalyst concentration had no significant effect on the yield of reaction but lower catalyst concentration furnished lower yield (Fig. 9).

After standardizing all the important reaction parameters, nano-FDP was used for synthesizing a series of pyrano-pyrazole derivatives. Various aromatic aldehydes, active methylene compounds, hydrazine or phenyl hydrazine were used as starting materials (Scheme 2). Nature and position of substituent on phenyl rings had no significant effect on the overall yield of the product as shown in Table 2.
Scheme 2: One-pot four component synthesis of pyran derivatives using nano-FDP

Table 2: Synthesis of various pyrano-pyrazolone derivatives

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Aldehydes</th>
<th>Products</th>
<th>Time (min.)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>4-ClC₆H₅ (8a)</td>
<td>12a</td>
<td>10</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>4-NO₂C₆H₅ (8b)</td>
<td>12b</td>
<td>10</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>4-MeC₆H₅ (8c)</td>
<td>12c</td>
<td>12</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>C₆H₅ (8d)</td>
<td>13a</td>
<td>4</td>
<td>95</td>
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<tr>
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<td>4-MeC₆H₅ (8c)</td>
<td>13b</td>
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<td>89</td>
</tr>
<tr>
<td>6</td>
<td>4-FC₆H₅ (8e)</td>
<td>13c</td>
<td>3</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>4-NO₂C₆H₅ (8b)</td>
<td>13d</td>
<td>4</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>4-BrC₆H₅ (8f)</td>
<td>13e</td>
<td>2</td>
<td>97</td>
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<tr>
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<td>11</td>
<td>3-NO₂C₆H₅ (8h)</td>
<td>13h</td>
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<td>96</td>
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<tr>
<td>12</td>
<td>2-ClC₆H₅ (8i)</td>
<td>13i</td>
<td>6</td>
<td>95</td>
</tr>
</tbody>
</table>

* Reaction condition: Ethylacetoacetate (11, 1 mmol), hydrazine hydrate/phenyl hydrazine (10/14, 1.5 mmol), aldehyde (8, 1 mmol), malononitrile (9, 1 mmol), 0.006g nano-FDP, 5ml water and ultrasonication; † isolated yield.

Scheme 3 shows plausible mechanism for the synthesis of pyrano-pyrazolone derivatives by using nano-FDP as catalyst. In the first step ethylacetoacetate (11) reacts instantly with hydrazine hydrate (10) or phenyl hydrazine (14) leading to the formation of pyrazolone derivatives (15a,b). Then, in the second step nano-FDP binds
with aldehyde forming iminium intermediate (16) which reacts with malononitrile (9) in Knoevenagel fashion to give cyano-olefin compound (18). Finally nano-FDP activates pyrazolones (15a, b) to react with cyano-olefin compound 18 to form intermediate 21. This 21 undergoes intramolecular cyclization to form pyranopyrazolones (12 or 13).

Scheme 3: Plausible mechanism

Since recovery and reusability of catalyst were our main objectives, so, we applied external magnetic field for separation of nano-FDP from reaction mixture. It was to our delight that the catalyst was easily separated without any hurdles and after washing and drying, it was applied in other sets of reaction. It was observed that, catalyst can easily be reused for another four runs without considerable loss in catalytic activity. (Fig.10).
A TEM analysis (Fig. 11) of nano-FDP after fifth consecutive run was also carried out in order to confirm the size and shape of reused nano-FDP and it was found to be in good agreement to that of TEM images of freshly prepared nano-FDP.

**Fig. 10:** Catalyst recycling

**Fig. 11:** After use TEM images of nano-FDP (A) at 50 nm, (B) at 5 nm and (C) SAED pattern

### 3.3. Conclusion:

In conclusion, we have successfully developed an efficient, magnetically recyclable and reusable nano-FDP organocatalyst. This catalyst was synthesized by using easily available starting materials and was characterized by various analytical techniques. Said nano-FDP showed excellent catalytic activity for the synthesis of pyrano-pyrazolones in water under ultrasonic irradiation at room temperature within a short interval of time. Recovery and reusability of nano-FDP for five consecutive runs made this procedure more economically viable and environment friendly.

