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# Antifungal agents. Part 5: Synthesis and antifungal activities of aminoguanidine derivatives of *N*-arylsulfonyl-3-acylindoles

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ABSTRACT

In order to discover more promising antifungal agents, a series of aminoguanidine derivatives of *N*-arylsulfonyl-3-acylindoles (**5a–r**) were prepared and evaluated in vitro for their antifungal activities against seven phytopathogenic fungi. Especially compounds **5n** and **5o** exhibited more potent antifungal activities than or comparable to hymexazol, a commercially available agricultural fungicide at the concentration of 100 μg/mL. Preliminary structure–activity relationships study demonstrated that introduction of electron-donating substituents $R^1$ and $R^2$, and the proper length of substituent $R^3$ were usually very important for their antifungal activities.



Recently, much attention has been paid to aminoguanidine derivatives (**I**, Fig. 1) due to their diverse biological activities, for instance, antibacterial activity,[1] serotonin 4 (5-$HT_4$) receptor and chemokine receptor-5 (CCR5) antagonists,[2] cardiotonic activity,[3] NO donors,[4] and potent lipopolysaccharide (LPS) binders.[5] In the meantime, more recently, *N*-arylsulfonyl-3-acylindole derivatives (**II**, Fig. 1) have displayed potent anti-human immunodeficiency virus type 1 (HIV-1) activity.[6] Nowadays, fragment-based lead discovery has emerged as a more rational and focused approach for molecular modification and drug design. Based upon these previous observations, and in continuation of our program aimed at the discovery and development of bioactive molecules,[7] consequently, we wanted to prepare a series of aminoguanidine derivatives of *N*-arylsulfonyl-3-acylindoles (**5a–r**, Fig. 1) by combining the aminoguanidine group with *N*-arylsulfonyl-3-acylindole moiety. On the other hand, it is well-known that phytopathogenic fungi are hard to control and easily infect many crops, and it is imperative to develop new compounds for effective inhibition of those agricultural diseases. Although Cole et al. described two aminoguanidine derivatives of *N*-arylsulfonyl-3-acylindoles exhibiting the binding affinity for 5-$HT_6$ receptor,[8] in this Letter, 18 aminoguanidine derivatives (**5a–r**) were bioevaluated in vitro as antifungal agents against seven phytopathogenic fungi. The structure–activity relationship (SAR) of these compounds was also preliminarily investigated.

As described in Scheme 1, four 3-formylindole derivatives (**2a–d**) were directly synthesized from indoles (**1a–d**) and *N*,*N*-dimethylformamide (DMF) in the presence of phosphorus oxychloride ($POCl_3$) by means of the Vilsmeier reaction.[9] Then **2a–d** reacted with arylsulfonyl chlorides in the presence of potassium carbonate ($K_2CO_3$) at reflux to afford **4a–i** in 59–93% yields. Meanwhile, *N*-arylsulfonyl-3-acylindole derivatives (**4j–r**) were prepared by the reaction of **1a–d** with arylsulfonyl chlorides in the presence of sodium hydroxide (NaOH) and triethylbenzylammonium chloride (TEBA), followed by treatment with acetic

