Triflic acid-mediated N-heteroannulation of β-anilino-β-(methylthio) acrylonitriles: A facile synthesis of 4-amino-2-(methylthio)quinolines

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Experimental Section

General Information

All reactions were performed by using the standard vial technique with a rubber septum. All solids were weighed in air. Triflic acid, TFA, AcOH, sodium hydride, Aldrich, Merck, TCI, Spectrochem, and Alfa-Aesar were used as received. Dried DMF, DMSO, Toluene and DCM were used. Isothiocyanates were synthesized from respective anilines, and few isothiocyanates were purchased from Aldrich. All other reagents were purchased from common suppliers and used without further purification. Flash chromatography was performed using Merck Silica gel (230-400 mesh). Fractions were monitored by thin-layer chromatography on precoated silica gel 60 F\textsubscript{254} plates (Merck & co.) and were visualized by UV. NMR data were recorded on Bruker ARX 400 and 700 spectrometers. \textsuperscript{13}C and \textsuperscript{1}H NMR spectra were recorded in CDCl\textsubscript{3} and DMSO-d\textsubscript{6} referenced according to signals of deutero solvents. ESI HR-MS measurements were performed on Bruker microTOF-Q-II mass-spectrometer. The X-ray quality crystals for the compound 4o were grown by slow diffusion of n-hexane over CH\textsubscript{2}Cl\textsubscript{2} solution. Single-crystal X-ray diffraction data of 4o were collected on a Rigaku SuperNova fine-focused dual diffractometer, with Cu Ka radiation ($\lambda = 1.54178$ Å) equipped with a PILATUS200K detector. Using Olex2, the structure 4o was solved with ShelXS structure solution program using Direct Methods and refined with the ShelXL refinement package using Least Squares minimization. All non-hydrogen atoms were refined with anisotropic displacement coefficients. The H atoms were placed at calculated positions and were refined as riding atoms.
Scheme S1. Synthesis of $\beta$-anilino acrylonitriles 3a-p

$$R\_\text{CN} + \text{ArNCS} \xrightarrow{\text{NaH (2.2 equiv)}} R\_\text{CN}$$

$R = \text{CN, CO}_2\text{Et, COPh}$

$\text{MeS} - \text{NHAr}$

4 - 5 h

$\text{DMF, 0 °C - rt}$

- **3a**, $R = \text{H}, 57%$
- **3b**, $R = \text{Me}, 64%$
- **3c**, $R = \text{Cl}, 89%$
- **3d**, $R = \text{Me}, 64%$
- **3e**, $R = \text{Cl}, 54%$
- **3f**, $R = \text{NO}_2, 69%$
- **3g**, $R = \text{Cl}, 88%$
- **3h**, $R = \text{Me}, 71%$
- **3i**, $R = \text{OMe}, 78%$
- **3j**, 50%
- **3k**, 63%
- **3l**, 56%
- **3m**, 40%
- **3n**, 30%
- **3o**, 29%

**General Procedure for the Synthesis of $\beta$-anilino acrylonitriles 3a-o and 5a-f**

To a stirring suspension of sodium hydride (13.2 mmol, 2.2 equiv) in DMF, a solution of aryl cyanides/substituted dicyanides (6 mmol, 1 equiv) in DMF was added dropwise at 0 °C. After being further stirred for 1 h at room temperature, a solution of isothiocyanates (6.6 mmol, 1.1 equiv) in DMF was added to the reaction mixture at 0 °C and followed by further stirring for 2 – 3 h at room temperature. Then a solution of methyl iodide (6.6 mmol, 1.1 equiv) in DMF was added and left for 30 min stirring at room temperature. After complete consumption of the starting materials (monitored by TLC), the reaction mixture was quenched with saturated
NH₄Cl solution and extracted with EtOAc. The combined organic layer washed with water (3 x 25 mL) and brine (25 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude products were purified by flash chromatography using hexane and EtOAc as eluent.