### 3.4. Experimental section:

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Spectrum BX FT-IR, Perkin Elmer ($\nu_{\text{max}}$ in cm$^{-1}$) on KBr disks. $^1$H NMR and $^{13}$C NMR (400, 300 MHz and 100 MHz respectively) spectra were
recorded on Bruker Advance II–400 and 300 spectrometer in CDCl₃ and (CH₃)₂SO-d₆ (chemical shifts in δ with TMS as internal standard). Mass spectra were recorded on Waters ZQ-4000 and maXis impact while CHN were recorded on CHN-OS analyser (Perkin Elmer 2400, Series II). Transmission Electron Microscope (TEM) was recorded on JEOL JSM 100CX, scanning electron microscope (SEM) was recorded on JSM-6360 (JEOL). EDX was recorded by using INCA Penta FET X-ray instrument. Silica gel G (E-mark, India) was used for TLC. PXRD analysis was carried out using a Bruker D8 Advance XRD instrument SWAX. VSM analysis was carried out by using Lakeshore, Model: 7410 series. Ultrasonicator model: RK52H, Incarp Germany (50/60 Hz, 60/240W) was used for experiments.

3.4.1. Design and synthesis nano-FDP (7):

A. Preparation of superparamagnetic nano-Fe₃O₄ (1):

A mixture of 3.4 g of ferric nitrate and 3 g of ferrous sulfate were taken in a 250 ml round bottom flask, 100 ml of deionized water was then added to it and stirred for 10 min. NH₄OH (25%) was then added slowly to the reaction mixture till its pH became 10. After that, the reaction mixture was heated at 50-60 ⁰C for 1h till the black precipitate appeared, it was then separated, washed with water till the pH became neutral (pH = 7) and dried in oven for 5h.

B. BOC-Protection of L-proline (5):

1 g of L-proline (4) in a saturated solution of NaHCO₃ (16 ml) was stirred in ice bath for 15 min. A mixture of BOC-anhydride (2.5 ml) and THF (6 ml) was added slowly in to it and stirred for another 19h at room temperature. THF was removed under vacuum and the residual solution was cooled to 0 ⁰C and acidified with 3N HCl to maintain pH 2-3. Reaction mixture was extracted with ethylacetate (3 x 10 ml). The combined organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The organic extract was concentrated under reduced pressure to yield desired product (5).

C. Synthesis of nano-Fe₃O₄–DOPA (3):

For accomplishing this step, we first took 2 g of synthesized nano-Fe₃O₄ (1) and dispersed it in 25 ml of deionized water by sonication at room temperature for 30 min. Dopamine hydrochloride (2) (2 g) was dissolved in 5 ml of deionized water and then added to it and ultrasonicated for another 2h. The dopamine coated nano-Fe₃O₄ (3) was precipitated by using acetone, isolated by an external magnet and dried.
D. Binding of BOC-L-proline with nano-Fe$_3$O$_4$-DOPA via amide bond formation to form intermediate (6):

A mixture of 0.04 ml DIPEA, 174 mg of HBTU in dry DMF (5ml) was added drop wise to a solution of BOC-L-proline (5) (100 mg) in dry DMF (10 ml), and stirred at room temperature for 1h. Then nano-Fe$_3$O$_4$-DOPA (3) (88 mg) was added to it and stirring was continued for 24h at room temperature. After that the desired product (6) was separated from the reaction mixture by external magnetic field, washed with acetone and dried.

E. Deprotection of BOC from nano-Fe$_3$O$_4$-DOPA-BOC-L-proline (6):

To a solution of nano-BOC-L-proline-Fe$_3$O$_4$-DOPA (6) (84 mg) in DCM (15 ml), TFA (1.5 ml) was added and stirred for 1h at room temperature. After stirring, the excess solvent was removed under reduced pressure. Following that, the resulting mixture was neutralized with saturated NaHCO$_3$ solution. The desired nano-FDP (7) was separated by external magnet, washed with acetone and dried in oven for 12h.

