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## COPPER ACCELERATED ONE-POT SEQUENTIAL TANDEM SYNTHESIS OF TETRAHYDROPURINOISOQUINOLINE DERIVATIVES

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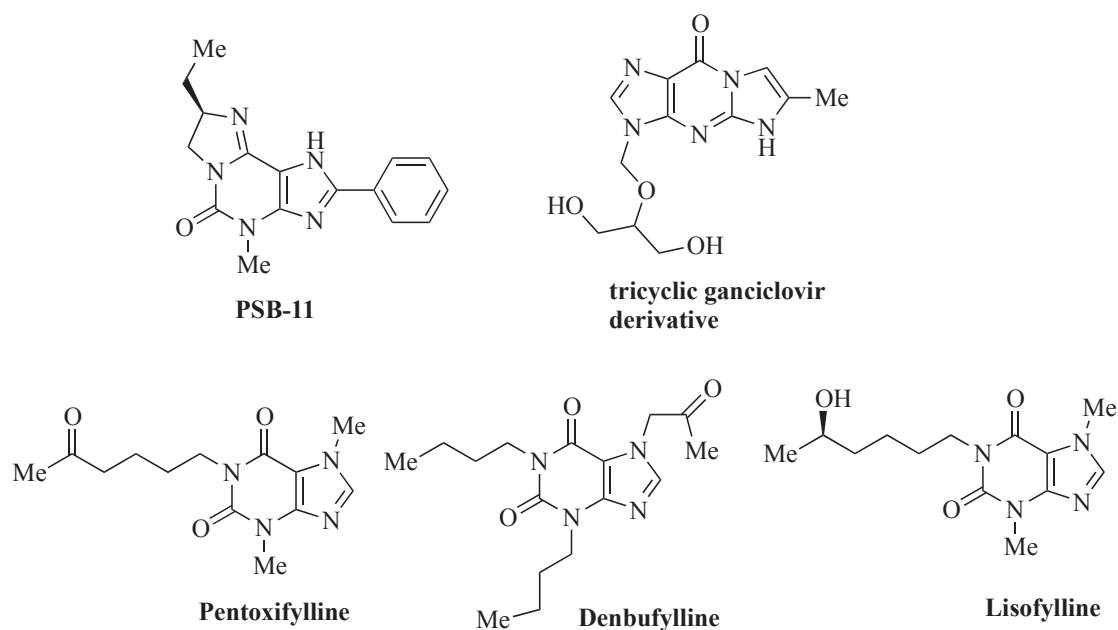
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**Abstract** – Copper catalyzed efficient and operationally simple tandem synthesis of purino[8,9-*a*]isoquinolinedione from 5,6-diamino-1,3-dimethyluracil and *in situ* generated alkenyl aldehyde has been described. In this cascade reaction C-C and C-N bonds are formed through Sonogashira coupling, 5-endo cyclization, and 6-endo cyclization in a same reaction vessel.

### INTRODUCTION

Recently, transition metal-catalyzed tandem processes<sup>1</sup> offered a promising method towards the efficient synthesis of heterocyclic compounds among which copper-catalyzed tandem cyclization<sup>2</sup> have gained considerable attention due to their capability to activate various  $\pi$ -systems at mild conditions even at low-catalyst loading. Heterocyclic compounds<sup>3</sup> due to their proven biological as well as pharmaceutical importance developed a significant impact among the synthetic community and form a largest division in organic chemistry. Therefore, organic chemists are making extensive efforts for strategic modification of known methods and development of new efficient synthetic routes for the synthesis of novel heterocycles. Nitrogen containing heterocycles particularly, the pyrimidine<sup>4</sup> and isoquinoline<sup>5</sup> ring systems belong to important class of heterocycles found in nature, as they represent the core structure of many biologically significant molecules. Purine and its derivatives are pharmacologically as well as biologically potent heterocycles which integrates imidazole and pyrimidine ring within its core structure such as imidazo[2,1-*i*]purinones (PSB-11) which act as a potent A<sub>3</sub> adenosine receptor antagonist<sup>6</sup> and imidazo[2,1-*a*]purines act as potent antiviral agents.<sup>7</sup>

