Tetrahedron Letters 52 (2011) 7099–7102

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An unexpected multi-component reaction to synthesis of 3-(5-amino-3-methyl-1*H*-pyrazol-4-yl)-3-arylpropanoic acids in ionic liquid

Zhiyong Xiao, Min Lei *, Lihong Hu *

Shanghai Research Center for Modernization of Traditional Chinese Medicine, Shanghai Institute of Materia Medica, Shanghai 201203, PR China

ARTICLE INFO

Article history:
Received 11 August 2011
Revised 18 October 2011
Accepted 18 October 2011
Available online 21 October 2011

Keywords:
Green chemistry
Multi-component reaction
[bmim]BF_4
Aldehyde
Meldrum's acid

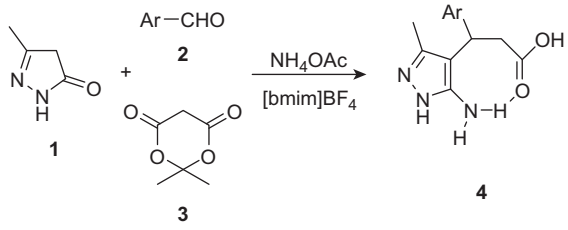
ABSTRACT

A new, one-pot, four-component condensation of 3-methyl-1*H*-pyrazol-5(4*H*)-one, ammonium acetate, aromatic aldehydes, and meldrum's acid in [bmim]BF_4 as solvent is described for the synthesis of 3-(5-amino-3-methyl-1*H*-pyrazol-4-yl)-3-arylpropanoic acid derivatives. This methodology resulting in excellent isolated yields in short reaction time is characterized by simple work up procedure and little environmental impact.

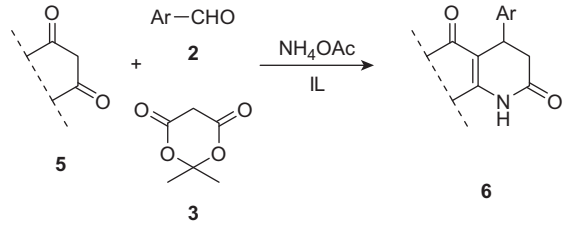
Multi-component reactions (MCRs) are attractive strategy for organic synthesis due to their atom efficiency, operational simplicity, and usually excellent productivity.[1] In particular, MCRs have been recognized as a powerful tool for the construction of the target products in a single operation without isolating the intermediates.[2] Thus, the reaction time is reduced and both energy and raw materials are saved. Therefore, development of novel, efficient, and green MCRs focused on a target product from readily available reagents is one of the major challenges in organic synthesis.

In recent years, organic reactions in ionic liquid (IL) media have received the considerable attention of synthetic organic chemists not only because IL is an environmentally friendly solvent, but also because IL exhibits unique reactivity different from those in conventional organic solvents.[3] As a part of our continual efforts toward the development of novel, efficient, and green procedures for multi-component reactions,[4] we turned our attention toward the four-component condensation of 3-methyl-1*H*-pyrazol-5(4*H*)-one, ammonium acetate, aldehyde, and meldrum's acid in [bmim]BF_4 as solvent. Herein, we describe a novel, efficient, and green procedure for the synthesis of 3-(5-amino-3-methyl-1*H*-pyrazol-4-yl)-3-arylpropanoic acid derivatives **4** via the four-component condensation (Scheme 1).

It was reported that 3,4-dihydropyridin-2(1*H*)-ones **6** could be obtained via a four-component condensation of β-dicarbonyl compounds **5**, aldehydes **2**, ammonium acetate, and meldrum's acid **3** in IL (Scheme 2).[5,6] β-Carbonyl enamine was regarded as the key intermediate of the four-component condensation. As shown in Scheme 3, Lipson and his co-workers[7] reported that the cyclization product **8** was obtained by a three-component



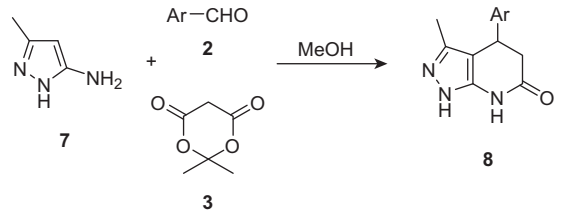
Scheme 1. Synthesis of 3-(5-amino-3-methyl-1*H*-pyrazol-4-yl)-3-arylpropanoic acid derivatives **4**.