3-Anilino-2-cyano-3-(methylthio)acrylonitrile (3a)

Yield: 57% (0.736 g), pale yellow solid; Rf: 0.15 in 20% ethyl acetate in hexanes; mp: 164 – 166 °C; IR (KBr, ν cm⁻¹) = 3678, 3289, 2999, 2367, 2201, 1594, 1450, 1297, 1079, 762, 494; ¹H NMR (400 MHz, DMSO-d₆) δ 10.56 (s, 1H), 7.42 (m, 2H), 7.28 (m, 3H), 2.52 (s, 3H). ¹³C NMR (100 MHz, DMSO-d₆) δ 171.6, 138.4, 129.3 (2C), 126.7, 123.9 (2C), 52.9, 15.8. HR-MS (ESI-TOF) m/z: cal. for C₁₁H₉N₃S [M+H]⁺: 216.0590, found: 216.0589.

2-Cyano-3-(2-methyl)anilino-3-(methylthio)acrylonitrile (3b)

Yield: 64% (0.880 g), pale yellow solid; Rf: 0.37 in 30% ethyl acetate in hexanes; mp: 129 – 131 °C; IR (KBr, ν cm⁻¹) = 3735, 3569, 3237, 2362, 2330, 2209, 1512, 1267, 1116, 757, 449. ¹H NMR (400 MHz, DMSO-d₆) δ 10.22 (s, 1H), 7.34 – 7.21 (m, 4H), 2.62 (s, 3H), 2.22 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 173.8, 135.8, 134.4, 131.4, 128.8, 127.2, 126.7, 115.3, 114.1, 55.0, 18.0, 16.5. HR-MS (ESI-TOF) m/z for C₁₂H₁₁N₃S [M+H]⁺: 230.0746, found: 230.0752.

3-(2-Chloro)anilino-2-cyano-3-(methylthio)acrylonitrile (3c)

Yield: 89% (1.330 g), white solid; Rf: 0.17 in 20% ethyl acetate in hexanes; mp: 158 – 160 °C; IR (KBr, ν cm⁻¹) = 3737, 3217, 3011, 2357, 2214, 1654, 1480, 1294, 1061, 762, 447. ¹H NMR (400 MHz, DMSO-d₆) δ 10.52 (s, 1H), 7.65 - 7.54 (m, 1H), 7.53 – 7.46 (m, 1H), 7.45 – 7.35 (m, 2H), 2.66 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 172.8, 134.4, 130.6, 129.62, 129.18, 128.1, 126.6, 114.2,
113.5, 59.7, 16.9. HR-MS (ESI-TOF) cal. for C\textsubscript{11}H\textsubscript{8}ClN\textsubscript{3}S [M+H]\(^+\): 250.0200, found: 250.0181.

2-Cyano-3-(4-methyl)anilino-3-(methylthio)acrylonitrile (3d)\(^4\)

Yield: 64% (0.880 g), pale yellow solid; \(R_f\): 0.13 in 20% ethyl acetate in hexanes; mp: 165 – 167 °C; IR (KBr, \(\nu\) cm\(^{-1}\)) = 3658, 3242, 3036, 2350, 2253, 1594, 1423, 1297, 965, 759, 489; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 10.31 (s, 1H), 7.02 (m, 4H), 2.32 (s, 3H), 2.12 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 172.8, 137.9, 134.7, 130.4, 124.3, 115.1, 114.6, 56.6, 21.2, 16.9. HR-MS (ESI-TOF) m/z cal. for C\textsubscript{12}H\textsubscript{11}N\textsubscript{3}S [M+H]\(^+\): 230.0746, found: 230.0732

3-(4-Chloro)anilino-2-cyano-3-(methylthio)acrylonitrile (3e)\(^4\)