Some other purine derivatives like denbufylline, lisofylline and pentoxifylline are pharmaceutically useful and used as phosphodiesterase inhibitors,<sup>8</sup> anti-inflammatory drugs<sup>9</sup> and medicine for peripheral vascular disease<sup>10</sup> respectively (**Figure 1**). So the molecular skeleton which incorporates isoquinoline as well as



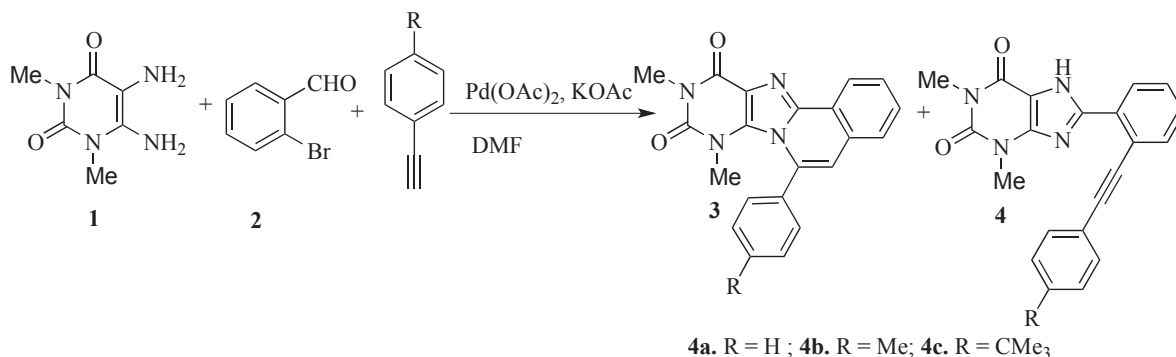
**Figure 1.** Pharmacologically active purine derivatives

purine moiety might possess properties of both and enhance the activity. Thus, the development of novel and efficient routes for rapid access to such functionalized isoquinolines under mild conditions is of high demand. There are various methods appeared in the literature for the synthesis of benzimidazoisoquinolines and its condensed analogs.<sup>11</sup> To the best of our knowledge, tandem synthesis of tetrahydropurino[8,9-*a*]isoquinoline-9,11-dione derivatives from *o*-alkynyl aldehydes catalyzed by copper(I) iodide has not been explored. We herein, report our results on the synthesis of tetrahydropurino[8,9-*a*]isoquinoline-9,11-dione derivatives *via* a CuI(I)-catalyzed sequential one-pot tandem cyclization in DMF using 5,6-diamino-1,3-dimethyluracil and *in situ* generated *o*-alkynyl aldehydes from *o*-bromobenzaldehyde and aryl or alkylalkynes (**Scheme 2**). This sequential approach affords a fused polycyclic heterocycles *via* the formation of three new carbon–nitrogen bonds simultaneously in one-pot.