Scheme 2. Synthesis of 3,4-dihydropyridin-2(1*H*)-ones **6**.

* Corresponding authors.
E-mail addresses: mlei@mail.shcnc.ac.cn (M. Lei), simmhulh@mail.shcnc.ac.cn (L. Hu).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.10.099



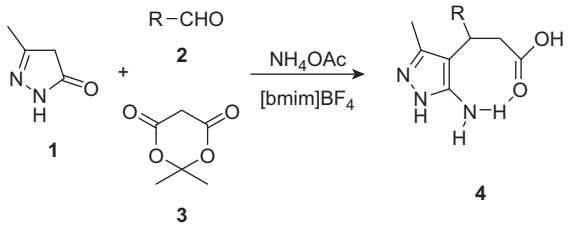
Scheme 3. Synthesis of 4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-ones **8**.

condensation of 3-methyl-1*H*-pyrazol-5-amine **7**, aromatic aldehyde **2**, and meldrum's acid **3** in MeOH as solvent (Scheme 3). Accordingly, we attempt to use 3-methyl-1*H*-pyrazol-5(4*H*)-one **1** replacing β-dicarbonyl compounds **5** in the synthesis of 4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-ones **8** via a four-component condensation of 3-methyl-1*H*-pyrazol-5(4*H*)-one **1**, aldehydes **2**, ammonium acetate, and meldrum's acid **3** in IL.

Initially, we carried out the four-component condensation of 3-methyl-1*H*-pyrazol-5(4*H*)-one **1**, ammonium acetate, benzaldehyde **2a**, and meldrum's acid **3** in [bmim]BF_4 as solvent at 100 °C. After the reaction was completed as indicated by TLC, the reaction mixture was cooled to room temperature, then water was added to the mixture and stirred for 5 min. The solid was filtered and recrystallized from EtOH/H_2O (3:1) to afford the pure product. To our surprise, this four-component condensation did not afford the cyclization product **8a**, while in contract, the products 3-(5-amino-3-methyl-1*H*-pyrazol-4-yl)-3-phenylpropanoic acid derivatives **4a**, shown in Scheme 1 and confirmed by NMR measurements, were obtained in good yield (92%).

