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ONE-STEP SYNTHESIS OF TETRAZOLO[1,5-*a*]PYRIMIDINES BY CYCLIZATION REACTION OF DIHYDROPYRIMIDINE-2-THIONES WITH SODIUM AZIDE

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Abstract – An novel, versatile and cost-effective approach for tetrazolo[1,5-*a*]pyrimidines and tetrazolo[1,5-*a*]quinazolines from cyclization reaction of dihydropyrimidinethiones with sodium azide in the presence of mercuric acetate is described. To compare this procedure with the conventional method, we carried out the cyclization reactions through direct functionalization of the pyrimidinethione core, which obtained from Biginelli 3,4-dihydropyrimidine-2-thiones or 4-aryl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thiones.

INTRODUCTION

3,4-Dihydropyrimidine-2-thiones,¹ as a core unit in most organic compounds, are chemical precursors of multifunctionalized pyrimidines in a broad range of medicinal agents. These complex heterocyclic scaffolds is assigned as one of the most fertile areas for both organic chemistry, medicinal chemistry and biochemistry, which display interesting pharmacological and biological properties such as calcium

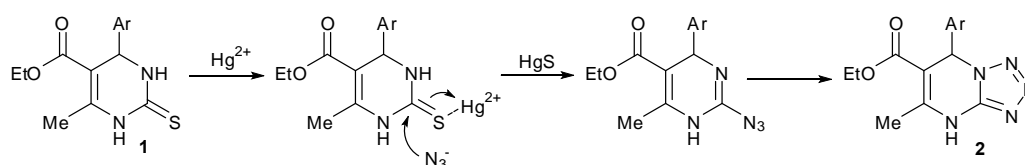
channel modulators, α_{1a} -adrenergic receptor antagonists, mitotic kinesin inhibitors and hepatitis B virus replication inhibitors.² Several marine alkaloids containing the pyrimidine core unit were found to show interesting biological activities such as antiviral, antibacterial and anti-inflammatory activity.³ Over the past decades, research interest in multifunctionalized pyrimidines, has surged rapidly, owing to the pharmacological properties associated with many derivatives of this privileged heterocyclic core.

Compounds containing the tetrazolo[1,5-*a*]pyrimidine scaffold have been reported to have more biological activities, there is considerable interest in the medicinal and biological applications of tetrazoles, such as antimicrobial activity,⁴ farnesyl transferase inhibitory,⁵ fungicidal activity,⁶ antihypertensive,⁷ KATP channel opening,⁸ central nervous system stimulating,⁹ *etc.*

However, after a detailed literature survey, we found that there were only limited publications devoted to the preparation of tetrazolopyrimidines. In general, these compounds were prepared by the multicomponent reaction between aminotetrazole, aldehyde and β -oxo carbonyl compounds or α , β -unsaturated carbonyl compounds using sulfamic acid,¹⁰⁻¹² iodine,¹³ treating with HCl subsequently with *p*-toluenesulfonic acid,¹⁴ or in the absence of catalysis at 130-170 °C,¹⁵ or using a base triethylamine in ethanol refluxing for 15 h.¹⁶ However, most of the synthetic protocols reported so far have some flaws, such as high temperatures, poor yields or prolonged reaction time.

Recently, structures change associated with mercury-promoted desulfurization reactions, including hydrolysis, cyclizations and eliminations, have been reported.¹⁷⁻²¹ Because of the strong thiophilic affinity of Hg^{2+} , mercuric acetate was used in the design of formation for HgS . We devised a strategy in which the azido group would be formed by desulfurization of 3,4-dihydropyrimidine-2-thiones using Hg^{2+} ion. The addition of the Hg^{2+} ion induced the N_3^- to attack the 2-C atom of pyrimidine, followed by the removal of HgS and the formation of intramolecular guanylation. Finally, a stable cyclic product tetrazolo[1,5-*a*]pyrimidine **2** was formed through an irreversible desulfurization reaction, as depicted in Scheme 1. To the best of our knowledge, elaboration of tetrazolo[1,5-*a*]pyrimidines through reactions of 3,4-dihydropyrimidine-2-thiones with sodium azide was unprecedented. In the context of our interest in the synthesis of functionalized DHPM derivatives, we became interested in combining tetrazole with the DHPM core. In this paper, we would like to describe a general and comprehensive strategy for the

