

# Synthesis of Some Fused Triazole Derivatives Containing 4-Isobutylphenylethyl and 4-Methylthiophenyl Moieties

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A series of substituted [1,3]thiazolo[3,2-*b*][1,2,4]triazole derivatives **4** were synthesized in good yield by condensing 2-substituted-1,2,4-triazole-5-thiols **3** with various *N*-aryl-maleimides in acetic acid media. All structures of the newly synthesized compounds were elucidated by elemental analyses and spectral data.

**Key words:** 1,2,4-Triazole-5-thiol, *N*-Aryl-maleimides, [1,3]Thiazolo[3,2-*b*][1,2,4]triazoles

## Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) such as Ibuprofen are widely used for the treatment of pain, fever and inflammation [1–3]. Prostaglandins are important biological mediators of inflammation, originating from biotransformation of arachidonic acid catalyzed by cyclooxygenase [4]. In the early 1990s, it was discovered that the enzyme exists as two isoforms, one constitutive (COX-1) and the other inducible (COX-2) [5]. COX-1 is constitutively expressed and provides cytoprotection in the gastrointestinal (GI) tract, while COX-2 is inducible and mediates inflammation [4, 6]. Prolonged use of NSAIDs like Ibuprofen has been associated with gastrointestinal complications ranging from stomach irritation to life-threatening gastrointestinal ulceration and bleeding [7, 8]. Therefore the development of new NSAIDs without these side effects has long been awaited. Selective COX-2 inhibitors with better safety profile have been marketed as a new generation of NSAIDs [9]. Thus, there remains a compelling need for effective NSAIDs with an improved safety profile.

It has also been reported that the presence of the 4-methylthiophenyl moiety [10] is found to increase the biological activity of the molecules. A few heterocyclic analogs containing *N*-bridged heterocycles bearing the 4-methylthiophenyl moiety possess good anti-inflammatory [10, 11] and antimicrobial [12, 13] activities.

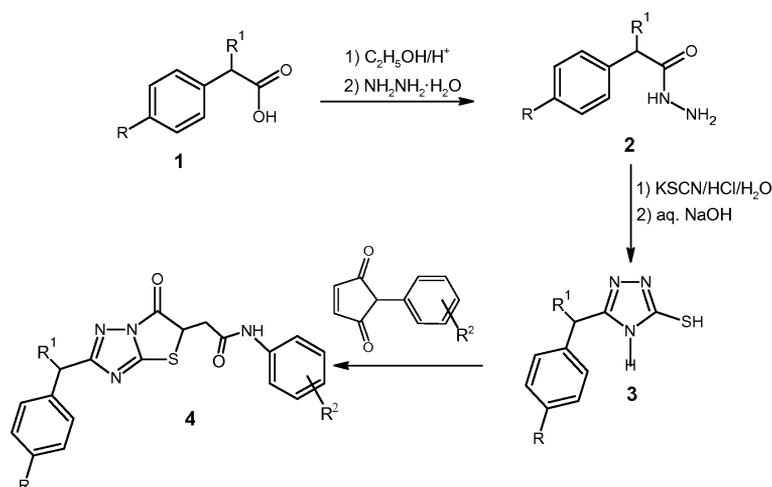
1,2,4-Triazole derivatives due to their wide range of biological activities such as antimicrobial, anti-inflammatory [14], anticancer [15], antitubercular [16] and antimycotic [17, 18] properties have received considerable attention. 1,2,4-Triazole rings have been incorporated into a variety of therapeutically interesting drug candidates such as Triazolam [19], Alprazolam [20], Etizolam [21], Furacyclin [22], and Ribavirin [23].

On the other hand, thiazoles have attracted continuing interest because of their varied biological activities [27–32]. There are also some drugs containing the thiazole moiety, for example: Fentiazac, Meloxicam [24, 25] (both anti-inflammatory agents), Nizatidine [26] (antiulcerative agent), and Sulfathiazole [26] (antimicrobial agent).

In view of these marked applications of [1,2,4]triazoles and [1,3]thiazoles, it was envisaged that chemical entities containing both of these moieties would result in compounds of interesting biological activities. It was considered to synthesize some substituted [1,3]thiazolo[3,2-*b*]-1,2,4-triazoles incorporating 2-(4-isobutylphenyl)ethyl and 4-methylthiophenyl moieties.