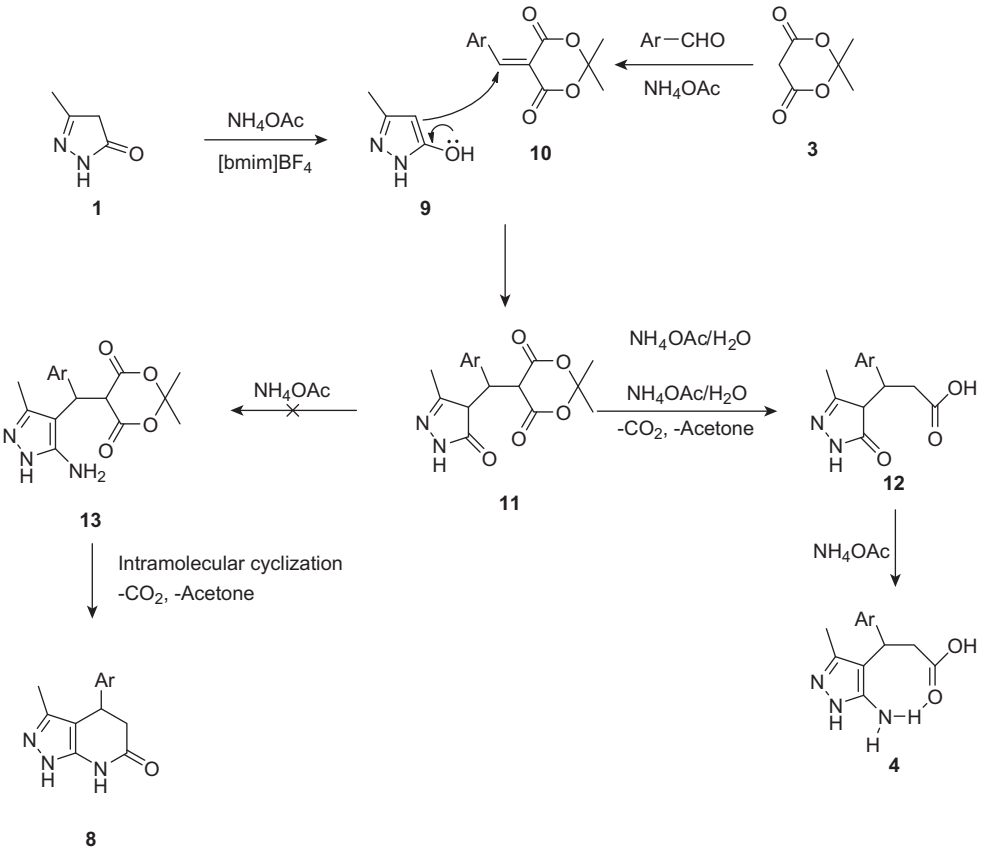
The scope and generality of this four-component condensation for the synthesis of 3-(5-amino-3-methyl-1*H*-pyrazol-4-yl)-3-aryl-

Table 1
Synthesis of 3-(5-amino-3-methyl-1*H*-pyrazol-4-yl)-3-arylpropanoic acid derivatives **4**[a]

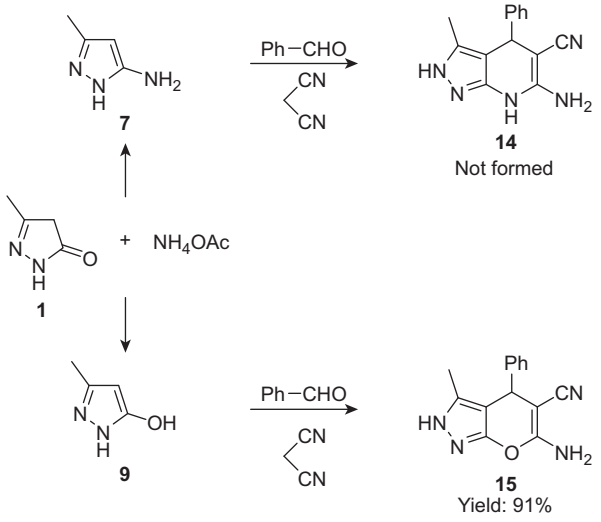


Entry	Ar	Time (min)	Product **4**	Yield (%)[b]
1	C_6H_5	20	**4a**	92, 90, 87[c]
2	4-$CH_3C_6H_4$	30	**4b**	90
3	4-$CH_3OC_6H_4$	15	**4c**	94
4	4-FC_6H_4	10	**4d**	94
5	4-BrC_6H_4	8	**4e**	94
6	2-ClC_6H_4	60	**4f**	82
7	3-ClC_6H_4	15	**4g**	92
8	4-ClC_6H_4	15	**4h**	87
9	2,4-$Cl_2C_6H_3$	120	**4i**	82
10	2-$NO_2C_6H_4$	150	**4j**	88
11	3-$NO_2C_6H_4$	6	**4k**	93
12	4-$NO_2C_6H_4$	10	**4l**	90
13	4-CNC_6H_4	10	**4m**	93
14	4-Pyridyl	8	**4n**	90
15	CH_3CH_2	150	**4o**	–[d]
16	$CH_3CH_2CH_2$	150	**4p**	–[d]
17	$C_6H_5CH_2$	150	**4q**	–[d]

[a] Reaction conditions: 3-methyl-1*H*-pyrazol-5(4*H*)-one **1** (5 mmol), ammonium acetate (10 mmol), aromatic aldehyde **2** (5 mmol) and meldrum's acid **3** (5 mmol), [bmim]BF_4 (2 mL), 100 °C.
[b] Isolated yields.
[c] [bmim]BF_4 was recovered and reused three times.
[d] Several side reactions were observed and the corresponding products failed to isolate.