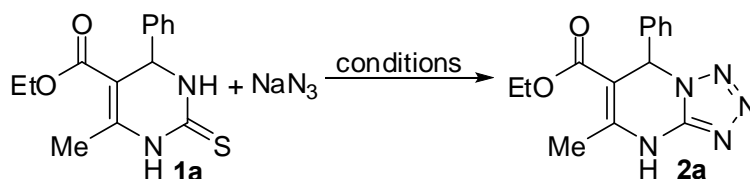
preparation of ethyl 5-methyl-7-aryl-4,7-dihydro-tetrazolo[1,5-*a*]pyrimidine-6-carboxylates and 6,6-dimethyl-9-aryl-5,6,7,9-tetrahydro-tetrazolo[1,5-*a*]quinazolin-8(4*H*)-ones through direct cyclization reactions from 3,4-dihydropyrimidine-2(1*H*)-thiones and 4-aryl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thiones with sodium azide.



Scheme 1. Hg²⁺-induced desulfurization and cyclization of DHPM

RESULTS AND DISCUSSIONS

Table 1. Optimization of reaction conditions for product 2a



Entry	<i>Equiv of 1a/NaN₃/reagent</i>	<i>of Solvent</i>	<i>Desulfurization reagent</i>	<i>Temp (°C)</i>	<i>Time (h)</i>	<i>Yield (%)^a</i>
1	1:2:1	HOAc	Hg(OAc) ₂	25	24	-
2	1:2:1	HOAc	Hg(OAc) ₂	80	6	70
3	1:2:1	HOAc	Hg(OAc) ₂	100	6	92
4	1:2:1	HOAc	Hg(OAc) ₂	110	6	92
5	1:2:0.5	HOAc	Hg(OAc) ₂	100	6	45
6	1:1:1	HOAc	Hg(OAc) ₂	100	6	56
7	1:2:1	DMF	Hg(OAc) ₂	100	6	75
8	1:2:1	EtOH	Hg(OAc) ₂	80	6	80
9	1:2:1	HOAc	HgCl ₂	100	6	80
10	1:2:1	DMF	HgCl ₂	25	12	66
11	1:2:1	DMF	HgCl ₂	100	6	85
12	1:2:1	HOAc	Zn(OAc) ₂	100	6	- ^b

13	1:2:1	HOAc	ZnCl ₂	100	6	-
14	1:2:1	HOAc	NiCl ₂	100	6	-
15	1:2:1	HOAc	CoCl ₂	100	6	-
16	1:2:1	HOAc	Cu(OAc) ₂	100	6	- ^c
17	1:2:1	HOAc	CuCl ₂	100	6	-
18	1:2:1	HOAc	FeCl ₃	100	6	-
19	1:2:1	HOAc	-	100	6	-

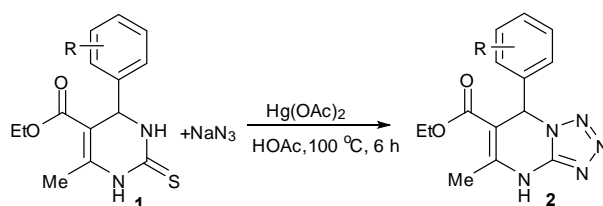
^a Isolated yields.

^b No product was isolated or detected by TLC.

^c The 3,4-dihydropyrimidine-2-thione (C=S) was transferred to 3,4-dihydropyrimidine-2-one (C=O).

Initially, we chose the reaction of 3,4-dihydropyrimidine-2(1*H*)-thione **1a** and sodium azide as a model reaction to optimize the reaction conditions. A series of experiments was performed to evaluate the feasibility of the formation of tetrazolo[1,5-*a*]pyrimidine and to identify the best cyclic agents. The results are shown in Table 1. By analogy with the mercury-promoted desulfurization reactions,¹⁷⁻²¹ the mixture of 1 equivalent of NaN₃ and Hg(OAc)₂ in acetic acid was heated at 100 °C to give the cyclization product **2a** in 56% yield (entry 6). It was found that Hg(OAc)₂ and a stoichiometric amount of NaN₃ are essential for the success of the reaction (entries 3-10) and 2 equivalent of NaN₃ obtained the best result (entry 3). Another source of mercuric catalyst HgCl₂ was used, but the reaction yield was slightly slower (entries 9-11). However, when using other catalysts Zn(OAc)₂, ZnCl₂, NiCl₂, CoCl₂, CuCl₂, FeCl₃, Cu(OAc)₂, compound **2a** was not detected by GC-Mass (or TLC), and starting DHPM **1a** was recovered. After experimentation with different catalysts, solvents and reaction temperatures, it was found that the optimal proportion of the reaction between 3,4-dihydropyrimidine-2(1*H*)-thione **1a**, sodium azide and mercuric acetate could be achieved 1: 2: 1 in acetic acid at 100 °C within 6 h.