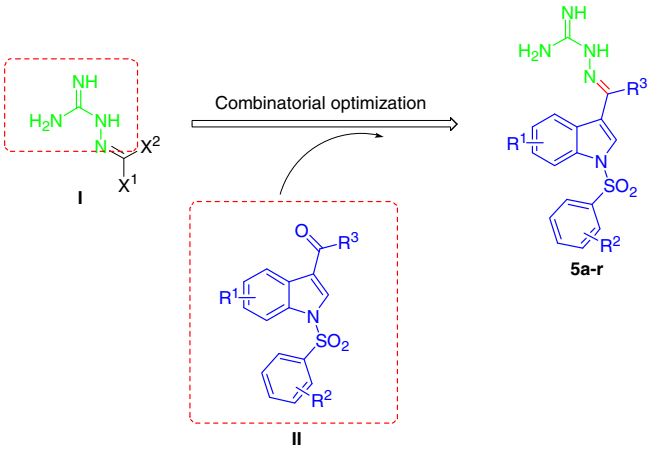


**Figure 1.** Design strategy of the target compounds **5a–r**.

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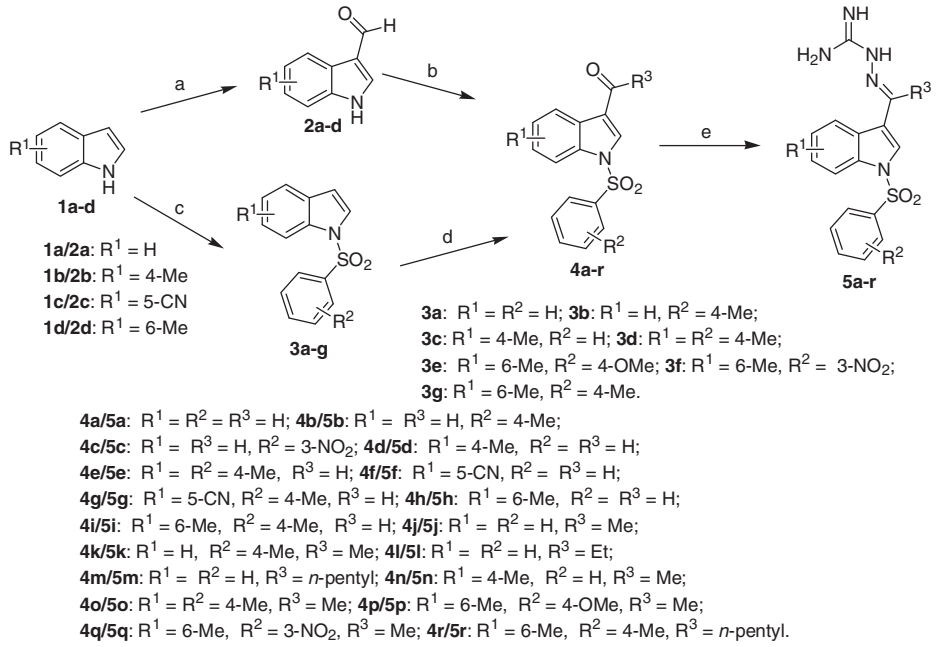


**Scheme 1.** The synthetic route of compounds **5a–r**. Reagents and conditions: (a) $POCl_3$, DMF, 35 °C, 1 h, adjust pH to 8–9, reflux, 1 h, 67–73%; (b) arylsulfonyl chlorides, $K_2CO_3$, $CH_2Cl_2$, reflux, 12 h, 59–93%; (c) arylsulfonyl chlorides, NaOH, TEBA, $CH_2Cl_2$, rt, 1 h, 74–93%; (d) acetic anhydride, propionic anhydride or *n*-hexanoyl chloride, $AlCl_3$, $CH_2Cl_2$, rt, 2 h, 56–88%; (e) aminoguanidine hydrochloride, HCl/MeOH, reflux, 3 h, 83–99%.

anhydride, propionic anhydride or *n*-hexanoyl chloride via a regioselective Friedel–Crafts acylation reaction.[10] Finally, target compounds **5a–r** were obtained in 83–99% yields by the reaction of **4a–r** with aminoguanidine hydrochloride under reflux for 3 h, followed by the purification by preparative thin-layer chromatography using dichloromethane and methanol as the eluent. The structures of two known compounds **5b** and **5j**[8] were conformed by $^1$H NMR, MS, and mp, and other 16 new target compounds were well characterized by $^1$H NMR, MS, HRMS, and mp.[11]

The antifungal activities of **5a–r** against seven phytopathogenic fungi (i.e., *Fusarium oxysporum* f. sp. *vasinfectum*, *Pyricularia oryzae, Alternaria alternata, Alternaria brassicae, Fusarium graminearum, Bipolaris sorokinianum,* and *Fusarium oxysporum* f. sp. *cucumarinum*) were investigated in vitro by poisoned food technique.[12] Hymexazol, a commercially available agricultural fungicide, was used as a positive control at the concentration of 100 μg/mL.