Yield: 54% (0.809 g), white solid; \(R_f\): 0.12 in 20% ethyl acetate in hexanes; mp: 162 – 164 °C; IR (KBr, \(\nu\) cm\(^{-1}\)) = 3849, 3651, 3210, 3001, 2357, 2211, 1488, 1277, 1091, 769, 501. \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 10.57 (s, 1H), 7.48 (d, \(J = 8.8\) Hz, 2H), 7.33 (d, \(J = 8.8\) Hz, 2H), 2.55 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 172.6, 135.9, 133.4, 130.0, 125.5, 114.51, 114.34, 58.3, 17.0. HR-MS (ESI-TOF) m/z cal. for C\textsubscript{11}H\textsubscript{8}ClN\textsubscript{3}S [M+H]\(^+\): 250.0200, found: 250.0218.

2-Cyano-3-methylthio-3-(4-nitro)anilinoacrylonitrile (3f)\(^7\)

Yield: 69% (1.080 g), orange solid; \(R_f\): 0.17 in 50% ethyl acetate in hexanes; mp: 149 – 151 °C; IR (KBr, \(\nu\) cm\(^{-1}\)) = 3745, 3252, 3009, 2925, 2367, 2216, 1597, 1260, 767, 439; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) = 10.95 (s, 1H), 8.27 (d, \(J = 8.8\) Hz, 2H), 7.52 (d, \(J = 8.8\) Hz, 2H), 2.55 (s, 3H). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) = 172.3, 145.0, 143.9, 125.0 (2C), 122.7 (2C), 57.4, 16.1. HR-MS (ESI-TOF) m/z cal. for C\textsubscript{11}H\textsubscript{8}N\textsubscript{4}O\textsubscript{2}S [M+Na]\(^+\): 283.0260, found: 283.0265.
2-Cyano-3-(4-methoxy)anilino-3-(methylthio)acrylonitrile (3g)

Yield: 90% (1.320 g), pale yellow solid; Rf: 0.30 in 30% ethyl acetate in hexanes; mp: 153 – 155 °C; IR (KBr, ν cm⁻¹) = 3849, 3628, 3239, 2843, 2357, 2209, 1609, 1438, 1252, 829, 516; ¹H NMR (400 MHz, CDCl₃) δ 8.16 (s, 1H), 7.17 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H), 2.28 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 173.1, 159.1, 129.8, 126.3, 115.1, 114.9, 114.7, 56.0, 55.7, 16.9. HR-MS (ESI) Calcd for C₁₂H₁₁N₃OS [M+H]⁺: 246.0696, found: 246.0704

3-(3-Chloro)anilino-2-cyano-3-(methylthio)acrylonitrile (3h)

Yield: 88% (1.320 g), white solid; Rf: 0.20 in 20% ethyl acetate in hexanes; mp: 150 -152 °C; IR (KBr, ν cm⁻¹) = 3784, 3668, 3224, 2360, 2243, 1557, 1497, 1297, 1061, 762, 529; ¹H NMR (400 MHz, DMSO-d₆) δ 10.59 (s, 1H), 7.48 – 7.37 (m, 2H), 7.35 – 7.24 (m, 2H), 2.55 (s, 3H). ¹³C NMR (100 MHz, DMSO-d₆) δ 171.9, 139.9, 133.4, 130.7 (2C), 126.3, 123.5 (2C), 122.4, 54.2, 15.9. HR-MS (ESI-TOF) m/z cal for C₁₁H₇ClN₃S [M+H]⁺: 250.0200, found: 250.0181

2-Cyano-3-methylthio-3-(3-methoxy)anilinoacrylonitrile (3i)