Under the optimized conditions, the substrate scope of the reaction was examined (Table 2). A variety dihydrotetrazolo[1,5-*a*]pyrimidines (**2a-i**) were regioselectively prepared through this method. The electronics of the aromatic groups of DHPMs did not appear to influence the process, as substrates substituted with methoxy or nitro groups gave comparable product yields. However, 3,4-dihydropyrimidine-2-thione with an *o*-nitro group on the phenyl ring do not give the desired product. We speculated that one possible reason is the big steric of nitro group.

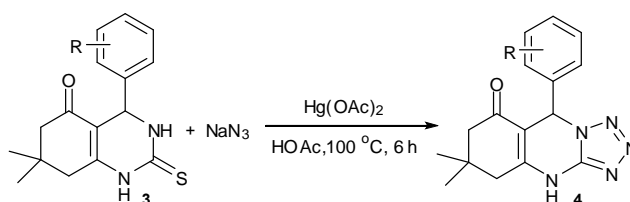
Table 2. Mercuric acetate catalyzed synthesis of dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylates^a

Entry	R	Product	Yield (%)
1	H	2a	92
2	2-Cl	2b	74
3	4-MeO	2c	86
4	2-Me	2d	85
5	4-Me	2e	87
6	4-Cl	2f	79
7	4-NO ₂	2g	73
8	4-Br	2h	80
9	3-NO ₂	2i	76

^a Reaction conditions: DHPM **1** (1 mmol), NaN₃ (2 mmol), Hg(OAc)₂ (1 mmol) in 5 mL acetic acid at 100 °C for 6 h.

Extension of the reaction to 4-aryl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolin-2-thiones **3** was successful, and compounds tetrahydrotetrazolo[1,5-*a*]quinazolines **4a-4h** were obtained in good yields (Table 3). To our delight, further research suggested that the mercuric acetate catalyzed one-pot synthesis of tetrazolo[1,5-*a*]pyrimidines proceeded smoothly.

All the compounds were characterized by ¹H NMR, ¹³C NMR, MS, and elemental analyses. The ¹H NMR spectrum of product **2** and **4** exhibited a singlet around δ 6.7 as the C₄-H, which confirmed the C2-N3 linked products tetrazolo[1,5-*a*]pyrimidines and tetrahydrotetrazolo[1,5-*a*]quinazolin-8(4*H*)-ones. According to previous study, when the methyl or *N*-allyl groups were in the *N1* position, two cross peaks between the hydrogen atoms of the *N*-methyl or *N*CH₂ groups of the allyl groups and C-2 and -6 were observed.²²

Table 3. Mercuric acetate catalyzed synthesis of tetrahydrotetrazolo[1,5-*a*]quinazolin-8(4*H*)-ones^a

<i>Entry</i>	<i>R</i>	<i>Product</i>	<i>Yield (%)</i>
1	H	4a	76
2	4-Cl	4b	68
3	4-MeO	4c	72
4	4-NO ₂	4d	67
5	3-NO ₂	4e	65
6	2-MeO	4f	70
7	4-Br	4g	69
8	4-Me	4h	71

^a Reaction conditions: **3** (1 mmol), sodium azide (2 mmol), mercuric acetate (1 mmol) in 5 mL acetic acid at $100\text{ }^\circ\text{C}$ for 6h.

The single crystal X-ray crystallography of product **2a** also confirmed the structures of obtained products (Figure 1). Crystallographic data for the structure analysis have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication (for **2a** CCDC No. CCDC 807622).

In conclusion, we have developed a novel and efficient synthetic method to prepare ethyl 5-methyl-7-aryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylates and 6,6-dimethyl-9-aryl-5,6,7,9-tetrahydrotetrazolo[1,5-*a*]quinazolin-8(4*H*)-ones by the cyclization reactions between 3,4-dihydropyrimidine-2-thiones or 4-aryl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolin-2-thiones, sodium azide and mercuric acetate. Compared to previously known approaches, the simplicity and higher efficiency make this method particularly attractive. These results provided, as well as other reported studies, this cyclization reaction conditions could be potentially applicable to other electron-deficient heterocyclic or aromatic systems. The present study also provides a readily accessible approach to construct multifunctionalized pyrimidine template for diversity-oriented synthesis.