## Results and Discussion

A synthetic approach to the title compounds is outlined in Scheme 1. The acid hydrazides **2** were prepared by the esterification of 2-(4-isobutylphenyl)propanoic acid and 4-methylthiophenyl acetic acid



R = CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, SCH<sub>3</sub>; R<sup>1</sup> = CH<sub>3</sub>, H; R<sup>2</sup> = H, 3-Cl-4-F, 4-F, 4-Cl, 4-CH<sub>3</sub>, 4-OCH<sub>3</sub>, 4-Br

	<b>4a</b>	<b>4b</b>	<b>4c</b>	<b>4d</b>	<b>4e</b>	<b>4f</b>	<b>4g</b>
<b>R</b>	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>						
<b>R<sup>1</sup></b>	CH <sub>3</sub>						
<b>R<sup>2</sup></b>	H	3-Cl-4-F	4-F	4-Cl	4-CH <sub>3</sub>	4-OCH <sub>3</sub>	4-Br
	<b>4h</b>	<b>4i</b>	<b>4j</b>	<b>4k</b>	<b>4l</b>	<b>4m</b>	<b>4n</b>
<b>R</b>	SCH <sub>3</sub>						
<b>R<sup>1</sup></b>	H	H	H	H	H	H	H
<b>R<sup>2</sup></b>	H	3-Cl-4-F	4-F	4-Cl	4-CH <sub>3</sub>	4-OCH <sub>3</sub>	4-Br

Scheme 1.

followed by treatment with hydrazine hydrate in absolute alcohol [33]. The resulting acid hydrazides on reaction with potassium thiocyanate in the presence of conc. hydrochloric acid yielded the corresponding thiosemicarbazides, which on cyclization with an aqueous 5% NaOH solution afforded 3-substituted-[1,2,4]triazole-5-thiols **3**. Condensation of these triazoles with various substituted *N*-aryl-maleimides in acetic acid media yielded 2-(2-substituted-6-oxo-5,6-dihydro[1,3]thiazolo[3,2-*b*][1,2,4]triazol-5-yl)-*N*-aryl-acetamides **4**. The substituted *N*-aryl-maleimides were prepared according to the literature procedures [34]. The formation of fused thiazotriazoles **4a–n** has been confirmed by the elemental analyses and spectral data of the products.

In the IR spectra of **3a** and **3b**, absorption bands due to an amide carbonyl function in the region 1760–1705 cm<sup>-1</sup> and to the NH-NH<sub>2</sub> moiety in the region 3455–3203 cm<sup>-1</sup> of their precursors were found to be absent. However, they showed a new absorption band at 3114 cm<sup>-1</sup> of an NH group supporting their formation.

The IR spectra of thiazotriazoles **4** showed the absorption bands corresponding to their C=O and C=N

groups in the region 1710–1725 cm<sup>-1</sup> and 1585–1610 cm<sup>-1</sup>, respectively, thus indicating their formation from **3** through cyclocondensation with *N*-aryl-maleimides.

The <sup>1</sup>H NMR spectrum of 1,2,4-triazole-5-thiol **3a** showed a downfield, broad singlet at δ = 12.64 ppm for the D<sub>2</sub>O-exchangeable NH and SH protons. The downfield shift of this signal indicates tautomerism in the triazole ring. Two distinct doublets at δ = 0.85 (*J* = 8.0 Hz) and δ = 1.68 (*J* = 8.0 Hz) were observed for the methyl protons. The isopropyl methyne proton was observed as a multiplet in the range δ = 1.80–1.88 ppm, and the other methyne proton was observed as a quartet at δ = 4.14 ppm. The methylene protons resonated as a doublet at δ = 2.45 ppm (*J* = 4.0 Hz). The aromatic protons appeared as two doublets at δ = 6.97 and 7.06 ppm with *J* = 8.0 Hz. Further, an LC-MS spectrum of **3a** showed the molecular ion peak at *m/z* = 261, in conformity with its molecular formula, C<sub>14</sub>H<sub>19</sub>N<sub>3</sub>S.

The <sup>1</sup>H NMR spectrum of **3b** also showed a downfield broad singlet at δ = 13.30 ppm corresponding to its D<sub>2</sub>O-exchangeable NH and SH protons. Two singlets at δ = 2.41 ppm and δ = 3.83 ppm have been attributed to the SCH<sub>3</sub> and CH<sub>2</sub> protons. The four ar-

matic protons of the 4-methylthiophenyl moiety resonated as two doublets at  $\delta = 7.18$  and  $7.20$  ppm ( $J = 8.3$  Hz), respectively. Further, an LC-MS spectrum of **3b** showed the molecular ion peak at  $m/z = 237$ , in conformity with its molecular formula,  $C_{10}H_{11}N_3S_2$ .

In the  $^1H$  NMR spectra of compounds **4a–n**, protons of a  $CH_2-CH$  fragment showed the characteristic pattern of an ABX system. The chemical shifts of the protons  $H^A$ ,  $H^B$  and  $H^X$  are at  $\delta \sim 3.32-3.38$ ,  $\sim 2.81-2.95$  and  $\sim 4.55-4.65$  ppm, respectively. Large values of  $J_{AB} = 12.0-18.0$  Hz,  $J_{AX} = 7.5-9.0$  Hz and  $J_{BX} = 4.0-8.0$  Hz were observed like in the structurally related 2-thioxo-4-thiazolidinones, referred to a “carbonyl effect” by Takahashi [35]. The acetamide NH proton appeared as a sharp singlet at  $\delta = 13.80-14.10$  ppm. In the  $^{13}C$  NMR spectra of **4** the acetamide carbonyl carbon and the thiazolidinone carbonyl carbon atoms appeared in the region  $\delta = 172.1-174.2$  and  $176.2-177.8$  ppm, respectively, in addition to other characteristic signals of the remaining carbon atoms.