## RESULTS AND DISCUSSION

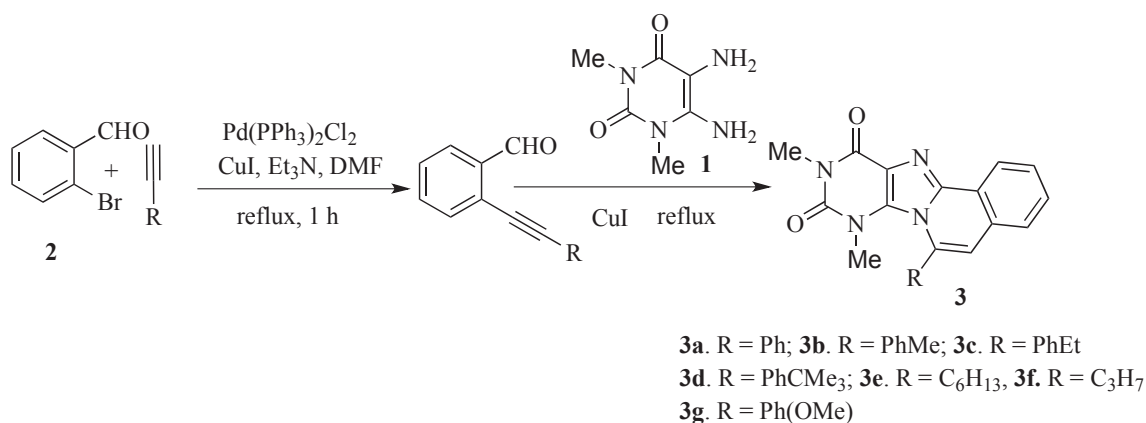
*o*-Bromobenzaldehyde, phenylacetylene and 5,6-diamino-1,3-dimethyluracil were chosen as model reactants for the present study through multicomponent approach. Initially the reaction mixture was allowed to reflux for 24 h in DMF with palladium acetate (1.5 mol%) as catalyst under nitrogen atmosphere, the desired product was obtained in 20% yields only. Then we changed the reaction condition, used potassium acetate (0.5 mmol) and tetrabutylammonium bromide (0.5 mmol) along with palladium acetate (2 mol%) and then reaction mixture was allowed to reflux in DMF for 20-24 h under nitrogen atmosphere which gave the desired product (**3a**) with little increased in yield (35%) along with the formation of product

(4a) (Scheme 1). The reaction was also attempted with CuI in place of KOAc and TBAB along with 2 mol% catalyst loading and allowed to reflux for 15 h but the results were remained same. Hence varying reaction conditions did not improve the result and yield of the desire product for this one-pot MCR



**Scheme 1**

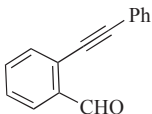
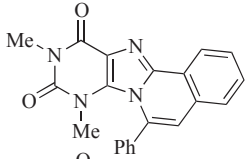
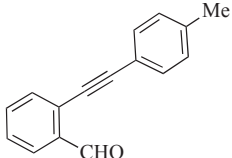
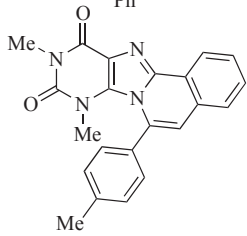
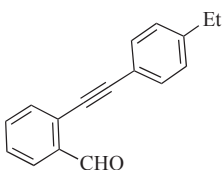
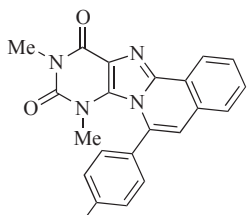
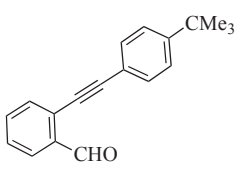
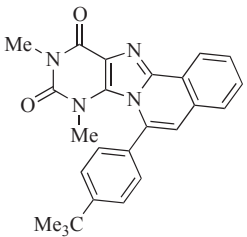
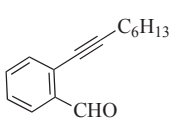
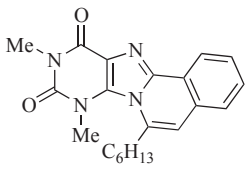
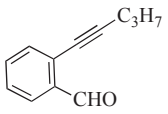
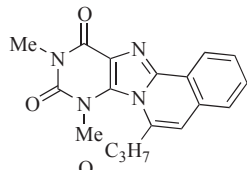
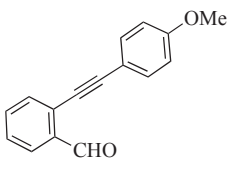
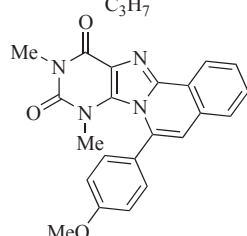
Then we turned the one-pot multicomponent reaction approach to sequential one-pot reaction. We first synthesized the alkenyl aldehyde by the Sonogashira coupling reaction using *o*-bromobenzaldehyde **2** and alkyl or arylalkyne. Then after completion of the coupling reaction, 5,6-diamino-1,3-dimethyluracil and additional (0.5 mol%) copper(I) iodide were added in the same reaction pot and allowed to reflux for 3 h which afforded the desire product in good yields. Initially, the reaction was carried out in absence of copper(I) iodide and formation of the desired product was obtained only in 45% yield. It also took long for completion. Interestingly, using additional (0.5 mol%) copper(I) showed the improvement of the result and it afforded the desire product in 65% yield in 6 h. Encouraged by this result, we shifted our