Scheme 4. Plausible mechanism for the synthesis of 3-(5-amino-3-methyl-1*H*-pyrazol-4-yl)-3-arylpropanoic acid derivatives **4**.



Scheme 5. Multi-component condensation.

propanoic acid derivatives **4** were illustrated with different aromatic aldehydes and the results are summarized in Table 1.

The results of Table 1 clearly indicated the feasibility of this four-component condensation in ionic liquid. The products **4** were synthesized in excellent yields (82–94%) at 100 °C for 6–150 min. Both the electron-rich and -deficient aldehydes as well as heterocyclic aldehyde worked well leading to good yields of products **4**. We also examined this four-component condensation with 2-substituted benzaldehydes, finding that the reaction time was longer and yields were somewhat lower than other aldehydes which were probably attributed to the steric hindrance (Table 1). Aliphatic aldehydes like propionaldehyde, butylaldehyde, and phenylacetaldehyde were also examined but their yields were not satisfactory and the corresponding products failed to isolate, even after stirring at 100 °C for 150 min.

Furthermore, the recyclable character of [bmim]BF_4 was also investigated (Table 1, entry 1). We obtained the desired product **4a** in 92%, 90%, and 87% yields after 1–3 runs, respectively.

A tentative mechanism to rationalize the products **4** formation is shown in Scheme 4, which is different from the reported pathway. This reaction may occur via condensation, addition, ring-opening, and amination mechanisms (Scheme 4).[6–8] Initially, 3-methyl-1*H*-pyrazol-5-ol **9** is formed by the isomerization of 3-methyl-1*H*-pyrazol-5(4*H*)-one **1** and the intermediate **10** is formed by Knoevenagel condensation of aldehyde **2** and meldrum's acid **3** by the action of ammonium acetate. Then, Michael addition of **9** on **10** leads to the formation of **11**, followed by ring-opening promoted by ammonium acetate, affording the intermediate **12**. Next, **12** is aminated by ammonium acetate to form the corresponding products **4** (Scheme 4). All the reported papers pointed out that the key intermediate was formed by the amination of the carbonyl group.[6–8] However, we believe that the aminated intermediate is not formed in this system, and the directed evidence comes from the fact shown in Scheme 5.[9,10]

We carried out the reaction of 3-methyl-1*H*-pyrazol-5(4*H*)-one **1**, and ammonium acetate in [bmim]BF_4 as solvent at 100 °C for 2 h. Then, benzaldehyde **2a** and malononitrile were added to the reaction mixture and it was stirred at 100 °C for 10 min. As shown in Scheme 5, the corresponding product **15** was obtained in 91% yield, while in contract, the product **14** was not obtained at all. If the intermediate **7** was formed in this system, the product **14** should be found. But in fact, the product **14** was not found which meant that the aminated intermediate cannot be produced under these conditions. This may explain why we only obtain the product **4** of the four-component condensation of 3-methyl-1*H*-pyrazol-5(4*H*)-one **1**, ammonium acetate, aldehyde **2** and meldrum's acid **3** in [bmim]BF_4 as solvent.