Yield: 78% (1.150 g), white solid; Rf: 0.25 in 30% ethyl acetate in hexanes; mp: 142 – 144 °C; IR (KBr, ν cm⁻¹) = 3851, 3651, 3232, 2939, 2360, 2332, 2215, 1609, 1490, 1151, 1039, 670; ¹H NMR (400 MHz, DMSO-d₆) δ = 10.54 (s, 1H), 7.31 (t, J = 8.4 Hz, 1H), 6.91 – 6.78 (m, 3H), 3.76 (s, 3H), 2.52 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ = 172.6, 160.6, 138.4, 130.5, 116.2, 114.9, 114.5, 113.0, 109.9, 57.4, 55.6, 16.8. HR-MS (ESI-TOF) m/z cal for C₁₁H₁₁N₃OS [M+Na]⁺: 268.0515, found: 268.0518.
2-Cyano-3-(3-methyl)anilino-3-(methylthio)acrylonitrile (3j)\textsuperscript{4}

![Chemical Structure]

Yield: 71% (0.977 g), white solid; R\textsubscript{f}: 0.15 in 20% ethyl acetate in hexanes; mp: 109 – 111 °C; IR (KBr, ν cm\textsuperscript{-1}) = 3737, 3237, 3006, 2367, 2206, 1510, 1279, 767, 432.\textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}) δ 10.51 (s, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.16 – 7.02 (m, 3H), 2.52 (s, 3H), 2.32 (s, 3H).\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 172.6, 139.9, 137.2, 129.4, 128.3, 124.6, 121.1, 115.2, 114.5, 56.4, 21.4, 16.7. HR-MS (ESI-TOF) m/z cal. for C\textsubscript{12}H\textsubscript{11}N\textsubscript{3}S [M+H]\textsuperscript{+}: 230.0746, found: 230.0740.

2-Cyano-3-(3,5-dimethyl)anilino-3-(methylthio)acrylonitrile (3k)

![Chemical Structure]

Yield: 50% (0.730 g), white solid; R\textsubscript{f}: 0.12 in 20% ethyl acetate in hexanes; mp: 164 – 166 °C; IR (KBr, ν cm\textsuperscript{-1}) = 3658, 3269, 3011, 2350, 2221, 1567, 1279, 764, 489; \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}) δ = 10.43 (s, 1H), 6.90 (s, 3H), 2.52 (s, 3H), 2.27 (s, 6H).\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ = 172.6, 139.8, 137.0, 129.5, 122.0, 114.92, 114.45, 57.2, 21.4, 17.0. HR-MS (ESI-TOF) m/z cal. for C\textsubscript{13}H\textsubscript{13}N\textsubscript{3}S [M+Na]\textsuperscript{+}: 266.0722, found: 266.0736

Ethyl 3-anilino-3-(methylthio)acrylonitrile-2-carboxylate (3l)\textsuperscript{4}

![Chemical Structure]

Yield: 63% (0.991 g), white solid; R\textsubscript{f}: 0.30 in 20% ethyl acetate in hexanes; mp: 82 – 84 °C; IR (KBr, ν cm\textsuperscript{-1}) = 3490, 3167, 2982, 2362, 2204, 1661, 1594, 1260, 1029, 767, 519; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 11.51 (s, 1H), 7.44 – 7.37 (m, 2H), 7.31 - 7.27 (m, 3H), 4.27 (q, J = 7.2 Hz, 2H), 2.24 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H).\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 170.2, 167.9, 137.7, 129.5, 127.3, 124.9, 117.7, 77.6, 61.3, 17.3, 14.4. HR-MS (ESI-TOF) m/z cal. for C\textsubscript{13}H\textsubscript{14}N\textsubscript{2}O\textsubscript{2}S [M+H]\textsuperscript{+}: 263.0849, found: 263.0848
Ethyl 3-methylthio-3-(3-methoxy)anilinoacrylonitrile-2-carboxylate (3m)

Yield: 56% (0.982 g), white solid; Rf: 0.17 in 20% ethyl acetate in hexanes; mp: 117 – 119 °C; IR (KBr, ν cm⁻¹) = 3690, 3009, 2984, 2318, 2204, 1552, 1374, 1262, 764; ¹H NMR (400 MHz, CDCl₃) δ 11.45 (s, 1H), 7.28 (t, J = 8.4 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.85 – 6.78 (m, 2H), 4.25 (q, J = 7.2 Hz, 2H), 3.80 (s, 3H), 2.25 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 170.2, 167.9, 160.4, 138.8, 130.3, 117.7, 117.0, 112.8, 110.5, 77.7, 61.3, 55.6, 17.4, 14.4. HR-MS (ESI-TOF) m/z cal. for C₁₄H₁₆N₂O₃S [M+Na]⁺: 315.0774, found: 315.0762.