**Scheme 2**

attention towards optimization of the reaction conditions using other transition metal-catalysts like InCl<sub>3</sub> and AgNO<sub>3</sub> for the same model reaction in DMF as solvent under reflux conditions but results were same obtained earlier. However, increasing the loading of catalyst to 1.5 mol% increased the yield of the desire product **3a** in 90% in 4 h (Scheme 2).

Table 1

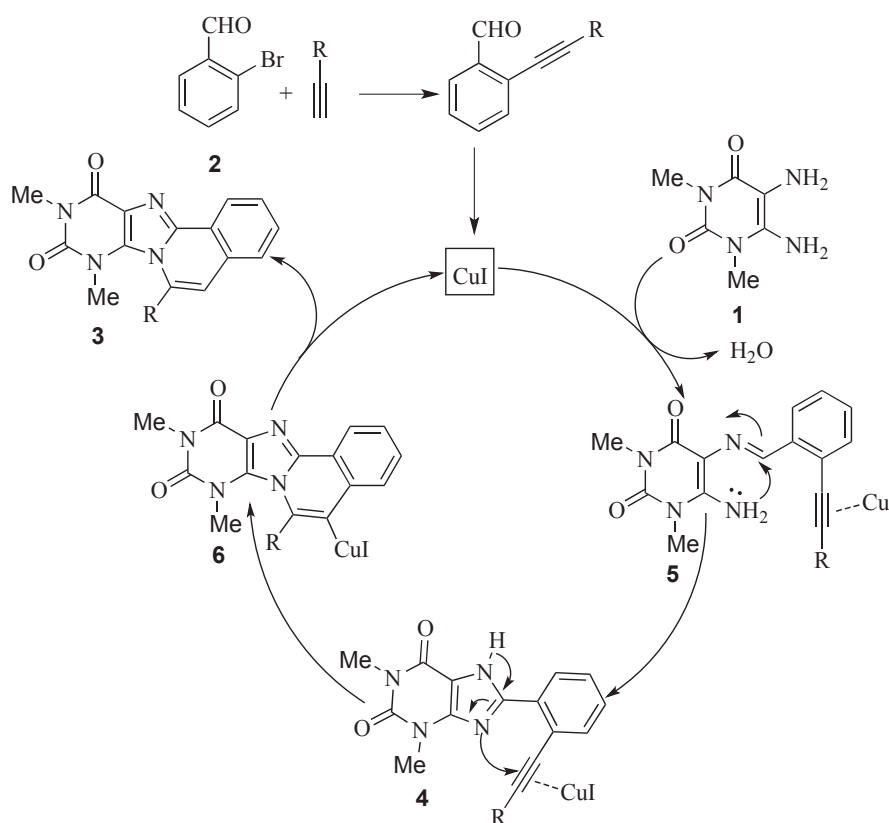
Entry	Alkenyl aldehyde	Product	Yield
1			85%
2			89%
3			86%
4			90%
5			95%
6			92%
7			94%

The reaction conditions were further optimized to obtain better result and it was found that loading of 2 mol% of copper iodide in DMF was optimum to get maximum yield (95%) in less time (3.5 h). Surprisingly, the addition of copper iodide not only reduced the reaction time but also increased yield of the product by activating the alkyne triple bond which facilitate the smooth cyclization and therefore the

formation of uncyclized product was reduced. Next, to find the best solvent for this transformation the same reaction was also screened in various solvents such as MeCN, CH<sub>2</sub>Cl<sub>2</sub>, DMF and THF in the presence of 2 mol% of copper iodide. Among all these solvents, DMF was found to be the best solvent for this transformation. To check the generality and versatility of this method, a study on the substrate scope was carried out under the optimized reaction conditions with *o*-bromobenzaldehyde, different terminal alkynes and 5,6-diamino-1,3-dimethyluracil (**Table 1**).