In conclusion, we have described a four-component condensation reaction for the preparation of a variety of 3-(5-amino-3-methyl-1*H*-pyrazol-4-yl)-3-arylpropanoic acid derivatives **4** from 3-methyl-1*H*-pyrazol-5(4*H*)-one **1**, ammonium acetate, aldehyde **2,** and meldrum's acid **3** in [bmim]BF_4 as a recyclable medium and promoter. The process has several advantages from economical and environmental points of view, such as short reaction time, high yields, and mild reaction conditions, which make it a useful process for the synthesis of 3-(5-amino-3-methyl-1*H*-pyrazol-4-yl)-3-arylpropanoic acid derivatives **4**.[11]

Acknowledgments

This work was supported by the Chinese National Science and Technology Major Project 'Key New Drug Creation and Manufacturing Program' (Grants 2009ZX09301-001, 2009ZX09102-022), the National Natural Science Foundation of China (Grant 30925040).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.099.

References and notes

1. (a) Zhao, L.; Cheng, G.; Hu, Y. *Tetrahedron Lett.* **2008**, *49*, 7364; (b) Wender, P. A. *Chem. Rev.* **1996**, *96*, 1; (c) Yang, T.; Ferrali, A.; Campbellb, L.; Dixon, D. J. *Chem. Commum.* **2008**, 2923; (d) Tonogaki, K.; Itami, K.; Yoshida, J. *J. Org. Chem.* **2006**, *8*, 1419; (e) Bossharth, E.; Desbordes, P.; Monteiro, N.; Balme, G. *Org. Lett.* **2003**, *5*, 2441.
2. (a) Xiang, J.; Zheng, L.; Xie, H.; Hu, X.; Dang, Q.; Bai, X. *Tetrahedron* **2008**, *64*, 9101; (b) Ogura, Y.; Watanabe, H. *Tetrahedron Lett.* **2010**, *51*, 3294; (c) Litvinov, V. P. *Russ. Chem. Rev.* **2003**, *72*, 69.
3. (a) Naik, P. U.; Harjani, J. R.; Nara, S. J.; Salunkhe, M. M. *Tetrahedron Lett.* **2004**, *45*, 1933; (b) Wang, C.; Guo, L.; Li, H.; Wang, Y.; Weng, J.; Wu, L. *Green Chem.* **2006**, *8*, 603; (c) Hemeon, I.; Singer, R. D. *Chem. Commum.* **2002**, 1884; (d) Welton, T. *Chem. Rev.* **1999**, *99*, 2071.
4. (a) Lei, M.; Ma, L.; Hu, L. *Monatsh. Chem.* **2010**, *141*, 1005; (b) Yu, C.; Lei, M.; Su, W.; Xie, Y. *Synth. Commum.* **2007**, *37*, 3301; (c) Lei, M.; Ma, L.; Hu, L. *Tetrahedron Lett.* **2009**, *50*, 6393; (d) Lei, M.; Ma, L.; Hu, L. *Tetrahedron Lett.* **2010**, *51*, 4746.
5. Fan, X. S.; Li, Y. Z.; Zhang, X. Y.; Qu, G. R.; Wang, J. J.; Hu, X. Y. *Heteroat. Chem.* **2006**, *17*, 382.
6. Tu, S.; Zhu, X.; Zhang, J.; Xu, J.; Zhang, Y.; Wang, Q.; Jia, R.; Jiang, B.; Zhang, J.; Yao, C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2925.
7. Lipson, V. V.; Desenko, S. M.; Shirobokova, M. G.; Shishkin, O. V.; Shishkina, S. V. *Russ. J. Org. Chem.* **2006**, *42*, 1022.
8. Zhang, X. Y.; Li, Y. Z.; Fan, X. S.; Qu, G. R.; Hu, X. Y.; Wang, J. J. *Chin. Chem. Lett.* **2006**, *17*, 150.
9. Al-Matar, H. M.; Khalil, K. D.; Meier, H.; Kolshorn, H.; Elnagdi, M. H. *ARKIVOC* **2008**, 288.
10. Nagarajan, A. S.; Reddy, B. S. R. *Synlett* **2009**, 2002; Peng, Y.; Song, G.; Dou, R. *Green Chem.* **2006**, *8*, 573.
11. General procedure for the synthesis of compounds **4**: a mixture of 3-methyl-1*H*-pyrazol-5(4*H*)-one 1 (5 mmol), and ammonium acetate (10 mmol) in [bmim]BF4 (2 mL) was heated to 100 °C under stirring for 10 min. Then, aromatic aldehyde 2 (5.5 mmol) and meldrum's acid **3** (5 mmol) were added to the reaction mixture and it was stirred at 100 °C for the given time (Table 1). After completion (by TLC), the reaction mixture was cooled to room temperature, then water (5 mL) was added to the mixture and stirred for 5 min. The solid was filtered and recrystallized from EtOH/H_2O (3:1) to afford the pure products **4**. The filtrate was concentrated under reduced pressure and dried at 100 °C to recover the ionic liquid for subsequent use.
Compound **4a**: White solid; mp: 235–237 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.03 (s, 3H), 2.71 (dd, J = 14.7, 7.4 Hz, 1H), 2.86 (dd, J = 14.7, 8.2 Hz, 1H), 4.21 (t, J = 7.8 Hz, 1H), 6.67 (br s, 1H), 7.10 (t, J = 7.2 Hz, 1H), 7.22 (t, J = 7.6 Hz, 2H), 7.26 (br s, 1H), 7.30 (d, J = 7.5 Hz, 2H), 10.40 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.70, 36.42, 40.37, 103.93, 126.01, 127.84, 128.42, 136.85, 145.78, 159.92, 173.51; MS (ESI): m/z 268 ([M+Na]$^+$); Anal. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.61; H, 6.15; N, 17.17.
Compound **4b**: White solid; mp: 215–217 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.02 (s, 3H), 2.22 (s, 3H), 2.69 (dd, J = 14.7, 7.4 Hz, 1H), 2.83 (dd, J = 14.6, 8.2 Hz, 1H), 4.17 (t, J = 7.7 Hz, 1H), 6.68 (br s, 1H), 7.02 (d, J = 7.8 Hz, 2H), 7.18 (d,