## Experimental Section

### Instruments and starting materials

The melting points were determined by an open capillary method and are uncorrected. The IR spectra (from KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. The  $^1H$  NMR and  $^{13}C$  NMR spectra were recorded on a Bruker Avance II-400 (400 MHz) spectrometer using TMS as an internal standard. Mass spectra were recorded in an Agilent Technology LC-mass spectrometer. The accelerating voltage was 10 kV, and spectra were recorded at r.t. Elemental analyses (CHNS) were performed on the CHNS analyzer. The progress of the reaction was monitored by thin-layer chromatography (TLC) on silica gel plates.

### General procedure for the preparation of acid hydrazides **2a, b**

The mixture of ethyl esters of substituted aromatic acids **1** (0.1 mol) and hydrazine hydrate (0.2 mol) was refluxed in absolute alcohol (50 mL) for 8 h. The excess solvent was then distilled off under reduced pressure, and the concentrated solution was quenched by its addition to ice cold water. The solid separated was filtered, washed and dried. The crude product was purified by recrystallization from ethanol.

**2a:** M. p. 71 °C; yield 85%. – IR (KBr):  $\nu = 3449$  (NH,  $NH_2$ ), 3275 ( $NH_2$ ), 2972 (C-H), 1695 (CO-NH)  $cm^{-1}$ . –  $^1H$  NMR ( $CDCl_3$ ):  $\delta = 0.85$  (d,  $J = 8$  Hz, 6 H,  $2 \times CH_3$ ), 1.68 (d,  $J = 8$  Hz, 3 H,  $CH_3$ ), 1.80–1.88 (m, 1 H, CH), 2.45 (d,  $J = 4$  Hz, 2 H,  $CH_2$ ), 4.0 (s, 2 H,  $NH_2$ ), 4.14 (q,  $J = 8$  Hz, 1 H,

CH), 7.5 (br s, 5 H,  $C_6H_4$  and NH). – LC-MS:  $m/z$  (%) = 220 (78)  $[M]^+$ . –  $C_{13}H_{20}N_2O$  (220.3): calcd. C 70.87, H 9.15, N 12.72; found C 70.85, H 9.13, N 12.70.

**2b:** M. p. 136 °C; yield 86%. – IR (KBr):  $\nu = 3344$  (NH,  $NH_2$ ), 3203 ( $NH_2$ ), 2963 (C-H), 1622 (CO-NH)  $cm^{-1}$ . –  $^1H$  NMR ( $CDCl_3$ ):  $\delta = 2.49$  (s, 3 H,  $SCH_3$ ), 3.53 (s, 2 H,  $CH_2$ ), 3.82 (br s, 2 H,  $NH_2$ ), 6.67 (br s, 1 H, NH), 7.18 (d,  $J = 8.3$  Hz, Ar-H), 7.26 (d,  $J = 8.3$  Hz, Ar-H). – LC-MS:  $m/z$  (%) = 196 (90)  $[M]^+$ . –  $C_9H_{12}N_2OS$  (196.2): calcd. C 55.09, H 6.16, N 14.27, S 16.34; found C 55.06, H 6.15, N 10.25, S 15.71.

### General procedure for the preparation of 1,2,4-triazole-3-thiols **3a, b**

Aroyl hydrazide **2** (0.1 mol) was dissolved in water (100 mL) containing concentrated hydrochloric acid (10 mL). Potassium thiocyanate (0.2 mol) was added, and the mixture was warmed on a water bath for 5 h. The reaction mixture was cooled. The precipitated solid was filtered, dried and recrystallized from ethanol to get the aroyl thiosemicarbazide. A mixture of aroyl thiosemicarbazide (0.01 mol) and sodium hydroxide (5%, 100 mL) was refluxed for 3 h. The reaction mixture was poured on crushed ice and acidified with dilute hydrochloric acid. The precipitate thus obtained was filtered, dried and recrystallized from ethanol.