In all these cases, the reactions were clean and the products were obtained with simple work-up. The structures of all the synthesized compounds were confirmed by spectroscopic data and its elemental analysis.

The plausible mechanism for the formation of desire product is depicted in **Scheme 3**. In this sequential one-pot reaction, the reaction is completed in four steps. The first step is the Sonogashira coupling reaction of *o*-bromobenzaldehyde and terminal alkyne afforded *o*-alkynyl aromatic aldehydes. The second step of the reaction is the intermolecular imine formation between *o*-alkynyl aromatic aldehydes and 5,6-diamino-1,3-dimethyluracil. In the third step copper iodide facilitates in the 1st intramolecular nucleophilic attack of NH<sub>2</sub> group onto the imine carbon followed by aerial oxidation to form **4** which after subsequent 2nd intramolecular nucleophilic attack of N atom onto the activated alkyne to form intermediate **6**, which after subsequent protonation leads to the formation of cyclized product.



**Scheme 3.** Plausible mechanism

In summary, we have demonstrated a CuI(I)-catalyzed tandem and efficient one-pot sequential synthetic route which provides a facile access to fused tetrahydropurino[8,9-*a*]isoquinoline-9,11-dione derivatives in good to excellent yields with high regioselectivity and diversity. The wide applicability of the strategy to a variety of substrate renders this method to be of high practical utility, and can be used for rapid library generation of different heterocycles.

## EXPERIMENTAL

Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrum II spectrometer on KBr disks.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at 300 and 75 MHz respectively in  $\text{CDCl}_3$  (chemical shift in  $\delta$ ) with TMS as internal standard. Mass spectra were recorded on a TOF MASS ES+ instrument respectively. Silica gel [(60-120 mesh), spectrochem, India] was used for chromatographic separation. Silica gel G [E-Merck (India)] was used for TLC. Petroleum ether refers to the fraction boiling between 60 °C-80 °C.

## GENERAL PROCEDURE

A mixture of 2-bromobenzaldehyde (1mmol), CuI (2 mol%) and  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (2 mol%) in DMF (5 mL) was degassed for 5 min under  $\text{N}_2$  atmosphere. Then the corresponding alkyne (1.5 equiv) along with 2 mL of triethylamine was added to this mixture and allowed to stir at room temperature under  $\text{N}_2$  atmosphere for 2 h. After completion of the reaction indicated by TLC, 5,6-diamino-1,3-dimethyluracil hydrate (1 mmol) and additional (2 mol%) CuI was added to this mixture in the same reaction vessel. Then the mixture was allowed to reflux for 3-4 h at 120 °C in open air and progress of the reaction was monitored by TLC. After completion of the reaction, solvent was removed under reduced pressure. The organic layer extracted with EtOAc ( $3 \times 10$  mL) and washed with brine water, dried over  $\text{Na}_2\text{SO}_4$ . The organic extract was concentrated under reduced pressure. The crude product was purified by column chromatography with EtOAc: petroleum ether (3:7) as eluent to get the desired compound.

**3a.** Yield: 85%, mp 180 °C, IR (KBr): 1663, 1703  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ : 3.26 (s, 3H), 3.79 (s, 3H), 7.19 (s, 1H), 7.46-7.56 (m, 5H), 7.68-7.73 (m, 2H), 7.78-7.81 (m, 1H), 8.72 (t,  $J = 9\text{Hz}$ , 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 28.62, 30.13, 104.83, 116.24, 121.16, 124.78, 126.81, 127.44, 128.15, 128.24, 129.21, 130.57, 131.54, 136.58, 137.73, 147.92, 151.33, 151.82$ . MS  $m/z = 379$  ( $\text{M}^+ + \text{Na}$ ), Anal. Calcd for  $\text{C}_{21}\text{H}_{16}\text{N}_4\text{O}_2$ : C, 70.77; H, 4.53; N, 15.72. Found: C, 70.78; H, 4.51; N, 15.80.