As outlined in Table 1, among all the derivatives, compounds **5j**, **5l**, **5n**, and **5o** exhibited a good and broad spectrum of antifungal activities against the seven phytopathogenic fungi tested at the concentration of 100 μg/mL. Especially the inhibition rates of **5n** and **5o** against *F. oxysporum* f. sp. *vasinfectum*, *P. oryzae, A. alternata, A. brassicae, F. graminearum, B. sorokinianum*, and *F. oxysporum* f. sp. *cucumarinum* were 64.94%/55.63%, 79.64%/84.84%, 79.15%/82.98%, 52.03%/56.87%, 52.30%/46.57%, 82.28%/80.58%, and 63.15%/57%, respectively. In the meantime, preliminary SAR analysis showed the following interesting characteristics: (1) generally, introduction of electron-withdrawing group ($R^1$) on the indolyl ring would lead to less potent compounds than those with electron-donating group (**5f** versus **5d** and **5h**; **5g** versus **5e** and **5i**). For example, the inhibition rates of **5a** and **5b** against *F. oxysporum* f. sp. *vasinfectum, P. oryzae, A. alternata, A. brassicae, F. graminearum, B. sorokinianum*, and *F. oxysporum* f. sp. *cucumarinum* were 47.83%/51.77%,

**Table 1**
Antifungal activities of compounds **5a–r** at 100 μg/mL

| Compd | Antifungal activities (inhibition %) | | | | | | |
|---|---|---|---|---|---|---|---|
| | *F. oxysporum* f. sp. *vasinfectum* | *P. oryzae* | *A. alternata* | *A .brassicae* | *F. graminearum* | *B. sorokinianum* | *F. oxysporum* f. sp. *cucumarinum* |
| **5a** | 47.83 (±0.98) | 57.80 (±0.63) | 61.45 (±2.09) | 38.84 (±1.15) | 46.34 (±0) | 66.51 (±1.15) | 33.70 (±1.26) |
| **5b** | 51.77 (±1.14) | 56.70 (±1.27) | 65.26 (±1.16) | 34.86 (±0.58) | 44.15 (±0.35) | 66.05 (±1.33) | 36.54 (±2.19) |
| **5c** | 28.57 (±1.87) | 42.31 (±2.26) | 51.06 (±2.13) | 29.98 (±2.01) | 31.36 (±1.35) | 36.89 (±2.43) | 28.01 (±0.71) |
| **5d** | 19.91 (±2.86) | 46.83 (±1.13) | 42.55 (±1.84) | 21.08 (±1.48) | 25.98 (±1.35) | 36.89 (±2.43) | 26.29 (±0.71) |
| **5e** | 41.56 (±2.16) | 72.17 (±0.65) | 70.85 (±0.61) | 49.13 (±1.12) | 48.18 (±0.67) | 72.57 (±1.85) | 44.72 (±1.23) |
| **5f** | 14.07 (±2.50) | 20.14 (±1.31) | 23.40 (±2.13) | 9.09 (±1.93) | 25.98 (±1.35) | 13.84 (±2.43) | 11.06 (±0.71) |
| **5g** | 13.04 (±2.17) | 16.27 (±2.39) | 15.16 (±1.22) | 10.43 (±0.98) | 13.34 (±0.69) | 16.98 (±2.42) | 6.55 (±1.21) |
| **5h** | 40.04 (±0.62) | 64.25 (±2.35) | 69.15 (±1.06) | 48.36 (±2.01) | 47.78 (±0.78) | 59.47 (±1.85) | 41.03 (±2.46) |
| **5i** | 40.55 (±1.50) | 58.24 (±0) | 59.24 (±2.53) | 30.88 (±1.15) | 39.02 (±0.61) | 46.19 (±1.33) | 43.54 (±0.63) |
| **5j** | 60.04 (±1.14) | 74.29 (±1.27) | 73.49 (±1.53) | 40.24 (±1.00) | 37.80 (±0.61) | 75.29 (±1.33) | 49.67 (±0) |
| **5k** | 58.27 (±1.14) | 52.31 (±1.27) | 62.85 (±1.00) | 37.85 (±1.15) | 48.78 (±1.22) | 58.43 (±0) | 37.20 (±1.26) |
| **5l** | 56.71 (±2.16) | 75.57 (±1.73) | 73.83 (±1.23) | 43.33 (±1.12) | 50.47 (±1.55) | 69.17 (±0.70) | 48.40 (±2.13) |
| **5m** | 30.74 (±1.87) | 52.04 (±1.73) | 60.64 (±1.06) | 29.98 (±0.56) | 39.43 (±1.17) | 50.24 (±1.21) | 38.57 (±2.46) |
| **5n** | 64.94 (±2.25) | 79.64 (±1.73) | 79.15 (±0.61) | 52.03 (±2.43) | 52.30 (±0.78) | 82.28 (±0.70) | 63.15 (±0) |
| **5o** | 55.63 (±1.87) | 84.84 (±0.65) | 82.98 (±0) | 56.87 (±1.48) | 46.57 (±0.67) | 80.58 (±1.21) | 57.00 (±1.23) |
| **5p** | 24.24 (±2.16) | 42.99 (±2.61) | 42.55 (±2.13) | 18.18 (±2.23) | 44.82 (±1.78) | 34.95 (±1.40) | 25.80 (±0.71) |
| **5q** | 23.16 (±1.08) | 50.68 (±1.73) | 50.64 (±1.63) | 33.27 (±0.97) | 20.59 (±1.35) | 37.62 (±3.05) | 34.89 (±1.23) |
| **5r** | 33.26 (±0.63) | 44.50 (±2.76) | 54.74 (±1.05) | 22.83 (±1.14) | 28.47 (±0.69) | 50.47 (±1.78) | 39.81 (±1.85) |
| Hym | 63.20 (±2.16) | 75.11 (±2.26) | 70.85 (±0.61) | 58.03 (±1.12) | 67.97 (±0.39) | 61.89 (±0.70) | 59.95 (±0.71) |