Ethyl 3-(3,5-dimethyl)anilino-3-(methylthio)acrylonitrile-2-carboxylate (3n)

Yield: 40% (0.700 g), white solid; Rf: 0.40 in 20% ethyl acetate in hexanes; mp: 135 – 137 °C; IR (KBr, ν cm⁻¹) = 3735, 3063, 2996, 2362, 2209, 1649, 1379, 1257, 1039, 858, 516; ¹H NMR (400 MHz, DMSO-d₆) δ 10.96 (s, 1H), 6.97 (s, 2H), 6.92 (s, 1H), 4.13 (q, J = 7.2 Hz, 2H), 2.27 (s, 6H), 2.24 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H). ¹³C NMR (100 MHz, DMSO-d₆) δ 169.8, 165.8, 138.6, 138.2, 128.0, 121.5, 117.7, 76.2, 60.5, 20.8, 16.6, 14.2. HR-MS (ESI-TOF) m/z cal. for C₁₅H₁₈N₂O₂S [M+Na]⁺: 313.0981, found: 313.1013

3-Anilino-2-benzoyl-3-(methylthio)acrylonitrile (3o)

Yield: 30% (0.530 g), yellow jelly; Rf: 0.30 in 20% ethyl acetate in hexanes; IR (KBr, ν cm⁻¹) = 3849, 3730, 3009, 2280, 2199, 1733, 1589, 1450, 1374, 1277, 757, 420; ¹H NMR (400 MHz, DMSO-d₆) δ 12.90 (s, 1H), 7.74 – 7.68 (m, 2H), 7.59 - 7.51 (m, 1H), 7.51 – 7.45 (m, 3H), 7.44 - 7.39 (m, 3H), 7.35 – 7.29 (m, 1H), 2.34 (s, 3H). ¹³C NMR (100 MHz, DMSO-d₆) δ 190.2, 172.4, 138.5, 137.9, 131.7, 129.5, 128.17, 128.04, 127.1, 124.4, 119.9, 85.1, 16.9. HR-MS (ESI-TOF) m/z cal. for C₁₇H₁₄N₂OS [M+H]⁺: 295.0900, found: 295.0892
2-Benzoyl-3-(3,5-dimethyl)anilino-3-(methylthio)acrylonitrile (3p)

Yield: 29% (0.560 g), yellow solid; Rf: 0.37 in 20% ethyl acetate in hexanes; mp: 139 – 141 °C; IR (KBr, ν cm\(^{-1}\)) = 3680, 2999, 2974, 2315, 1760, 1572, 1460, 1374, 1272, 769, 412; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) δ 12.95 (s, 1H), 7.80 - 7.63 (m, 2H), 7.60 - 7.40 (m, 3H), 7.01 (s, 2H), 6.96 (s, 1H), 2.38 (s, 3H), 2.28 (s, 6H). \(^13\)C NMR (100 MHz, DMSO-\(d_6\)) δ 190.7, 172.8, 139.3, 139.0, 138.1, 132.0, 129.1, 128.6, 128.4, 122.3, 120.3, 85.3, 21.2, 17.5. HR-MS (ESI-TOF) m/z cal. for C\(_{19}\)H\(_{18}\)N\(_2\)OS [M+H]\(^+\): 323.1213, found: 323.1220

Procedure for Synthesis of 2-(ethoxymethylene)malonitrile

\[
\text{NC} = \text{CN} + \text{EtO} = \text{EtO} \xrightarrow{\text{Ac}_2\text{O}} \text{NC} \rightarrow \text{OEt} \quad 130 ^\circ \text{C, 24 h} \quad 50%
\]