**3a:** M. p. 198 °C; yield 85%. – IR (KBr):  $\nu = 3100$  (Ar-H), 2972 (C-H), 1215 (C=S)  $cm^{-1}$ . –  $^1H$  NMR ( $CDCl_3$ ):  $\delta = 0.85$  (d,  $J = 8$  Hz, 6 H,  $2 \times CH_3$ ), 1.68 (d,  $J = 8$  Hz, 3 H,  $CH_3$ ), 1.80–1.88 (m, 1 H, CH), 2.45 (d,  $J = 4.0$  Hz, 2 H,  $CH_2$ ), 4.15 (q,  $J = 8.0$  Hz, 1 H, CH), 6.97 (d,  $J = 8$  Hz, 2 H, ArH), 7.06 (d,  $J = 8$  Hz, 2 H, ArH), 12.64 (br s, 2 H, NH/SH). –  $^{13}C$  NMR ( $[D_6]DMSO$ ):  $\delta = 18.34$ , 18.78, 22.42, 30.28, 37.48, 126.13, 126.32, 128.25, 128.43, 136.20, 139.05, 161.05, 167.15. – LC-MS:  $m/z$  (%) = 261 (86)  $[M]^+$ . –  $C_{14}H_{19}N_3S$  (261.3): calcd. C 64.31; H 7.33; N 16.08; S 12.27; found C 64.30; H 7.33; N 16.09; S 12.27.

**3b:** M. p. 197 °C; yield 85%. – IR (KBr):  $\nu = 3154$  (NH), 1206 (C=S)  $cm^{-1}$ . –  $^1H$  NMR ( $[D_6]DMSO$ ):  $\delta = 2.49$  (s, 3 H,  $SCH_3$ ), 3.83 (s, 2 H,  $CH_2$ ), 7.18 (d,  $J = 8.36$  Hz, Ar-H), 7.26 (d,  $J = 8.36$  Hz, Ar-H), 13.30 (br s, 2 H, NH/SH). –  $^{13}C$  NMR ( $[D_6]DMSO$ ):  $\delta = 16.12$ , 32.13, 127.51, 128.25, 131.99, 139.21, 152.16, 167.10. – LC-MS:  $m/z$  (%) = 237 (89)  $[M]^+$ . –  $C_{10}H_{11}N_3S_2$  (237.3): calcd. C 50.60, H 4.67, N 17.70, S 27.02; found C 50.56, H 4.71, N 17.79, S 27.05.

### General procedure for the preparation of substituted [1,3]thiazolo[3,2-b][1,2,4]triazole derivatives **4a–n**

A mixture of a 1,2,4-triazole-5-thiol (10 mmol) and the appropriate *N*-arylmaleimide (10 mmol) was refluxed for 2 h in 10 mL of glacial acetic acid. After cooling to r.t., the reaction mixture was poured into 50 mL of water. The precipitated colorless powder was filtered off, washed with methanol and recrystallized from ethanol.

**4a:** M.p. 157 °C; yield 85%. – IR (KBr):  $\nu = 3126$  (NH), 3022 (Ar-H), 2954 (C-H), 1715 (C=O), 1596 (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([D<sub>6</sub>]DMSO):  $\delta = 0.83$  (d,  $J = 8$  Hz, 6 H,  $2 \times \text{CH}_3$ ), 1.51 (d,  $J = 8$  Hz, 3 H, CH<sub>3</sub>), 1.74–1.81 (m, 1 H, CH), 2.38 (d,  $J = 8$  Hz, 2 H, CH<sub>2</sub>), 2.90 (dd,  $J = 16$  Hz, 1 H), 3.37 (dd,  $J = 16$ , 8 Hz, 1 H), 4.19 (q,  $J = 4$  Hz, 1 H, CH), 4.61 (dd,  $J = 8.7$ , 4 Hz, 1 H), 7.05 (d,  $J = 8$  Hz, 2 H, Ar-H), 7.08 (d,  $J = 8$  Hz, 2 H, Ar-H), 7.12–7.74 (m, 5 H, phenyl), 13.93 (s, 1 H, NH). –  $^{13}\text{C}$  NMR ([D<sub>6</sub>]DMSO):  $\delta = 18.8$ , 19.2, 22.8, 30.6, 34.6, 37.7, 39.6, 127.4, 127.8, 129.8, 130.2, 139.0, 152.4, 169.5, 173.4, 179.7. – LC-MS:  $m/z$  (%) = 434 (55) [M]<sup>+</sup>. – C<sub>24</sub>H<sub>26</sub>N<sub>4</sub>O<sub>2</sub>S (434.5): calcd. C 70.87, H 9.15, N 12.72; found C 70.85, H 9.13, N 12.70.