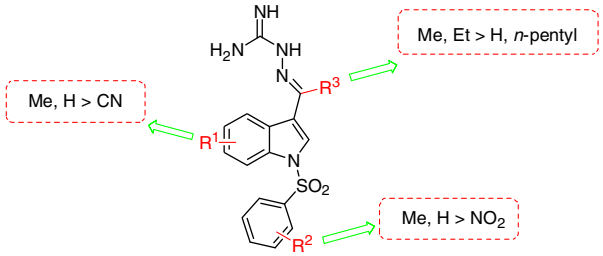


**Figure 2.** The preliminary graphical depiction of the SAR for compounds **5a–r**.

57.8%/56.7%, 61.45%/65.26%, 38.84%/34.86%, 46.34%/44.15%, 66.51%/66.05%, and 33.70%/36.54%, respectively. However, when the cyano group was introduced at 5-position on the indolyl ring of **5a** or **5b** to afford **5f** or **5g**, respectively, the inhibition rates of **5f** and **5g** against *F. oxysporum* f. sp. *vasinfectum, P. oryzae, A. alternata, A. brassicae, F. graminearum, B. sorokinianum*, and *F. oxysporum* f. sp. *cucumarinum* were 14.07%/13.04%, 20.14%/16.27%, 23.4%/15.16%, 9.09%/10.43%, 25.98%/13.34%, 13.84%/16.98%, and 11.06%/6.55%, respectively, and vice versa. (2) In general, when $R^2$ was introduced as the electron-withdrawing group, the corresponding compound exhibited less potent activities than that possessing electron-donating one (**5c** versus **5b**). For example, the inhibition rates of **5c** ($R^2$ = 3-$NO_2$) and **5b** ($R^2$ = 4-Me) against *F. oxysporum* f. sp. *vasinfectum, P. oryzae, A. alternata, A. brassicae, F. graminearum, B. sorokinianum*, and *F. oxysporum* f. sp. *cucumarinum* were 28.57%/51.77%, 42.31%/56.7%, 51.06%/65.26%, 29.98%/34.86%, 31.36%/44.15%, 36.89%/66.05%, and 28.01%/36.54%, respectively. (3) The proper length of substituent $R^3$ of **5a–r** were usually very important for their antifungal activities. For example, the inhibition rates of **5a** ($R^3$ = H) against *F. oxysporum* f. sp. *vasinfectum, P. oryzae, A. alternata, A. brassicae, F. graminearum, B. sorokinianum*, and *F. oxysporum* f. sp. *cucumarinum* were 47.83%, 57.8%, 61.45%, 38.84%, 46.34%, 66.51%, and 33.7%, respectively; the inhibition rates of **5j** ($R^3$ = Me) and **5l** ($R^2$ = Et) against *F. oxysporum* f. sp. *vasinfectum, P. oryzae, A. alternata, A. brassicae, F. graminearum, B. sorokinianum*, and *F. oxysporum* f. sp. *cucumarinum* were 60.04%/56.71%, 74.29%/75.57%, 73.49%/73.83%, 40.24%/43.33%, 37.8%/50.47%, 75.29%/69.17%, and 49.67%/48.4%, respectively; while the inhibition rates of **5m** ($R^3$ = *n*-pentyl) against *F. oxysporum* f. sp. *vasinfectum, P. oryzae, A. alternata, A. brassicae, F. graminearum, B. sorokinianum*, and *F. oxysporum* f. sp. *cucumarinum* were 30.74%, 52.04%, 60.64%, 29.98%, 39.43%, 50.24%, and 38.57%, respectively. The same results were also found between **5d** and **5n**, and between **5e** and **5o**.