J = 7.8 Hz, 2H), 7.25 (br s, 1H), 10.45 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.70, 21.01, 36.00, 40.47, 104.06, 127.71, 128.95, 134.80, 136.71, 142.76, 159.85, 173.54; MS (ESI): m/z 282 ([M+Na]$^+$); Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 64.81; H, 6.57; N, 16.23.

Compound **4c**: White solid; mp: 215–217 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.03 (s, 3H), 2.68 (dd, J = 14.6, 7.4 Hz, 1H), 2.82 (dd, J = 14.6, 8.3 Hz, 1H), 3.68 (s, 3H), 4.16 (t, J = 7.7 Hz, 1H), 6.68 (br s, 1H), 6.78 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 7.25 (br s, 1H), 10.47 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.68, 35.62, 40.69, 55.38, 104.23, 113.78, 128.75, 136.69, 137.83, 157.66, 159.84, 173.59; MS (ESI): m/z 298 ([M+Na]$^+$); Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.04; H, 6.20; N, 15.30.

Compound **4d**: White solid; mp: 242–244 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.04 (s, 3H), 2.69 (dd, J = 14.7, 7.2 Hz, 1H), 2.86 (dd, J = 14.7, 8.4 Hz, 1H), 4.21 (t, J = 7.8 Hz, 1H), 6.70 (br s, 1H), 7.04 (t, J = 8.9 Hz, 1H), 7.28 (br s, 1H), 7.32 (dd, J = 8.5, 5.7 Hz, 2H), 10.51 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.63, 35.76, 40.54, 103.77, 114.88 and 115.09 ($^2J_{CF}$ = 20.7 Hz), 129.51 and 129.58 ($^3J_{CF}$ = 7.8 Hz), 136.74, 141.91 and 141.94 ($^4J_{CF}$ = 2.9 Hz), 159.65 and 162.05 ($^1J_{CF}$ = 239.7 Hz), 159.80, 173.32; MS (ESI): m/z 286 ([M+Na]$^+$; Anal. Calcd for $C_{13}H_{14}FN_3O_2$: C, 59.31; H, 5.36; N, 15.96. Found: C, 59.26; H, 5.32; N, 15.99.