**4b:** M.p. 118 °C; yield 77%. – IR (KBr):  $\nu = 3126$  (NH), 3050 (Ar-H), 2956 (C-H), 1713 (C=O), 1584 (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([D<sub>6</sub>]DMSO):  $\delta = 0.83$  (d,  $J = 8$  Hz, 6 H,  $2 \times \text{CH}_3$ ), 1.50 (d,  $J = 8$  Hz, 3 H, CH<sub>3</sub>), 1.73–1.79 (m, 1 H, CH), 2.38 (d,  $J = 8$  Hz, 2 H, CH<sub>2</sub>), 2.91 (dd,  $J = 16$  Hz, 1 H), 3.34 (dd,  $J = 16$ , 8 Hz, 1 H), 4.19 (q,  $J = 4$  Hz, 1 H, CH), 4.60 (dd,  $J = 8.7$ , 4 Hz, 1 H), 7.08 (d,  $J = 8$  Hz, 2 H, Ar-H), 7.12 (d,  $J = 8$  Hz, 2 H, Ar-H), 7.32–7.47 (m, 4 H, 3-chloro-4-fluorophenyl), 13.96 (s, 1 H, NH). –  $^{13}\text{C}$  NMR ([D<sub>6</sub>]DMSO):  $\delta = 18.7$ , 19.2, 22.8, 30.4, 34.5, 37.0, 39.8, 127.8, 128.5, 130.4, 132.0, 140.0, 153.1, 168.7, 173.2, 179.6. – LC-MS:  $m/z$  (%) = 486 (54) [M]<sup>+</sup>, 488 (18) [M]<sup>+</sup>. – C<sub>24</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>ClFS (486.9): calcd. C 70.87, H 9.15, N 12.72; found C 70.85, H 9.13, N 12.70.

**4c:** M.p. 124 °C; yield 72%. – IR (KBr):  $\nu = 3128$  (NH), 3058 (Ar-H), 2946 (C-H), 1703 (C=O), 1598 (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([D<sub>6</sub>]DMSO):  $\delta = 0.82$  (d,  $J = 8$  Hz, 6 H,  $2 \times \text{CH}_3$ ), 1.51 (d,  $J = 8$  Hz, 3 H, CH<sub>3</sub>), 1.74–1.81 (m, 1 H, CH), 2.38 (d,  $J = 8$  Hz, 2 H, CH<sub>2</sub>), 2.88 (dd,  $J = 16$  Hz, 1 H), 3.39 (dd,  $J = 16$ , 8 Hz, 1 H), 4.18 (q,  $J = 4$  Hz, 1 H, CH), 4.63 (dd,  $J = 8.7$ , 4 Hz, 1 H), 7.04–7.10 (m, 4 H, Ar-H), 7.26–7.38 (m, 4 H, 4-fluorophenyl), 13.99 (s, 1 H, NH). –  $^{13}\text{C}$  NMR ([D<sub>6</sub>]DMSO):  $\delta = 18.7$ , 19.2, 22.8, 30.4, 34.6, 37.2, 39.0, 126.6, 127.8, 129.6, 130.4, 141.2, 152.9, 168.1, 173.1, 179.5. – LC-MS:  $m/z$  (%) = 452 (72) [M]<sup>+</sup>. – C<sub>24</sub>H<sub>25</sub>N<sub>4</sub>O<sub>2</sub>FS (452.5): calcd. C 70.87, H 9.15, N 12.72; found C 70.85, H 9.13, N 12.70.

**4d:** M.p. 170 °C; yield 85%. – IR (KBr):  $\nu = 3130$  (NH), 3068 (Ar-H), 2961 (C-H), 1710 (C=O), 1602 (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([D<sub>6</sub>]DMSO):  $\delta = 0.83$  (d,  $J = 8$  Hz, 6 H,  $2 \times \text{CH}_3$ ), 1.52 (d,  $J = 8$  Hz, 3 H, CH<sub>3</sub>), 1.76–1.82 (m, 1 H, CH), 2.38 (d,  $J = 8$  Hz, 2 H, CH<sub>2</sub>), 2.86 (dd,  $J = 16$  Hz, 1 H), 3.35 (dd,  $J = 16$ , 8 Hz, 1 H), 4.19 (q,  $J = 4$  Hz, 1 H, CH), 4.72 (dd,  $J = 8.7$ , 4 Hz, 1 H), 7.06 (d,  $J = 8$  Hz, 2 H, Ar-H), 7.10 (d,  $J = 8$  Hz, 2 H, Ar-H), 7.32–7.48 (m, 4 H, 4-chlorophenyl), 13.98 (s, 1 H, NH). –  $^{13}\text{C}$  NMR ([D<sub>6</sub>]DMSO):  $\delta = 18.6$ , 19.3, 22.8, 30.4, 34.5, 37.6, 40.3, 127.2, 128.4, 130.4, 132.1, 141.2, 153.4, 169.1, 173.4, 179.8. – LC-MS:  $m/z$  (%) = 468 (60) [M]<sup>+</sup>, 470 (20) [M]<sup>+</sup>. – C<sub>24</sub>H<sub>25</sub>N<sub>4</sub>O<sub>2</sub>ClS (468.9):

calcd. C 70.87, H 9.15, N 12.72; found C 70.85, H 9.13, N 12.70.