Finally, according to the above SAR study, the preliminary graphical depiction of the SAR for the antifungal activities of **5a–r** was summarized in Figure 2.

In conclusion, 18 aminoguanidine derivatives of *N*-arylsulfonyl-3-acylindoles (including 16 new compounds) were prepared and bioevaluated in vitro as antifungal agents against seven phytopathogenic fungi. Especially compounds **5n** and **5o** showed more potent antifungal activities than or comparable to hymexazol, a commercially available agricultural fungicide at 100 μg/mL. Preliminary SAR study indicated that introduction of electron-donating substituents $R^1$ and $R^2$, and the proper length of substituent $R^3$ were very usually important for their antifungal activities.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.10.084.

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11. *Spectra data for* **5a**: White solid, mp 186–188 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.49 (s, 1H), 8.36–8.40 (m, 2H), 8.03 (d, $J$ = 8 Hz, 2H), 7.96 (d, $J$ = 8 Hz, 1H), 7.71 (t, $J$ = 7.6 Hz, 1H), 7.61 (t, $J$ = 7.6 Hz, 2H), 7.43 (t, $J$ = 7.6 Hz, 1H), 7.33 (t, $J$ = 7.6 Hz, 1H); ESI-MS $m/z$ 342 ([M+H]$^+$, 100); HRMS-ESI: Calcd for $C_{16}H_{16}N_5O_2S$ [M+H]$^+$: 342.1019. Found: 342.1010. **5b**: White solid, mp 138–140 °C (lit. [8a] not reported); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.34–8.38 (m, 3H), 7.89–7.96 (m, 3H), 7.40–7.45 (m, 3H), 7.32 (t, $J$ = 7.6 Hz, 1H), 2.32 (s, 3H, $CH_3$); ESI-MS $m/z$ 356 ([M+H]$^+$, 100). **5c**: Yellow solid, mp 148–150 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.68 (s, 1H), 8.58 (s, 1H), 8.50–8.54 (m, 2H), 8.37–8.39 (m, 2H), 8.02 (d, $J$ = 8 Hz, 1H), 7.91 (t, $J$ = 8 Hz, 1H), 7.47 (t, $J$ = 7.6 Hz, 1H), 7.36–7.40 (m, 1H); ESI-MS $m/z$ 387 ([M+H]$^+$, 100); HRMS-ESI: Calcd for $C_{16}H_{15}N_6O_4S$ [M+H]$^+$: 387.0870. Found: 387.0864. **5d**: White solid, mp 136–138 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.58–8.60 (m, 2H), 8.01 (d, $J$ = 7.6 Hz, 2H), 7.82 (d, $J$ = 8.4 Hz, 1H), 7.71–7.73 (m, 1H), 7.61 (t, $J$ = 7.6 Hz, 2H), 7.25 (t, $J$ = 7.6 Hz, 1H), 7.09 (d, $J$ = 7.2 Hz, 1H), 2.57 (s, 3H, $CH_3$); ESI-MS $m/z$ 356 ([M+H]$^+$, 100); HRMS-ESI: Calcd for $C_{17}H_{18}N_5O_2S$ [M+H]$^+$: 356.1176. Found: 356.1170. **5e**: White solid, mp 154–155 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.63–8.67 (m, 2H), 7.89 (d, $J$ = 8 Hz, 2H), 7.80 (d, $J$ = 8.4 Hz, 1H), 7.41 (d, $J$ = 8.4 Hz, 2H), 7.25 (t, $J$ = 7.6 Hz, 1H), 7.09 (d, $J$ = 7.2 Hz, 1H), 2.57 (s, 3H, $CH_3$), 2.32 (s, 3H, $CH_3$); ESI-MS $m/z$ 370 ([M+H]$^+$, 100); HRMS-ESI: Calcd for $C_{18}H_{20}N_5O_2S$ [M+H]$^+$: 370.1332. Found: 370.1339. **5f**: White solid, mp 165–166 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.81 (s, 1H), 8.51 (s, 1H), 8.30 (s, 1H), 8.12 (d, $J$ = 9.2 Hz, 1H), 8.06 (d, $J$ = 8 Hz, 2H), 7.82–7.84 (m, 1H), 7.76–7.81 (m, 1H), 7.62 (t, $J$ = 7.6 Hz, 2H); ESI-MS $m/z$ 367 ([M+H]$^+$, 100); HRMS-ESI: Calcd for $C_{17}H_{15}N_6O_2S$ [M+H]$^+$: 367.0972. Found: 367.0966. **5g**: White solid, mp 164–166 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.81 (s, 1H), 8.48 (s, 1H), 8.31 (s, 1H), 8.11 (d, $J$ = 8.8 Hz, 1H), 7.94 (d, $J$ = 8 Hz, 2H), 7.81 (d, $J$ = 9.2 Hz, 1H), 7.43 (d, $J$ = 8 Hz, 2H), 2.34 (s, 3H, $CH_3$); ESI-MS $m/z$ 381 ([M+H]$^+$, 100); HRMS-ESI: Calcd for $C_{18}H_{17}N_6O_2S$ [M+H]$^+$: 381.1128. Found: 381.1137. **5h**: White solid, mp 190–192 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$: 8.37 (s, 1H), 8.35 (s, 1H), 8.21 (d, $J$ = 8 Hz, 1H), 8.03 (d, $J$ = 7.5 Hz, 2H), 7.78 (s, 1H), 7.72 (t, $J$ = 7.5 Hz, 1H), 7.62 (t, $J$ = 7.5 Hz, 2H), 7.17 (d, $J$ = 8.5 Hz, 1H), 2.47 (s, 3H, $CH_3$); ESI-MS $m/z$ 356 ([M+H]$^+$, 100); HRMS-ESI: Calcd for $C_{17}H_{18}N_5O_2S$ [M+H]$^+$: 356.1176. Found: 356.1181. **5i**: White solid, mp 159–161 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.29–8.31 (m, 2H), 8.20 (d, $J$ = 8 Hz, 1H), 7.90 (d, $J$ = 8.4 Hz, 2H), 7.76 (s, 1H), 7.40 (d, $J$ = 8 Hz, 2H), 7.15 (d, $J$ = 8.4 Hz, 1H), 2.46 (s, 3H, $CH_3$), 2.32 (s, 3H, $CH_3$); ESI-MS $m/z$ 370 ([M+H]$^+$, 100); HRMS-ESI: Calcd for $C_{18}H_{20}N_5O_2S$ [M+H]$^+$: 370.1332. Found: 370.1337. **5j**: White solid, mp 148–150 °C (lit. [8a,8b] not reported); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.42 (s, 1H), 8.27 (d, $J$ = 7.6 Hz, 1H), 8.07 (d, $J$ = 7.6 Hz, 2H), 7.96 (d, $J$ = 8 Hz, 1H), 7.70–7.74 (m, 1H), 7.60 (t, $J$ = 7.6 Hz, 2H), 7.40–7.44 (m, 1H), 7.31 (t, $J$ = 7.6 Hz, 1H), 2.45 (s, 3H, $CH_3$); ESI-MS $m/z$ 356 ([M+H]$^+$, 100). **5k**: White solid, mp 188–190 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.40 (s, 1H), 8.27 (d, $J$ = 7.6 Hz, 1H), 7.95–7.97 (m, 3H), 7.74 (s, 1H, NH), 7.40–7.43 (m, 3H), 7.30–7.34 (m, 1H), 2.46 (s, 3H, $CH_3$), 2.32 (s, 3H, $CH_3$); ESI-MS $m/z$ 370 ([M+H]$^+$, 100); HRMS-ESI: Calcd for $C_{18}H_{20}N_5O_2S$ [M+H]$^+$: 370.1332. Found: 370.1324. **5l**: White solid, mp 122–124 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.39 (s, 1H), 8.23 (d, $J$ = 7.6 Hz, 1H), 8.07 (d, $J$ = 8 Hz, 2H), 7.97 (d, $J$ = 8.4 Hz, 1H), 7.69 (t, $J$ = 7.6 Hz, 1H), 7.59 (t, $J$ = 7.6 Hz, 2H), 7.40 (t, $J$ = 7.6 Hz, 1H), 7.30–7.34 (m, 1H), 2.91–2.94 (m, 2H, $CH_2$), 1.11 (t, $J$ = 7.6 Hz,