Compound **4e**: White solid; mp: 229–231 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.05 (s, 3H), 2.70 (dd, J = 14.8, 7.1 Hz, 1H), 2.88 (dd, J = 14.8, 8.5 Hz, 1H), 4.20 (t, J = 7.8 Hz, 1H), 6.74 (br s, 1H), 7.26 (d, J = 8.5 Hz, 2H), 7.32 (br s, 1H), 7.42 (d, J = 8.4 Hz, 2H), 10.59 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.64, 35.96, 40.18, 103.39, 119.06, 130.15, 131.25, 136.91, 145.15, 159.86, 173.28; MS (ESI): m/z 346, 348 ([M+Na]$^+$); Anal. Calcd for $C_{13}H_{14}BrN_3O_2$: C, 48.17; H, 4.35; N, 12.96. Found: C, 48.14; H, 4.38; N, 12.98.

Compound **4f**: White solid; mp: 226–228 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.06 (s, 3H), 2.74 (dd, J = 14.8, 7.2 Hz, 1H), 2.81 (dd, J = 14.9, 8.3 Hz, 1H), 4.61 (t, J = 7.7 Hz, 1H), 6.70 (br s, 1H), 7.16 (t, J = 7.8 Hz, 1H), 7.26 (t, J = 7.4 Hz, 1H), 7.28 (br s, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 6.9 Hz, 1H), 10.46 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.78, 32.97, 39.50, 102.06, 127.17, 127.78, 129.45, 129.94, 132.83, 137.17, 142.13, 160.13, 172.91; MS (ESI): m/z 302, 304 ([M+Na]$^+$); Anal. Calcd for $C_{13}H_{14}ClN_3O_2$: C, 55.82; H, 5.04; N, 15.02. Found: C, 55.78; H, 5.01; N, 15.06.

Compound **4g**: White solid; mp: 239–241 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.06 (s, 3H), 2.68 (dd, J = 14.8, 6.9 Hz, 1H), 2.91 (dd, J = 14.7, 8.6 Hz, 1H), 4.22 (t, J = 7.6 Hz, 1H), 6.74 (br s, 1H), 7.14–7.29 (m, 3H), 7.32 (br s, 1H), 7.35 (s, 1H), 10.55 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.60; 36.25, 40.13, 103.27, 126.05, 126.67, 127.64, 130.29, 133.06, 136.93, 148.32, 159.82, 173.16; MS (ESI): m/z 302, 304 ([M+Na]$^+$); Anal. Calcd for $C_{13}H_{14}ClN_3O_2$: C, 55.82; H, 5.04; N, 15.02. Found: C, 55.80; H, 5.00; N, 15.07.

Compound **4h**: White solid; mp: 234–236 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.05 (s, 3H), 2.69 (dd, J = 14.8, 7.1 Hz, 1H), 2.88 (dd, J = 14.8, 8.5 Hz, 1H), 4.21 (t, J = 7.8 Hz, 1H), 6.72 (br s, 1H), 7.26–7.33 (m, 5H), 10.54 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.63, 35.90, 40.24, 103.45, 128.32, 129.72, 130.58, 136.84, 144.75, 159.83, 173.25; MS (ESI): m/z 302, 304 ([M+Na]$^+$); Anal. Calcd for $C_{13}H_{14}ClN_3O_2$: C, 55.82; H, 5.04; N, 15.02. Found: C, 55.79; H, 5.07; N, 15.00.