**4e:** M.p. 142 °C; yield 88%. – IR (KBr):  $\nu = 3483$  (NH), 3080 (Ar-H), 2958 (C-H), 1720 (C=O), 1607 (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([D<sub>6</sub>]DMSO):  $\delta = 0.82$  (d,  $J = 8$  Hz, 6 H,  $2 \times \text{CH}_3$ ), 1.51 (d,  $J = 8$  Hz, 3 H, CH<sub>3</sub>), 1.74–1.81 (m, 1 H, CH), 2.33 (s, 3 H, Ar-CH<sub>3</sub>), 2.38 (d,  $J = 8$  Hz, 2 H, CH<sub>2</sub>), 2.93 (dd,  $J = 16$  Hz, 1 H), 3.40 (dd,  $J = 16$ , 8 Hz, 1 H), 4.19 (q,  $J = 4$  Hz, 1 H, CH), 4.61 (dd,  $J = 8.7$ , 4 Hz, 1 H), 7.04–7.08 (m, 4 H, Ar-H), 7.10–7.25 (m, 4 H, 4-methylphenyl), 13.93 (s, 1 H, NH). –  $^{13}\text{C}$  NMR ([D<sub>6</sub>]DMSO):  $\delta = 18.7$ , 19.2, 20.4, 22.8, 30.5, 34.7, 38.2, 39.7, 126.4, 127.8, 129.2, 131.6, 141.2, 153.2, 168.6, 173.2, 179.6. – LC-MS:  $m/z$  (%) = 448 (58) [M]<sup>+</sup>. – C<sub>25</sub>H<sub>28</sub>N<sub>4</sub>O<sub>3</sub>S (448.5): calcd. C 70.87, H 9.15, N 12.72; found C 70.85, H 9.13, N 12.70.

**4f:** M.p. 158 °C; yield 68%. – IR (KBr):  $\nu = 3249$  (NH), 3062 (Ar-H), 2976 (C-H), 1710 (C=O), 1604 (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([D<sub>6</sub>]DMSO):  $\delta = 0.83$  (d,  $J = 8$  Hz, 6 H,  $2 \times \text{CH}_3$ ), 1.52 (d,  $J = 8$  Hz, 3 H, CH<sub>3</sub>), 1.76–1.82 (m, 1 H, CH), 2.38 (d,  $J = 8$  Hz, 2 H, CH<sub>2</sub>), 2.92 (dd,  $J = 16$  Hz, 1 H), 3.41 (dd,  $J = 16$ , 8 Hz, 1 H), 3.92 (s, 3 H, OCH<sub>3</sub>), 4.19 (q,  $J = 4$  Hz, 1 H, CH), 4.72 (dd,  $J = 8.7$ , 4 Hz, 1 H), 7.04 (d,  $J = 8$  Hz, 2 H, Ar-H), 7.08 (d,  $J = 8$  Hz, 2 H, Ar-H), 7.34–7.44 (m, 4 H, 4-methoxyphenyl), 13.93 (s, 1 H, NH). –  $^{13}\text{C}$  NMR ([D<sub>6</sub>]DMSO):  $\delta = 18.7$ , 19.2, 22.8, 30.5, 35.3, 38.2, 39.7, 60.4, 126.2, 127.0, 128.8, 130.2, 140.0, 153.5, 168.4, 173.0, 179.6. – LC-MS:  $m/z$  (%) = 464 (63) [M]<sup>+</sup>. – C<sub>25</sub>H<sub>28</sub>N<sub>4</sub>O<sub>3</sub>S (464.5): calcd. C 70.87, H 9.15, N 12.72; found C 70.85, H 9.13, N 12.70.

**4g:** M.p. 152 °C; yield 83%. – IR (KBr):  $\nu = 3216$  (NH), 3048 (Ar-H), 2964 (C-H), 1704 (C=O), 1607 (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([D<sub>6</sub>]DMSO):  $\delta = 0.83$  (d,  $J = 8$  Hz, 6 H,  $2 \times \text{CH}_3$ ), 1.52 (d,  $J = 8$  Hz, 3 H, CH<sub>3</sub>), 1.76–1.82 (m, 1 H, CH), 2.38 (d,  $J = 8$  Hz, 2 H, CH<sub>2</sub>), 2.87 (dd,  $J = 16$  Hz, 1 H), 3.39 (dd,  $J = 16$ , 8 Hz, 1 H), 4.19 (q,  $J = 4$  Hz, 1 H, CH), 4.66 (dd,  $J = 8.7$ , 4 Hz, 1 H), 7.04 (d,  $J = 8$  Hz, 2 H, Ar-H), 7.08 (d,  $J = 8$  Hz, 2 H, Ar-H), 7.34–7.44 (m, 4 H, 4-bromophenyl), 14.00 (s, 1 H, NH). –  $^{13}\text{C}$  NMR ([D<sub>6</sub>]DMSO):  $\delta = 18.6$ , 19.3, 22.8, 30.4, 34.5, 37.6, 40.3, 126.2, 127.4, 129.4, 130.1, 140.2, 153.2, 168.8, 173.4, 179.5. – LC-MS:  $m/z$  (%) = 512 (62) [M]<sup>+</sup>, 514 (62) [M]<sup>+</sup>. – C<sub>24</sub>H<sub>25</sub>N<sub>4</sub>O<sub>2</sub>BrS (513.4): calcd. C 70.87, H 9.15, N 12.72; found C 70.85, H 9.13, N 12.70.