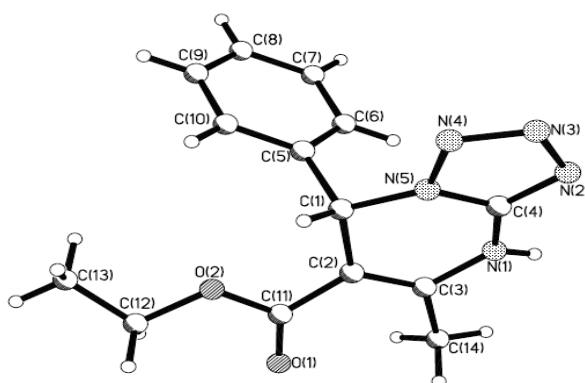


Figure 1. The crystal structure of **2a**

EXPERIMENTAL

Commercially available reagents were used without further purification. Solvents were treated prior to use according to the standard methods. Melting points were determined on an XT-4 electrothermal micromelting point apparatus and are uncorrected. NMR spectra were recorded at 400 (^1H) and 100 (^{13}C) MHz, respectively, on a Varian Mercury plus-400 instrument using CDCl_3 and $\text{DMSO}-d_6$ as solvent and TMS as an internal standard. Mass spectra were obtained on a Bruker Daltonics APEXII 47e FT-ICR spectrometer. The Biginelli 3,4-dihydropyrimidine-2-thiones **1** and 4-aryl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thiones **3** were readily prepared according to the procedures reported.^{23,24}

General procedure. The mixture of 3,4-dihydropyrimidine-2(1*H*)-thione (1 mmol), sodium azide (2 mmol) and mercuric acetate (1 mmol) in HOAc (5 mL) was stirred at 100 °C for 6 h. After completion of the reaction (monitored by thin layer chromatography), the black sediment (HgS) was filtrated. Then water was added to the filtrate to give the crude product. It was recrystallization from EtOH to give the pure products **2** and **4**.

2a: Yield 92%, mp 213-215 °C. ^1H NMR (400 MHz, CDCl_3): δ = 1.13 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.70 (s, 3H, 5- CH_3), 4.05-4.14 (m, 2H, OCH_2CH_3), 6.73 (s, 1H, CH), 7.26-7.37 (m, 5H, ArH), 10.90 (s, 1H, NH). ^{13}C NMR (100 MHz, CDCl_3): δ = 14.01, 19.54, 59.59, 60.51, 99.35, 127.30, 128.86, 128.97, 139.68, 145.92, 148.68, 164.85. Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{N}_5\text{O}_2$: C, 58.94; H, 5.30; N, 24.55. Found: C, 58.85; H, 5.23; N, 24.45. ESI-MS: m/z = 285 ($[\text{M} + \text{H}^+]$).

2b: Yield 74%, mp 221-223 °C. ^1H NMR (400 MHz, CDCl_3): δ = 1.11 (t, J = 7.2 Hz, 3H, OCH_2CH_3),

2.70 (s, 3H, 5-CH₃), 4.03-4.09 (m, 2H, OCH₂CH₃), 7.19 (s, 1H, CH), 7.23-7.42 (m, 4H, ArH), 10.98 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃): δ = 13.90, 19.49, 56.78, 60.51, 98.35, 127.41, 129.67, 130.18, 130.20, 133.41, 137.15, 146.65, 148.56, 164.60. Anal. Calcd for C₁₄H₁₄ClN₅O₂: C, 52.59; H, 4.41; N, 21.90. Found: C, 52.68; H, 4.49; N, 21.98. ESI-MS: m/z = 319 ([M + H⁺]).