**3b.** Yield: 89%, mp 258 °C, IR (KBr): 1665, 1701  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ : 2.47 (s, 3H), 3.27 (s, 3H), 3.78 (s, 3H), 7.15 (s, 1H), 7.27 (d,  $J = 8.1$  Hz, 2H), 7.46 (d,  $J = 8.1$  Hz, 2H), 7.66-7.73 (m, 2H), 7.77-7.94 (m, 1H), 8.71 (t,  $J = 9$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$ : 21.65, 28.64, 30.12, 116.18, 121.08, 124.77, 126.76, 127.15, 128.09, 128.89, 130.52, 131.66, 133.85, 137.92, 139.05, 148.02, 151.36, 151.88, 153.16. MS  $m/z = 393$  ( $\text{M}^+ + \text{Na}$ ), Anal. Calcd for  $\text{C}_{22}\text{H}_{18}\text{N}_4\text{O}_2$ : C, 71.34; H, 4.90; N, 15.13.

Found: C, 71.33; H, 4.82; N, 15.22.

**3c.** Yield: 86%, mp 276 °C, IR (KBr): 1667, 1702  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ : 1.34 (t,  $J = 7.5$  Hz, 3H), 2.75 (q,  $J = 7.5$  Hz, 2H), 3.26 (s, 3H), 3.78 (s, 3H), 7.16 (s, 1H), 7.29 (d,  $J = 7.8$  Hz, 2H), 7.45 (d,  $J = 7.8$  Hz, 2H), 7.66-7.73 (m, 2H), 7.76-7.79 (m, 1H), 8.72 (t,  $J = 9$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$ : 15.27, 28.80, 28.81, 30.11, 116.19, 121.10, 124.76, 126.76, 127.22, 127.63, 128.08, 130.51, 131.67, 137.96, 145.27, 148.02, 151.36, 151.90. MS  $m/z = 407$  ( $\text{M}^+ + \text{Na}$ ), Anal. Calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}_2$ : C, 71.86; H, 5.25; N, 14.57. Found: C, 71.89; H, 5.16; N, 14.65.

**3d.** Yield: 90%, mp 252 °C, IR (KBr): 1666, 1702  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ : 1.41 (s, 9H), 3.25 (s, 3H), 3.79 (s, 3H), 7.48 (s, 4H), 7.17 (s, 1H), 7.68-7.71 (m, 2H), 7.76-7.79 (m, 1H), 8.72 (t,  $J = 9$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$ : 28.46, 30.07, 31.30, 34.81, 104.88, 116.12, 121.08, 124.71, 125.0, 126.73, 126.96, 128.03, 130.45, 131.63, 133.68, 137.91, 147.94, 151.28, 151.90, 152.13, 152.97. MS  $m/z = 435$  ( $\text{M}^+ + \text{Na}$ ), Anal. Calcd for  $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O}_2$ : C, 72.80; H, 5.86; N, 13.58. Found: 72.77; H, 5.81; N, 13.61.

**3e.** Yield: 95%, mp 120 °C, IR (KBr): 1710, 1725  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ : 0.85 (t,  $J = 6.9$  Hz, 3H), 1.25 (m, 4H), 1.40-1.47 (m, 2H), 1.62-1.78 (m, 2H), 3.49 (s, 3H), 3.68 (t,  $J = 7.2$  Hz, 2H), 3.76 (s, 3H), 7.01 (s, 1H), 7.58-7.71 (m, 3H), 8.62 (d,  $J = 7.8$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 14.16$ , 22.65, 28.65, 29.01, 29.13, 30.23, 31.82, 34.78, 105.34, 113.0, 120.87, 124.96, 125.92, 130.50, 131.81, 140.44, 148.20, 151.46, 151.64, 154.15. MS  $m/z = 387$  ( $\text{M}^+ + \text{Na}$ ), Anal. Calcd for  $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_2$ : C, 69.21; H, 6.64; N, 15.37. Found: C, 69.17; H, 6.55; N, 15.45.