**4h:** M.p. 157 °C; yield 78%. – IR (KBr):  $\nu = 3334$  (NH), 3062 (Ar-H), 2924 (C-H), 1711 (C=O), 1599 (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([D<sub>6</sub>]DMSO):  $\delta = 2.42$  (s, 3 H, SCH<sub>3</sub>), 2.89 (dd,  $J = 16$  Hz, 1 H), 3.39 (dd,  $J = 16$ , 8 Hz, 1 H), 3.98 (s, 2 H, CH<sub>2</sub>), 4.62 (dd,  $J = 8.7$ , 4 Hz, 1 H), 7.12–7.23 (m, 5 H, Ar-H), 7.41–7.48 (m, 4 H, phenyl), 14.00 (s, 1 H, NH). –  $^{13}\text{C}$  NMR ([D<sub>6</sub>]DMSO):  $\delta = 16.1$ , 32.3, 35.2, 41.2, 124.3, 127.5, 128.5, 129.9, 139.9, 152.1, 167.0, 172.7, 177.8. – LC-MS:  $m/z$  (%) = 410 (78) [M]<sup>+</sup>. – C<sub>20</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub> (410.5): calcd. C 70.87, H 9.15, N 12.72; found C 70.85, H 9.13, N 12.70.

**4i:** M.p. 160 °C; yield 72%. – IR (KBr):  $\nu$  = 3107 (NH), 3017 (Ar-H), 2920 (C-H), 1712 (C=O), 1596 (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 2.41 (s, 3 H, SCH<sub>3</sub>), 2.85 (dd,  $J$  = 16 Hz, 1 H), 3.38 (dd,  $J$  = 16, 8 Hz, 1 H), 3.97 (s, 2 H, CH<sub>2</sub>), 4.62 (dd, 1 H,  $J$  = 8.7, 4 Hz), 7.12–7.18 (m, 4 H, Ar-H), 7.20–7.55 (m, 3 H, 3-chloro-4-fluorophenyl), 13.99 (s, 1 H, NH). –  $^{13}\text{C}$  NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 16.1, 32.3, 35.8, 40.2, 127.6, 128.5, 128.7, 130.8, 139.2, 140.5, 152.1, 167.0, 172.8, 177.7. – LC-MS:  $m/z$  (%) = 462 (69) [M]<sup>+</sup>, 464 (23) [M]<sup>+</sup>. – C<sub>20</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub>ClFS<sub>2</sub> (462.9): calcd. C 70.87, H 9.15, N 12.72; found C 70.85, H 9.13, N 12.70.

**4j:** M.p. 182 °C; yield 68%. – IR (KBr):  $\nu$  = 3319 (NH), 3056 (Ar-H), 2923 (C-H), 1711 (C=O), 1603 (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 2.43 (s, 3 H, SCH<sub>3</sub>), 2.86 (dd,  $J$  = 16 Hz, 1 H), 3.38 (dd,  $J$  = 16, 8 Hz, 1 H), 3.98 (s, 2 H, CH<sub>2</sub>), 4.60 (dd,  $J$  = 8.7, 4 Hz, 1 H), 7.14–7.24 (m, 4 H, Ar-H), 7.29–7.33 (m, 4 H, 4-fluorophenyl), 14.01 (s, 1 H, NH). –  $^{13}\text{C}$  NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 16.2, 32.1, 35.3, 40.7, 127.5, 128.1, 129.1, 129.4, 140.4, 152.1, 167.0, 172.7, 177.5. – LC-MS:  $m/z$  (%) = 428 (64) [M]<sup>+</sup>. – C<sub>20</sub>H<sub>17</sub>N<sub>4</sub>O<sub>2</sub>FS<sub>2</sub> (428.5): calcd. C 70.87, H 9.15, N 12.72; found C 70.85, H 9.13, N 12.70.