2c: Yield 86%, mp 208-209 °C. ¹H NMR (400 MHz, CDCl₃): δ = 1.15 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 2.68 (s, 3H, 5-CH₃), 3.78 (s, 3H, OCH₃), 4.06-4.14 (m, 2H, OCH₂CH₃), 6.70 (s, 1H, 7-CH), 6.85 (d, J = 8 Hz, 2H, ArH), 7.29 (d, J = 8.8 Hz, 2H, ArH), 11.09 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃): δ = 14.05, 19.48, 55.27, 59.08, 60.46, 99.46, 114.13, 128.57, 132.05, 145.68, 148.63, 159.90, 164.95. Anal. Calcd for C₁₅H₁₇N₅O₃: C, 57.13; H, 5.43; N, 22.21. Found: C, 57.05; H, 5.49; N, 22.30. ESI-MS: m/z = 315 ([M + H⁺]).

2d: Yield 85%, mp 250-252 °C. ¹H NMR (400 MHz, CDCl₃): δ = 1.08 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 2.71 (s, 6H, 2CH₃), 4.01-4.08 (m, 2H, OCH₂CH₃), 6.98 (s, 1H, 7-CH), 7.12-7.26 (m, 4H, ArH), 11.25 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃): δ = 13.90, 19.31, 19.40, 55.65, 60.39, 99.33, 126.75, 127.09, 128.80, 130.74, 136.09, 138.37, 146.16, 148.46, 164.85. Anal. Calcd for C₁₅H₁₇N₅O₂: C, 60.19; H, 5.72; N, 23.40. Found: C, 60.07; H, 5.78; N, 23.49. ESI-MS: m/z = 299 ([M + H⁺]).

2e: Yield 87%, mp 209-211 °C. ¹H NMR (400 MHz, CDCl₃): δ = 1.15 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 2.31 (s, 3H, CH₃), 2.67 (s, 3H, CH₃), 4.06-4.13 (m, 2H, OCH₂CH₃), 6.70 (s, 1H, 7-CH), 7.13 (d, J = 8 Hz, 2H, ArH), 7.24 (d, J = 7.6 Hz, 2H, ArH), 11.07 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃): δ = 14.03, 19.46, 21.14, 59.33, 60.45, 99.41, 127.17, 129.39, 136.88, 138.82, 145.79, 148.71, 164.94. Anal. Calcd for C₁₅H₁₇N₅O₂: C, 60.19; H, 5.72; N, 23.40. Found: C, 60.07; H, 5.63; N, 23.52. ESI-MS: m/z = 299 ([M + H⁺]).

2f: Yield 79%, mp 244-246 °C. ¹H NMR (400 MHz, CDCl₃): δ = 1.15 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 2.69 (s, 3H, 5-CH₃), 4.08-4.13 (m, 2H, OCH₂CH₃), 6.71 (s, 1H, CH), 7.27 (d, J = 8.8 Hz, 2H, ArH), 7.29 (d, J = 8.8 Hz, 2H, ArH), 11.22 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃): δ = 14.04, 19.53, 58.94, 60.62, 98.87, 128.71, 129.09, 134.94, 138.17, 146.27, 148.61, 164.67. Anal. Calcd for C₁₄H₁₄ClN₅O₂: C, 52.59; H, 4.41; N, 21.90. Found: C, 52.65; H, 4.49; N, 21.98. ESI-MS: m/z = 319 ([M + H⁺]).

2g: Yield 73%, mp 225-227 °C. ¹H NMR (400 MHz, CDCl₃): δ = 1.16 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 2.73 (s, 3H, 5-CH₃), 4.09-4.15 (m, 2H, OCH₂CH₃), 6.84 (s, 1H, 7-CH), 7.57 (d, J = 9.2 Hz, 2H, ArH), 8.22 (d, J = 8.4 Hz, 2H, ArH), 11.35 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃): δ = 14.05, 19.70, 58.82, 60.88, 98.27, 124.17, 128.44, 146.04, 146.91, 148.10, 148.58, 164.39. Anal. Calcd for C₁₄H₁₄N₆O₄: C, 50.91; H, 4.27; N, 25.44. Found: C, 50.98; H, 4.18; N, 25.53. ESI-MS: m/z = 330 ([M + H⁺]).

2h: Yield 80%, mp 242-244 °C. ^1H NMR (400 MHz, CDCl_3): δ = 1.16 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.67 (s, 3H, 5- CH_3), 4.06-4.13 (m, 2H, OCH_2CH_3), 6.69 (s, 1H, CH), 7.25 (d, J = 8.8 Hz, 2H, ArH), 7.47 (d, J = 8.8 Hz, 2H, ArH), 10.98 (s, 1H, NH). ^{13}C NMR (100 MHz, CDCl_3): δ = 14.07, 19.56, 59.01, 60.65, 98.83, 123.15, 129.01, 132.07, 138.69, 146.24, 148.60, 164.67. Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{BrN}_5\text{O}_2$: C, 46.17; H, 3.87; N, 19.23. Found: C, 46.05; H, 3.80; N, 19.31. ESI-MS: m/z = 363 ($[\text{M} + \text{H}^+]$).