An equimolar amount of malonitrile (20 mmol, 1 equiv) and triethyorthoformate (20 mmol, 1 equiv) were heated at 130 °C in Ac\(_2\)O (30 ml) for 24 h to ensure complete conversion. After completion of the reaction, acetic anhydride was evaporated under reduced pressure, and the crude product was purified by column chromatography using column chloroform as eluent. Yield: 50%; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.65 (s, 1H), 4.39 (q, \(J = 7.2\) Hz, 2H), 1.44 (t, \(J = 7.2\) Hz, 3H). \(^13\)C NMR (100 MHz, CDCl\(_3\)) δ 174.3, 112.2, 110.0, 75.1, 67.0, 15.2.

Procedure for Synthesis of 2-(phenylamino)methylene malononitrile 3q

\[
\text{NC} = \text{CN} + \text{EtO} = \text{EtO} + \text{NH}_2 \rightarrow \text{EtOH} \quad \text{rt, 1 h} \quad 78%
\]

To a saturated solution of 2-(ethoxymethylene)malononitrile (6 mmol, 1 equiv) in ethanol (20 ml), aniline (7.2 mmol, 1.2 equiv) was added under stirring. After 1 h, the resulting
precipitate was filtered and washed with ethanol and diethyl ether. The product was not purified further used as such for the next step. Yield: 78%; $^1$H NMR (700 MHz, DMSO-d$_6$) $\delta$ 11.11 (s, 1H), 8.49 (s, 1H), 7.43 (d, $J = 8.4$ Hz, 2H), 7.37 (t, $J = 8.4$ Hz, 2H), 7.17 (t, $J = 7.7$ Hz, 1H).

$^{13}$C NMR (175 MHz, DMSO-d$_6$) $\delta$ 155.8, 139.2, 129.4, 125.2, 118.0, 116.5, 114.2, 51.8. HR-MS (ESI-TOF) m/z: cal. for C$_{10}$H$_7$N$_3$ [M+H]$^+$: 170.0713, found: 170.0708

**General Procedure for optimization of β-anilino acrylonitrile 3a$^{13}$**

An oven-dried sealed tube was charged with the respective β-anilino acrylonitrile (0.5 mmol) 3a, acid (mmol), in solvent (2.0 mL). The mixture was stirred at room temperature or 60 °C for 6 – 24 h. The reaction mixture was monitored by TLC. After the starting material was completely consumed, the reaction mixture was quenched with saturated NaHCO$_3$ solution and extracted with EtOAc. The combined organic layer washed with water (3 x 25 mL) and brine (25 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography using hexane and EtOAc as eluent.

**References:**


**Crystal Data** for 4m in CH$_2$Cl$_2$/n-hexane: C$_{15}$H$_{18}$N$_2$O$_2$S, Mw = 290.37, monoclinic, space group P 1 21/c 1, a = 9.3141(1) Å, b = 7. 60332(10) Å, c = 20.7811(2) Å, $\alpha$ = 90 °, $\beta$ = 93.9407(9) °, $\gamma$ = 90 °, V = 1468.20(3) Å$^3$, Z = 4, $D_{calc}$ = 1.314 g/cm$^3$, T = 297 K, R1 = 0.0414(2769), wR2 = 0.1186(2960), GOF = 1.038
$^1$H Spectrum of 3a in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 3a in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 3b in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 3b in CDCl$_3$ (100 MHz)
$^1$H Spectrum of 3c in DMSO-$d_6$ (400 MHz)

$^{13}$C Spectrum of 3c in CDCl$_3$ (100 MHz)
$^1$H Spectrum of 3d in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 3d in CDCl$_3$ (100 MHz)
$^1$H Spectrum of 3e in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 3e in CDCl$_3$ (100 MHz)
$^1$H Spectrum of 3f in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 3f in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 3g in CDCl$_3$ (400 MHz)