3.4.2. Synthesis of pyran derivatives (12 & 13):

Firstly ethylacetoacetate (1 mmol) and hydrazine hydrate or phenyl hydrazine (1.5 mmol) were mixed together and a white colored solid was formed. This solid was then dissolved in water (10 ml) followed by addition of aryl aldehydes (1 mmol) and malononitrile (1 mmol) in to it. Reaction mixture was then sonicated at room temperature with nano-FDP (0.006 g). Within 2-12 min (Table-2), total conversion of the starting materials to desired products were observed. After completion of the reaction (monitored by TLC), nano-FDP was removed from it by using an external magnet and the reaction mixture was extracted with ethylacetate (3x5 ml). Recovered nano-FDP was then washed with ethanol, acetone and dried. This was then reused in further reactions. The combined organic extract was washed with water (3x10 ml), brine and dried over anhydrous Na$_2$SO$_4$. The crude reaction mass was purified by column chromatography using ethylacetate and hexane as eluent.
3.5. Analytical and spectral data:

Intermediate: 3-methyl-1H-pyrazol-5(4H)-one (15a)

White solid. M.P. 222-224 °C. IR (KBr): 3434, 1623 cm⁻¹. ¹H NMR (DMSO-d₆+ CDCl₃, 400 MHz): δ = 7.71 (s, 1H), 2.17 (s, 2H), 1.25 (s, 3H).

1. Compound 12a

Yellow solid. M.P.: 232-234 °C. IR (KBr): 3288, 3231, 3125, 2196 cm⁻¹. ¹H NMR (DMSO-d₆, 400 MHz): δ = 12.15 (s, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.93 (s, 2H), 4.63 (s, 1H), 1.78 (s, 3H). ¹³C NMR (DMSO-d₆, 100MHz): δ = 161.0, 151.7, 146.3, 145.5, 128.7, 123.8, 122.9, 103.1, 35.8, 32.8, 10.2. ESI-MS: m/z 287, 289 [M + H]⁺. Anal. Calcd. for C₁₄H₁₁ClN₄O: C, 58.65; H, 3.87; N, 19.54. Found: C, 58.73; H, 3.66; N, 19.67.

2. Compound 12b

Yellow solid. M.P.: 254-256 °C. IR (KBr): 3396, 3356, 3199, 2216 cm⁻¹. ¹H NMR (DMSO-d₆, 400 MHz): δ = 11.81 (s, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 6.55 (s, 2H), 4.35 (s, 1H), 1.33 (s, 3H). ¹³C NMR (DMSO-d₆, 100MHz): δ = 160.7, 143.1, 139.8, 129.7, 129.3, 127.4, 103.3, 55.9, 32.4, 10.6. ESI-MS: m/z 298 [M + H]⁺. Anal. Calcd. for C₁₄H₁₁N₃O₃: C, 56.56; H, 3.73; N, 23.56. Found: C, 56.31; H, 3.75; N, 23.50.
3. **Compound 12c**

Yellow solid. M.P.: 207-210 °C. IR (KBr): 3408, 3316, 3191, 2193 cm\(^{-1}\). \(^1\)H NMR (DMSO-\(d_6\), 400 MHz): \(\delta = 12.08\) (s, 1H), 7.11-7.01 (m, 4H), 6.84 (s, 2H), 4.52 (s, 1H), 2.25 (s, 3H), 1.76 (s, 3H). \(^{13}\)C NMR (DMSO-\(d_6\), 100MHz): \(\delta = 160.7, 154.7, 141.4, 135.6, 135.5, 128.9, 127.3, 120.7, 97.6, 57.2, 38.7, 20.5, 9.7\). ESI-MS: m/z 267 [M + H]\(^+\). Anal. Calcd. for C\(_{15}\)H\(_{14}\)N\(_4\)O: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.57; H, 5.45; N, 20.87.

4. **Compound 13a**

White solid. M.P.: 168-170 °C. IR (KBr): 3476, 3330, 2196 cm\(^{-1}\). \(^1\)H NMR (DMSO-\(d_6\), 400 MHz): \(\delta = 7.72\) (d, \(J = 8.0\) Hz, 4H), 7.45-7.38 (m, 5H), 7.26-7.17 (m, 3H), 4.92 (s, 1H), 2.49 (s, 3H). \(^{13}\)C NMR (DMSO-\(d_6\), 100MHz): \(\delta = 153.5, 146.2, 142.3, 128.8, 128.0, 127.1, 125.8, 125.4, 120.4, 82.2, 33.0, 11.6\). ESI-MS: m/z 329 [M + H]\(^+\). Anal. Calcd. for C\(_{20}\)H\(_{16}\)N\(_4\)O: C, 73.15; H, 4.91; N, 17.06. Found: C, 73.30; H, 5.05; N, 16.97.
5. Compound 13b