3H, $CH_3$); ESI-MS *m*/*z* 370 ([M+H]$^+$, 100); HRMS-ESI: Calcd for $C_{18}H_{20}N_5O_2S$ [M+H]$^+$: 370.1332. Found: 370.1328. **5m**: White solid, mp 108–110 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.38 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 7.2 Hz, 2H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.69 (t, *J* = 7.2 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.31–7.35 (m, 1H), 2.94–2.96 (m, 2H, $CH_2(CH_2)_3CH_3$), 1.27–1.52 (m, 6H, $CH_2(CH_2)_3CH_3$), 0.82 (t, *J* = 7.2 Hz, 3H, $(CH_2)_4CH_3$); ESI-MS *m*/*z* 412 ([M+H]$^+$, 100); HRMS-ESI: Calcd for $C_{21}H_{26}N_5O_2S$ [M+H]$^+$: 412.1802. Found: 412.1798. **5n**: White solid, mp 140–142 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$: 8.04–8.10 (m, 3H), 7.80–7.83 (m, 1H), 7.71–7.76 (m, 1H), 7.61–7.67 (m, 2H), 7.26–7.32 (m, 1H), 7.07–7.09 (m, 1H), 2.35–2.41 (m, 4.4H, $CH_3$), 2.26 (s, 1.6H, $CH_3$); ESI-MS *m*/*z* 370 ([M+H]$^+$, 100); HRMS-ESI: Calcd for $C_{18}H_{20}N_5O_2S$ [M+H]$^+$: 370.1332. Found: 370.1335. **5o**: White solid, mp 153–155 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$: 8.08 (s, 0.58H), 8.06 (s, 0.42H), 7.92–7.97 (m, 2H), 7.79–7.81 (m, 1H), 7.61 (s, 0.42H, NH), 7.41–7.45 (m, 2H), 7.25–7.31 (m, 1H), 7.06–7.08 (m, 1H), 2.33–2.39 (m, 7.4H, $CH_3$), 2.26 (s, 1.6H, $CH_3$); ESI-MS *m*/*z* 384 ([M+H]$^+$, 100); HRMS-ESI: Calcd for $C_{19}H_{22}N_5O_2S$ [M+H]$^+$: 384.1489. Found: 384.1497. **5p**: White solid, mp 172–174 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.29 (s, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.77 (s, 1H), 7.10-7.15 (m, 3H), 3.79 (s, 3H, $OCH_3$), 2.45 (s, 3H, $CH_3$), 2.41 (s, 3H, $CH_3$); ESI-MS *m*/*z* 400 ([M+H]$^+$, 100); HRMS-ESI: Calcd for $C_{19}H_{22}N_5O_3S$[M+H]$^+$: 400.1438. Found: 400.1447. **5q**: Yellow solid, mp 155–156 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.75 (s, 1H), 8.50–8.55 (m, 2H), 8.38 (s, 1H), 8.15 (d, *J* = 8 Hz, 1H), 7.89–7.93 (m, 1H), 7.83 (s, 1H), 7.48 (s, 1H, NH), 7.16 (d, *J* = 8.4 Hz, 1H), 2.47 (s, 3H, $CH_3$), 2.42 (s, 3H, $CH_3$); ESI-MS *m*/*z* 415 ([M+H]$^+$, 100); HRMS-ESI: Calcd for $C_{18}H_{19}N_6O_4S$ [M+H]$^+$: 415.1183. Found: 415.1175. **5r**: White solid, mp 120–122 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$: 8.23 (s, 1H), 8.05 (d, *J* = 8 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.77 (s, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8 Hz, 1H), 2.88 (t, *J* = 7.5 Hz, 2H, $CH_2(CH_2)_3CH_3$), 2.45 (s, 3H, $CH_3$), 2.31 (s, 3H, $CH_3$), 1.27–1.50 (m, 6H, $CH_2(CH_2)_3CH_3$), 0.83 (t, *J* = 7 Hz, 3H, $(CH_2)_4CH_3$); ESI-MS *m*/*z* 440 ([M+H]$^+$, 100); HRMS-ESI: Calcd for $C_{23}H_{30}N_5O_2S$ [M+H]$^+$: 440.2115. Found: 440.2105.

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