2i: Yield 76%, mp 219-221 °C. ^1H NMR (400 MHz, CDCl_3): δ = 1.17 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.74 (s, 3H, 5- CH_3), 4.09-4.15 (m, 2H, OCH_2CH_3), 6.85 (s, 1H, 7-CH), 7.57 (t, J = 8.8 Hz, 1H, ArH), 7.74 (d, J = 8 Hz, 1H, ArH), 8.20-8.22 (m, 2H, ArH), 11.28 (s, 1H, NH). ^{13}C NMR (100 MHz, CDCl_3): δ = 14.05, 19.78, 58.96, 60.88, 98.35, 122.38, 124.03, 130.03, 133.53, 141.73, 146.92, 148.48, 148.58, 164.39. Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_6\text{O}_4$: C, 50.91; H, 4.27; N, 25.44. Found: C, 50.99; H, 4.19; N, 25.51. ESI-MS: m/z = 330 ($[\text{M} + \text{H}^+]$).

4a: Yield 76%, mp 326-327 °C. ^1H NMR (400 MHz, d_6 -DMSO/TMS): δ = 1.00 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.12-2.26 (m, 2H, CH_2), 2.60 (s, 2H, CH_2), 6.60 (s, 1H, 9-CH), 7.26-7.35 (m, 5H, ArH), 11.63 (s, 1H, NH). ^{13}C NMR (100 MHz, d_6 -DMSO/TMS): δ = 26.99, 28.27, 32.32, 49.80, 57.44, 57.46, 105.65, 127.16, 128.34, 128.60, 140.46, 148.45, 150.50, 193.03. Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{N}_5\text{O}$: C, 65.07; H, 5.80; N, 23.71. Found: C, 65.15; H, 5.73; N, 23.82. ESI-MS: m/z = 295 ($[\text{M} + \text{H}^+]$).

4b: Yield 68%, mp 272-274 °C. ^1H NMR (400 MHz, d_6 -DMSO/TMS): δ = 1.00 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.12-2.25 (m, 2H, CH_2), 2.60 (s, 2H, CH_2), 6.63 (s, 1H, 9-CH), 7.33 (d, J = 8.4 Hz, 2H, ArH), 7.40 (d, J = 8.8 Hz, 2H, ArH), 11.67 (s, 1H, NH). ^{13}C NMR (100 MHz, d_6 -DMSO/TMS): δ = 27.09, 28.15, 32.34, 49.77, 56.85, 105.28, 128.60, 129.19, 132.95, 139.41, 148.38, 150.68, 193.07. Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{ClN}_5\text{O}$: C, 58.27; H, 4.89; N, 21.24. Found: C, 58.18; H, 4.94; N, 21.31. ESI-MS: m/z = 329 ($[\text{M} + \text{H}^+]$).

4c: Yield 72%, mp 270-272 °C. ^1H NMR (400 MHz, CDCl_3): δ = 1.12 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 2.26-2.35 (m, 2H, CH_2), 2.65-2.75 (m, 2H, CH_2), 3.77 (s, 3H, OCH_3), 6.70 (s, 1H, 9-CH), 6.84 (d, J = 8.8 Hz, 2H, ArH), 7.26 (d, J = 8.8 Hz, 2H, ArH), 11.36 (s, 1H, NH). ^{13}C NMR (100 MHz, CDCl_3): δ = 27.56, 28.87, 32.88, 40.82, 50.50, 53.37, 57.77, 107.62, 114.09, 128.40, 131.57, 135.38, 148.79, 153.40, 193.74. Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{N}_5\text{O}_2$: C, 62.75; H, 5.89; N, 21.52. Found: C, 62.66; H, 5.83; N, 21.43. ESI-MS: m/z = 325 ($[\text{M} + \text{H}^+]$).