$^{13}$C Spectrum of 3g in CDCl$_3$ (400 MHz)
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$^{13}$C Spectrum of 3h in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 3i in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 3i in CDCl$_3$ (100 MHz)
$^1$H Spectrum of 3j in DMSO-$d_6$ (400 MHz)

$^{13}$C Spectrum of 3j in CDCl$_3$ (100 MHz)
$^1$H Spectrum of 3k in DMSO-$d_6$ (400 MHz)

$^{13}$C Spectrum of 3k in CDCl$_3$ (100 MHz)
$^1$H Spectrum of 3l in CDCl$_3$ (400 MHz)

$^{13}$C Spectrum of 3l in CDCl$_3$ (100 MHz)
$^1$H Spectrum of 3m in CDCl$_3$ (400 MHz)

$^{13}$C Spectrum of 3m in CDCl$_3$ (100 MHz)
$^1$H Spectrum of 3n in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 3n in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 3o in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 3o in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 3p in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 3p in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 3r in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 3r in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 5a in DMSO-$d_6$ (400 MHz)

$^{13}$C Spectrum of 5a in DMSO-$d_6$ (100 MHz)
$^1$H Spectrum of 5b in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 5b in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 5c in CDCl$_3$ (400 MHz)

$^{13}$C Spectrum of 5c in CDCl$_3$ (100 MHz)
$^1$H Spectrum of 5d in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 5d in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 5e in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 5e in DMSO-d$_6$ (400 MHz)
$^{1}$H Spectrum of 4a in DMSO-$d_6$ (400 MHz)

$^{13}$C Spectrum of 4a in DMSO-$d_6$ (100 MHz)
$^1$H Spectrum of 4b in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 4b in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 4c in DMSO-$d_6$ (400 MHz)

$^{13}$C Spectrum of 4c in DMSO-$d_6$ (100 MHz)
$^1$H Spectrum of 4d in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 4d in DMSO-d$_6$ (400 MHz)
$^1$H Spectrum of 4e in DMSO-d$_6$ (400 MHz)

$^1$H Spectrum of 4e in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 4h in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 4h in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 4i in DMSO-$d_6$ (400 MHz)

$^{13}$C Spectrum of 4i in DMSO-$d_6$ (100 MHz)
$^1$H Spectrum of 4j in DMSO-$d_6$ (400 MHz)

$^{13}$C Spectrum of 4j in DMSO-$d_6$ (100 MHz)
$^1$H Spectrum of $4k$ in TFA-d (400 MHz)

$^{13}$C Spectrum of $4k$ in TFA-d (100 MHz)
$^1$H Spectrum of 4l in DMSO-$d_6$ (400 MHz)

$^{13}$H Spectrum of 4l in DMSO-$d_6$ (100 MHz)
$^1$H Spectrum of 4m in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 4m in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 4n in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 4n in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 4o in DMSO-$d_6$ (400 MHz)

$^{13}$C Spectrum of 4o in DMSO-$d_6$ (175 MHz)

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$^1$H Spectrum of $4p$ in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of $4o$ in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 6a in DMSO-$d_6$ (400 MHz)

$^{13}$C Spectrum of 6a in DMSO-$d_6$ (100 MHz)
$^1$H Spectrum of 6b in CDCl$_3$ (400 MHz)

$^{13}$C Spectrum of 6b in CDCl$_3$ (100 MHz)
$^1$H Spectrum of 6c in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 6c in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 6d in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 6d in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 6e in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 6e in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 7a in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 7a in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 7b in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 7b in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 7c in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 7c in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 7d in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 7d in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 7e in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 7e in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 8a in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 8a in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 8e in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 8e in DMSO-d$_6$ (100 MHz)
$^1$H Spectrum of 9a in DMSO-d$_6$ (400 MHz)

$^{13}$C Spectrum of 9a in DMSO-d$_6$ (100 MHz)