![Chemical Structure](image)

Yellow solid. M.P.: 175-178 °C. IR (KBr): 3475, 3326, 2196 cm⁻¹. ¹H NMR (CDCl₃+DMSO-d₆, 400 MHz): δ = 7.68 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 8.0 Hz, 2H), 7.29-7.25 (m, 1H), 7.11 (s, 4H), 5.48 (s, 2H), 4.58 (s, 1H), 2.30 (s, 3H), 1.86 (s, 3H). ¹³C NMR (CDCl₃+DMSO-d₆, 100MHz): δ = 158.8, 145.5, 143.6, 139.4, 137.3, 136.1, 128.78, 128.70, 127.2, 125.8, 120.2, 119.7, 98.1, 60.1, 36.5, 20.5, 12.4. ESI-MS: m/z 343 [M + H]⁺. Anal. Calcd. for C₂₁H₁₈N₄O: C, 73.67; H, 5.30; N, 16.36. Found: C, 73.38; H, 5.37; N, 16.49.

6. Compound 13c

![Chemical Structure](image)

White solid. M.P.: 171-173 °C. IR (KBr): 3420, 3310, 2196 cm⁻¹. ¹H NMR (CDCl₃+DMSO-d₆, 400 MHz): δ = 7.58 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 7.8 Hz, 2H), 7.27 (t, J = 7.4 Hz, 1H), 7.18-7.14 (m, 3H), 7.00 (t, J = 8.6 Hz, 2H), 4.64 (s, 2H), 4.60 (s, 1H), 1.81 (s, 3H). ¹³C NMR (CDCl₃+DMSO-d₆, 100MHz): δ = 167.6, 165.2, 164.4, 150.4, 148.9, 144.1, 142.6, 134.48, 134.40, 134.0, 131.0, 125.2, 120.0, 103.1, 63.8, 41.5, 17.7. ESI-MS: m/z 347 [M + H]⁺. Anal. Calcd. for C₂₀H₁₅FN₄O: C, 69.35; H, 4.37; N, 16.18. Found: C, 69.42; H, 4.40; N, 16.20.
7. Compound 13d

Yellow solid. M.P.: 188-190 °C. IR (KBr): 3462, 3376, 2230 cm⁻¹. ¹H NMR (CDCl₃+DMSO-d₆ 400 MHz): δ = 8.15 (d,  J = 8.8 Hz, 2H), 7.72 (d,  J = 8.0 Hz, 2H), 7.45-7.38 (m, 4H), 7.25 (t,  J = 7.4 Hz, 1H), 6.89 (s, 2H), 4.74 (s, 1H), 1.78 (s, 3H). ¹³C NMR (CDCl₃+DMSO-d₆, 100 MHz): δ = 159.4, 150.3, 146.5, 145.0, 143.8, 137.2, 128.8, 128.6, 125.9, 123.4, 120.1, 119.4, 96.9, 57.4, 36.8, 12.4. ESI-MS: m/z 374 [M + H]+. Anal. Calcd. for C₂₀H₁₅N₅O₃: C, 64.34; H, 4.05; N, 18.76. Found: C, 64.52; H, 4.12; N, 18.89.

8. Compound 13e

White solid. M.P.: 183-186 °C. IR (KBr): 3456, 3330, 2196 cm⁻¹. ¹H NMR (CDCl₃+DMSO-d₆, 400 MHz): δ = 7.65 (d,  J = 8.0 Hz, 2H), 7.41-7.37 (m, 4H), 7.25 (t,  J = 7.2 Hz, 1H), 7.09 (d,  J = 8.4 Hz, 2H), 5.96 (s, 2H), 4.55 (s, 1H), 1.81 (s, 3H). ¹³C NMR (CDCl₃+DMSO-d₆, 100 MHz): δ = 200.4, 167.7, 163.7, 155.0, 137.1, 133.4, 124.4, 123.6, 117.2, 114.8, 62.3, 55.1, 41.0, 36.9, 33.6, 32.2. ESI-MS: m/z 407, 409 [M + H]+. Anal. Calcd. for C₂₀H₁₅BrN₄O: C, 58.98; H, 3.71; N, 13.76. Found: C, 58.73; H, 3.60; N, 13.61.
9. **Compound 13f**