4d: Yield 67%, mp 248-249 °C. ^1H NMR (400 MHz, d_6 -DMSO/TMS): δ = 0.99 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.12-2.26 (m, 2H, CH_2), 2.61 (s, 2H, CH_2), 6.78 (s, 1H, 9-CH), 7.62 (d, J = 8.8 Hz, 2H, ArH), 8.19 (d, J = 8.8 Hz, 2H, ArH), 11.78 (s, 1H, NH). ^{13}C NMR (100 MHz, d_6 -DMSO/TMS): δ = 17.12, 18.05,

18.60, 22.33, 39.69, 46.90, 94.89, 113.69, 117.57, 118.80, 137.03, 138.41, 141.09, 183.04. Anal. Calcd for $C_{16}H_{16}N_6O_3$: C, 56.47; H, 4.74; N, 24.69. Found: C, 56.52; H, 4.79; N, 24.77. ESI-MS: $m/z = 340$ ($[M + H^+]$).

4e: Yield 65%, mp 281-283 °C. 1H NMR (400 MHz, $CDCl_3$): $\delta = 1.15$ (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 2.29-2.39 (m, 2H, CH_2), 2.73-2.84 (m, 2H, CH_2), 6.84 (s, 1H, 9-CH), 7.58 (t, $J = 8$ Hz, 1H, ArH), 7.84 (d, $J = 8$ Hz, 1H, ArH), 8.09-8.21 (m, 2H, ArH), 11.49 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 27.62$, 28.77, 33.04, 40.92, 50.35, 57.69, 106.46, 121.93, 124.04, 130.03, 133.95, 140.92, 148.57, 148.62, 149.83, 193.71. Anal. Calcd for $C_{16}H_{16}N_6O_3$: C, 56.47; H, 4.74; N, 24.69. Found: C, 56.56; H, 4.82; N, 24.75. ESI-MS: $m/z = 340$ ($[M + H^+]$).

4f: Yield 70%, mp 296-298 °C. 1H NMR (400 MHz, $CDCl_3$): $\delta = 1.06$ (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.21-2.32 (m, 2H, CH_2), 2.63-2.72 (m, 2H, CH_2), 3.67 (s, 3H, OCH_3), 6.84 (s, 1H, 9-CH), 6.95-7.54 (m, 4H, ArH), 11.23 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.84$, 29.09, 32.81, 40.91, 50.50, 55.36, 56.29, 106.40, 111.20, 120.68, 126.35, 130.38, 130.68, 149.45, 149.59, 157.22, 193.71. Anal. Calcd for $C_{17}H_{19}N_5O_2$: C, 62.75; H, 5.89; N, 21.52. Found: C, 62.68; H, 5.82; N, 21.63. ESI-MS: $m/z = 325$ ($[M + H^+]$).

4g: Yield 69%, mp 326-328 °C. 1H NMR (400 MHz, d_6 -DMSO/TMS): $\delta = 0.87$ (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.00-2.21 (m, 2H, CH_2), 2.24-2.43 (m, 2H, CH_2), 7.18 (d, $J = 8.4$ Hz, 2H, ArH), 7.52 (d, $J = 8.4$ Hz, 2H, ArH), 7.81 (s, 1H, 9-CH), 9.53 (s, 1H, NH). ^{13}C NMR (100 MHz, d_6 -DMSO/TMS): $\delta = 26.83$, 28.66, 32.26, 49.74, 51.53, 106.94, 128.47, 129.46, 131.19, 143.98, 151.69, 152.54, 192.85. Anal. Calcd for $C_{16}H_{16}BrN_5O$: C, 51.35; H, 4.31; N, 18.71. Found: C, 51.28; H, 4.39; N, 18.63. ESI-MS: $m/z = 373$ ($[M + H^+]$).

4h: Yield 71%, mp 304-305 °C. 1H NMR (400 MHz, $CDCl_3$): $\delta = 1.12$ (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.31 (s, 2H, CH_2), 2.67-2.78 (m, 2H, CH_2), 6.71 (s, 1H, 9-CH), 7.13 (d, $J = 8$ Hz, 2H, ArH), 7.23 (d, $J = 8$ Hz, 2H, ArH), 11.47 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.15$, 27.54, 28.84, 32.90, 40.80, 50.49, 58.03, 107.60, 127.02, 129.58, 136.34, 138.84, 148.80, 149.05, 193.75. Anal. Calcd for $C_{17}H_{19}N_5O$: C, 66.00; H, 6.19; N, 22.64. Found: C, 66.12; H, 6.26; N, 22.71. ESI-MS: $m/z = 309$ ($[M + H^+]$).

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