Compound **4i**: White solid; mp: 230–232 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07 (s, 3H), 2.76 (d, J = 7.8 Hz, 2H), 4.56 (t, J = 7.7 Hz, 1H), 6.72 (br s, 1H), 7.32 (br s, 1H), 7.36 (dd, J = 8.5, 1.9 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 10.54 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.7, 32.65, 39.35, 101.60, 127.28, 128.77, 131.20, 131.31, 133.75, 137.17, 141.27, 160.04, 172.68; MS (ESI): m/z 336, 338 ([M+Na]$^+$); Anal. Calcd for $C_{13}H_3Cl_2N_3O_2$: C, 49.70; H, 4.17; N, 13.38. Found: C, 49.68; H, 4.20; N, 13.40.

Compound **4j**: White solid; mp: 244–246 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.02 (s, 3H), 2.77–2.88 (m, 2H), 4.74 (t, J = 7.7 Hz, 1H), 6.74 (br s, 1H), 7.31 (br s, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 7.9 Hz, 1H), 10.62 (br s,2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.37, 30.72, 39.48, 102.09, 123.84, 127.41, 130.39, 132.58, 137.40, 138.65, 149.91, 160.10, 172.66; MS (ESI): m/z 313 ([M+Na]$^+$); Anal. Calcd for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.76; H, 4.88; N, 19.34.

Compound **4k**: White solid; mp: 261–263 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.09 (s, 3H), 2.72 (dd, J = 14.9, 6.9 Hz, 1H), 2.98 (dd, J = 14.9, 8.8 Hz, 1H), 4.35 (t, J = 7.8 Hz, 1H), 6.76 (br s, 1H), 7.37 (br s, 1H), 7.54 (t, J = 7.9 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 8.01 (dd, J = 8.1, 1.8 Hz, 1H), 8.19 (s, 1H), 10.54 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.57, 36.26, 40.14, 102.79, 121.26, 122.39, 129.94, 134.98, 136.99, 148.05, 148.10, 159.81, 172.93; MS (ESI): m/z 313 ([M+Na]$^+$); Anal. Calcd for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.75; H, 4.89; N, 19.33.

Compound **4l**: Yellow solid; mp: 253–255 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.08 (s, 3H), 2.74 (dd, J = 14.4, 6.2 Hz, 1H), 2.98 (dd, J = 14.1, 8.7 Hz, 1H), 4.35 (t, J = 7.5 Hz, 1H), 6.78 (br s, 1H), 7.38 (br s, 1H), 7.56 (d, J = 7.8 Hz, 2H), 8.11 (d, J = 7.6 Hz, 2H), 10.59 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.58, 36.48, 39.68, 102.62, 123.72, 129.07, 137.10, 146.04, 153.79, 159.85, 172.96; MS (ESI): m/z 313 ([M+Na]$^+$); Anal. Calcd for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.82; H, 4.84; N, 19.33.

Compound **4m**: White solid; mp: 248–250 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.06 (s, 3H), 2.70 (dd, J = 14.9, 7.0 Hz, 1H), 2.94 (dd, J = 14.9, 8.6 Hz, 1H), 4.29 (t, J = 7.7 Hz, 1H), 6.75 (br s, 1H), 7.35 (br s, 1H), 7.49 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 8.1 Hz, 2H), 10.55 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.58, 36.64, 39.72, 102.80, 108.88, 119.53, 128.93, 132.46, 137.00, 151.56, 159.83, 173.00; MS (ESI): m/z 293 ([M+Na]$^+$); Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.18; H, 5.20; N, 20.74.

Compound **4n**: White solid; mp: 258–260 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07 (s, 3H), 2.70 (dd, J = 14.9, 7.1 Hz, 1H), 2.94 (dd, J = 14.9, 8.4 Hz, 1H), 4.22 (t, J = 7.7 Hz, 1H), 6.78 (br s, 1H), 7.29 (d, J = 5.7 Hz, 2H), 7.37 (br s, 1H), 8.41 (d, J = 5.7 Hz, 2H), 10.60 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.59, 35.76, 39.70, 102.49, 123.33, 137.09, 149.69, 154.22, 159.89, 173.04; MS (ESI): m/z 269 ([M+Na]$^+$); Anal. Calcd for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.50; H, 5.71; N, 22.79.