**3f.** Yield: 92%, mp 182 °C, IR (KBr): 1648, 1691  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ : 1.00 (t,  $J = 7.2$  Hz, 3H), 1.66 (q,  $J = 7.5$  Hz, 2H), 3.49 (s, 3H), 3.63 (t,  $J = 7.5$  Hz, 2H), 3.75 (s, 3H), 7.00 (s, 1H) 7.57-7.70 (m, 3H), 8.61 (d,  $J = 7.8$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$ : 14.06, 22.59, 25.23, 29.18, 30.11, 31.53, 115.51, 123.47, 124.27, 132.93, 133.85, 150.08, 150.89, 153.79, 155.87, 159.68, 165.20. MS  $m/z = 345$  ( $\text{M}^+ + \text{Na}$ ), Anal. Calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}_2$ : C, 67.07; H, 5.63; N, 17.38. Found: C, 67.01; H, 5.72; N, 17.42.

**3g.** Yield : 94%, mp 234 °C, IR (KBr): 1638, 1701  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ : 3.28 (s, 3H), 3.79 (s, 3H), 3.90 (s, 3H), 7.01 (d,  $J = 8.7$  Hz, 2H), 7.14 (s, 1H), 7.50 (d, 2H,  $J = 8.7$  Hz), 7.65-7.79 (m, 3H), 8.73 (d,  $J = 9.3$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$ : 22.62, 28.61, 30.09, 31.55, 55.24, 104.88, 113.50, 115.98, 121.01, 124.76, 126.67, 127.99, 128.68, 129.22, 130.50, 131.70, 137.73, 148.07, 151.38, 151.85, 153.13, 160.19. MS  $m/z = 387$  ( $\text{M}^+ + \text{H}$ ), Anal. Calcd for  $\text{C}_{22}\text{H}_{18}\text{N}_4\text{O}_3$ : C, 68.38; H, 4.70; N, 14.50. Found: C, 68.32; H, 4.78; N, 14.62.

**4a.** Yield: 47%, mp 278 °C, IR (KBr): 1708, 1649  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ : 3.59 (s, 3H), 3.80 (s, 3H), 7.23 (s, 1H), 7.42 (t,  $J = 7.5$  Hz, 1H), 7.51 (d,  $J = 8.4$  Hz, 1H), 7.26 (m, 3H), 7.80 (m, 2H), 7.92 (d,  $J = 8.4$  Hz, 1H), 9.92 (s, 1H), MS  $m/z = 356$  ( $\text{M}^+$ ), Anal. Calcd for  $\text{C}_{21}\text{H}_{16}\text{N}_4\text{O}_2$ : C, 70.77; H, 4.53; N, 15.72. Found: C, 70.65; H, 4.61; N, 15.63.

**4b.** Yield: 45%, mp 274 °C, IR (KBr): 1651, 1648  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 2.53 (s, 3H), 3.57 (s, 3H), 3.78 (s, 3H), 7.23 (m, 1H), 7.41 (m, 3H), 7.60 (d,  $J = 8.8$  Hz, 1H), 7.71 (d,  $J = 8$  Hz, 2H), 7.89 (d,  $J = 8.4$  Hz, 1H), 9.87 (s, 1H), MS  $m/z = 370$  ( $\text{M}^+$ ), Anal. Calcd for  $\text{C}_{22}\text{H}_{18}\text{N}_4\text{O}_2$ : C, 71.34; H, 4.90; N, 15.13. Found: C, 71.26; H, 4.85; N, 15.26.

**4c.** Yield: 60%, mp 280 °C, IR (KBr): 1699, 1641  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 1.14 (s, 9H), 3.58 (s, 3H), 3.80 (s, 3H), 7.27 (m, 1H), 7.42 (m, 1H), 7.61 (m, 3H), 7.77 (q, 2H), 7.91 (d,  $J = 8$  Hz, 1H), 9.91 (s, 1H), MS  $m/z = 412$  ( $\text{M}^+$ ), Anal. Calcd for  $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O}_2$ : C, 72.80; H, 5.86; N, 13.58. Found: C, 72.89; H, 5.81; N, 13.65.

## ACKNOWLEDGEMENTS

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