**4k:** M.p. 171 °C; yield 80%. – IR (KBr):  $\nu$  = 3248 (NH), 3084 (Ar-H), 2978 (C-H), 1713 (C=O), 1614 (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 2.48 (s, 3H, SCH<sub>3</sub>), 2.85 (dd,  $J$  = 16 Hz, 1 H), 3.38 (dd,  $J$  = 16, 8 Hz, 1 H), 4.01 (s, 2 H, CH<sub>2</sub>), 4.61 (dd,  $J$  = 8.7, 4 Hz, 1 H), 7.12–7.16 (m, 4 H, Ar-H), 7.34–7.38 (m, 4 H, 4-chlorophenyl), 13.94 (s, 1 H, NH). –  $^{13}\text{C}$  NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 16.2, 32.3, 35.2, 40.9, 126.5, 127.2, 128.4, 129.2, 140.8, 151.2, 167.1, 172.9, 177.3. – LC-MS:  $m/z$  (%) = 444 (75) [M]<sup>+</sup>, 446 (25) [M]<sup>+</sup>. – C<sub>20</sub>H<sub>17</sub>N<sub>4</sub>O<sub>2</sub>ClS<sub>2</sub> (444.9): calcd. C 70.87, H 9.15, N 12.72; found C 70.85, H 9.13, N 12.70.

**4l:** M.p. 130 °C; yield 76%. – IR (KBr):  $\nu$  = 3308 (NH), 3067 (Ar-H), 2965 (C-H), 1709 (C=O), 1603 (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 2.33 (s, 3 H, Ar-

CH<sub>3</sub>), 2.41 (s, 3 H, SCH<sub>3</sub>), 2.86 (dd,  $J$  = 16 Hz, 1 H), 3.38 (dd,  $J$  = 16, 8 Hz, 1 H), 3.98 (s, 2 H, CH<sub>2</sub>), 4.62 (dd,  $J$  = 8.7, 4 Hz, 1 H), 7.10–7.16 (m, 4 H, Ar-H), 7.29–7.33 (m, 4 H, 4-methylphenyl), 13.97 (s, 1 H, NH). –  $^{13}\text{C}$  NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 16.2, 21.6, 32.4, 35.2, 40.6, 126.8, 127.6, 128.6, 129.4, 141.3, 151.4, 167.2, 172.2, 177.5. – LC-MS:  $m/z$  (%) = 424 (61) [M]<sup>+</sup>. – C<sub>21</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub> (424.5): calcd. C 70.87, H 9.15, N 12.72; found C 70.85, H 9.13, N 12.70.

**4m:** M.p. 138 °C; yield 79%. – IR (KBr):  $\nu$  = 3304 (NH), 3086 (Ar-H), 2927 (C-H), 1715 (C=O), 1608 (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 2.50 (s, 3 H, SCH<sub>3</sub>), 2.87 (dd,  $J$  = 16 Hz, 1 H), 3.38 (dd,  $J$  = 16, 8 Hz, 1 H), 3.85 (s, 3 H, OCH<sub>3</sub>), 4.02 (s, 2 H, CH<sub>2</sub>), 4.61 (dd,  $J$  = 8.7, 4 Hz, 1 H), 7.08–7.14 (m, 4 H, Ar-H), 7.36–7.42 (m, 4 H, 4-methoxyphenyl), 13.94 (s, 1 H, NH). –  $^{13}\text{C}$  NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 16.2, 32.3, 35.2, 40.8, 61.5, 127.2, 127.9, 129.2, 130.4, 140.6, 151.4, 168.1, 172.6, 177.9. – LC-MS:  $m/z$  (%) = 440 (68) [M]<sup>+</sup>. – C<sub>21</sub>H<sub>20</sub>N<sub>4</sub>O<sub>3</sub>S<sub>2</sub> (440.5): calcd. C 70.87, H 9.15, N 12.72; found C 70.85, H 9.13, N 12.70.

**4n:** M.p. 170 °C; yield 68%. – IR (KBr):  $\nu$  = 3284 (NH), 3042 (Ar-H), 2926 (C-H), 1705 (C=O), 1598 (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 2.50 (s, 3 H, SCH<sub>3</sub>), 2.86 (dd,  $J$  = 16 Hz, 1 H), 3.38 (dd,  $J$  = 16, 8 Hz, 1 H), 4.02 (s, 2 H, CH<sub>2</sub>), 4.61 (dd,  $J$  = 8.7, 4 Hz, 1 H), 7.08–7.14 (m, 4 H, Ar-H), 7.36–7.42 (m, 4 H, 4-bromophenyl), 13.94 (s, 1 H, NH). –  $^{13}\text{C}$  NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 16.1, 32.2, 35.2, 41.1, 126.2, 127.1, 128.4, 129.8, 140.2, 151.4, 168.0, 172.4, 177.6. – LC-MS:  $m/z$  (%) = 488 (58) [M]<sup>+</sup>, 490 (58) [M]<sup>+</sup>. – C<sub>20</sub>H<sub>17</sub>N<sub>4</sub>O<sub>2</sub>BrS<sub>2</sub> (489.4): calcd. C 70.87, H 9.15, N 12.72; found C 70.85, H 9.13, N 12.70.

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