White solid. M.P.: 174-176 °C. IR (KBr): 3456, 3370, 2203 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 7.58$ (d, $J = 8.0$ Hz, 2H), 7.42 (t, $J = 7.4$ Hz, 3H), 7.27 (d, $J = 8.4$ Hz, 2H), 7.14(d, $J = 8.4$ Hz, 2H), 4.66 (s, 2H), 4.58 (s, 1H), 1.82 (s, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 158.2$, 146.2, 143.7, 140.5, 137.4, 133.4, 129.3, 129.2, 129.0, 126.9, 121.2, 118.9, 97.8, 63.2, 36.8, 12.9. ESI-MS: m/z 363, 365 [M + H]$^+$. Anal. Calcd. for C$_{20}$H$_{15}$ClN$_4$O: C, 66.21; H, 4.17; N, 15.44. Found: C, 66.36; H, 4.31; N, 15.35.

10. **Compound 13g**

Off-white solid. M.P.: 195-198 °C. IR (KBr): 3429, 3400, 2369 cm$^{-1}$. $^1$H NMR (CDCl$_3$+ DMSO-d$_6$, 400 MHz): $\delta = 7.79$ (d, $J = 8.0$ Hz, 2H), 7.71 (d, $J = 8.0$ Hz, 2H), 7.48-7.43 (m, 4H), 7.31 (t, $J = 7.4$ Hz, 1H), 6.93 (s, 2H), 4.74 (s, 1H), 1.84 (s, 3H). $^{13}$C NMR (CDCl$_3$+DMSO-d$_6$, 100 MHz): $\delta = 164.6$, 153.4, 150.3, 149.0, 142.4, 137.3, 134.0, 133.7, 131.1, 125.3, 124.6, 123.4, 115.5, 102.2, 62.8, 42.3, 17.7. ESI-MS: m/z 354 [M + H]$^+$. Anal. Calcd. for C$_{21}$H$_{15}$N$_5$O: C, 71.38; H, 4.28; N, 19.82. Found: C, 71.16; H, 4.52; N, 19.88.
11. Compound 13h

Yellow solid. M.P.: 187-190 °C. IR (KBr): 3456, 3363, 2190 cm⁻¹. ¹H NMR (CDCl₃+DMSO-d₆, 400 MHz): δ = 8.09-8.03 (m, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.42 (t, J = 7.8 Hz, 2H), 7.21 (t, J = 7.2 Hz, 1H), 6.08 (s, 2H), 4.73 (s, 1H), 1.80 (s, 3H). ¹³C NMR (CDCl₃+DMSO-d₆, 100 MHz): δ = 159.4, 147.9, 145.1, 137.2, 133.9, 129.4, 128.7, 125.9, 122.1, 121.9, 120.1, 119.4, 96.9, 57.7, 38.9, 36.7, 12.5. ESI-MS: m/z 374 [M + H]⁺. Anal. Calcd. for C₂₀H₁₅N₅O₃: C, 64.34; H, 4.05; N, 18.76. Found: C, 64.26; H, 4.16; N, 18.62.

12. Compound 13i

Off-white solid. M.P.: 192-194 °C. IR (KBr): 3389, 3214, 2192 cm⁻¹. ¹H NMR (DMSO-d₆, 400 MHz): δ = 7.85 (s, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.51-7.44 (m, 4H), 7.37-7.26 (m, 3H), 5.19 (s, 1H), 2.34 (s, 3H). ¹³C NMR (DMSO-d₆, 100 MHz): δ = 166.7, 145.8, 139.4, 131.7, 130.1, 129.3, 128.8, 127.9, 126.8, 125.5, 120.6, 108.0, 106.8, 79.5, 31.5, 11.8. ESI-MS: m/z 363, 365 [M + H]⁺. Anal. Calcd. for C₂₀H₁₅ClN₄O: C, 66.21; H, 4.17; N, 15.44. Found: C, 66.08; H, 4.08; N, 15.29.
3.6. Representative spectra:

3.6.1. FT-IR spectrum of compound 12b:
3.6.2. $^1$H NMR spectrum of compound 12b:
3.6.3. $^{13}$C NMR spectrum of compound 12b:
3.6.4. Mass spectrum of compound 12b:

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[M+H]^+ = 298.0921
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M.W.: 297
3.7. References:


