Asian Journal of Chemistry; Vol. 26, No. 14 (2014), 4399-4404

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.16751

Two-Step Synthesis of Some Novel Monoindolylmaleimides

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Received: 25 November 2013; *Accepted*: 16 January 2014; *Published online*: 5 July 2014; AJC-15484

Monoindolylmaleimides have been identified as potent glycogen synthase kinase-3β inhibitors. In this paper, a convenient methodology for the preparation of some new monoindolylmaleimides was developed by microwave assisted condensation of substituted monochloromaleimides with N-containing heterocycles followed by ammonolysis in good overall yield (up to 80 %). The products were characterized by ^{1}H NMR and ESI-MS.

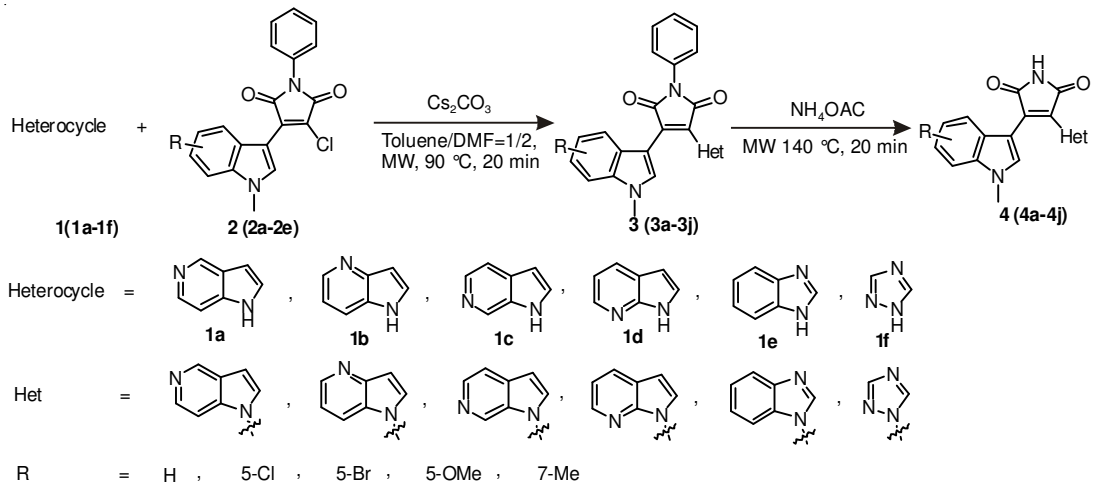
Keywords: Monindolylmaleimides, GSK-3β inhibitors, Microwave assisted condensation, Microwave assisted ammonolysis.

INTRODUCTION

Monoindolylmaleimides such as imidazo[1,2-a]pyridinylindolylmaleimides, indazolyl-indolylmaleinides and benzofuranylindolylmaleimides have been identified as potent inhibitors of Glycogen synthase kinase-3β (GSK-3β)[1-3], which are useful for the treatment of diseases such as cancer, diabetes type-2, chronic inflammatory processes, stroke, bipolar disorders and Alzheimer's disease[4-8]. These compounds were generally synthesized *via* condensation of a substituted indolyl-3-glyoxylate and a heteroaryl-3-acetamide using potassium *tert*-butoxide as a base[1-3]. In former, we have found that the traditional synthetic route was not suitable for some kinds of monoindolylmaleimides such as imidazolylindolyl-maleimides, 1,3,4-triazolylindolylmaleimides and benzisoxazolylindolylmaleimides, suffered from poor yields, rigid reaction conditions and difficulty to obtain pure products[9,10]. Here we report a convenient method to synthesize some novel monoindolylmaleimides through microwave assisted condensation and ammonolysis reaction by using substituted monochloroindolylmaleimides and N -containing heterocycles as the raw materials (**Scheme-I**).

EXPERIMENTAL

The reagents were obtained from commercial sources. DMF, MeCN were dried with CaH_2 and toluene was dried with Na. Microwave reactions were carried out using a CEM



Scheme-1

Discover instrument (CEM Corporation), in a 10 mL glass tube (CEM designed 10 mL pressure-rated reaction vial). Temperature was monitored by an infrared monitoring system. Nuclear magnetic resonance spectra were recorded on Bruker Avance III 500 MHz and chemical shifts are expressed in ppm using TMS as an internal standard. ESI (positive) was recorded on an Esquire-LC-00075 spectrometer.

General procedure for the synthesis of 3a-3j: A mixture of substituted monochloromaleimide (0.15 mmol), nitrogen-containing heterocycle (0.18 mmol), Cs_2CO_3 (0.3 mmol) and mixed solvent (3 mL, toluene/DMF =1/2, v/v) was heated by microwave irradiation at 90 °C for 20 min. After cooling, the resulted mixture was poured into water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phase was combined, washed with brine (3 × 60 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using ethyl acetate/petroleum ether (1/2, v/v) as eluent to afford compound **3a-3j**[11,12].

3-(1-Methyl-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo-[3,2-c]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (3a): Orange solid, m.p. > 250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (dd, *J* = 4.6, 1.3 Hz, 1H), 8.24 (s, 1H), 7.89 (d, *J* = 3.5 Hz, 1H), 7.60-7.52 (m, 4H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.48-7.42 (m, 2H), 7.05 (t, *J* = 7.7 Hz, 1H), 6.96-6.89 (m, 2H), 6.57 (t, *J* = 7.5 Hz, 1H), 6.00 (d, *J* = 8.1 Hz, 1H), 3.93 (s, 3H); EI-MS: 419 [M + 1]$^+$.

3-(5-Chloro-1-methyl-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-c]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (3b): Orange solid, m.p. 107-109 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.32 (dd, *J* = 4.6, 1.3 Hz, 1H), 8.25 (s, 1H), 7.90 (d, *J* = 3.5 Hz, 1H), 7.60-7.51 (m, 4H), 7.49-7.44 (m, 3H), 7.06 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.97-6.92 (m, 2H), 5.91 (d, *J* = 2.0 Hz, 1H), 3.92 (s, 3H); EI-MS: 453 [M + 1]$^+$.

3-(5-Bromo-1-methyl-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-c]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (3c): Orange solid, m.p. 103-105 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.32 (dd, *J* = 4.6, 1.3 Hz, 1H), 8.23 (s, 1H), 7.89 (d, *J* = 3.5 Hz, 1H), 7.61-7.50 (m, 4H), 7.50-7.39 (m, 3H), 7.17 (dd, *J* = 8.6, 1.6 Hz, 1H), 6.98-6.91 (m, 2H), 6.06 (d, *J* = 1.6 Hz, 1H), 3.92 (s, 3H); EI-MS: 498 [M + 1]$^+$.

3-(5-Methoxy-1-methyl-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-c]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (3d): Orange solid, m.p. 123-125 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.35 (dd, *J* = 4.6, 1.3 Hz, 1H), 8.21 (s, 1H), 7.86 (d, *J* = 3.5 Hz, 1H), 7.68-7.63 (m, 1H), 7.59-7.51 (m, 4H), 7.47-7.43 (m, 1H), 7.34 (d, *J* = 8.9 Hz, 1H), 7.03-7.00 (m, 1H), 6.88 (d, *J* = 3.5 Hz, 1H), 6.64 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.48 (d, *J* = 2.4 Hz, 1H), 3.91 (s, 3H), 2.97 (s, 3H); EI-MS: 499 [M + 1]$^+$.

3-(1,7-Dimethyl-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-c]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (3e): Red solid, m.p. 134-135 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31 (dd, *J* = 4.6, 1.3 Hz, 1H), 8.11 (s, 1H), 7.84 (d, *J* = 3.6 Hz, 1H), 7.59-7.51 (m, 5H), 7.47-7.43 (m, 1H), 6.98-6.94 (m, 1H), 6.89-6.87 (m, 1H), 6.72 (d, *J* = 7.1 Hz, 1H), 6.40 (t, *J* = 7.9 Hz, 1H), 5.88 (d, *J* = 8.0 Hz, 1H), 4.19 (s, 3H), 2.68 (s, 3H); EI-MS: 433 [M + 1]$^+$.

3-(1-Methyl-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo-[3,2-b]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (3f): Orange solid, m.p. > 250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (dd, *J* = 4.5, 1.1 Hz, 1H), 8.24 (s, 1H), 7.89 (d, *J* = 3.5 Hz, 1H), 7.61-7.52 (m, 4H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.48-7.41 (m, 2H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.97-6.87 (m, 2H), 6.57 (t, *J* = 7.5 Hz, 1H), 6.00 (d, *J* = 8.1 Hz, 1H), 3.93 (s, 3H); EI-MS: 419 [M + 1]$^+$.

3-(1-Methyl-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo-[2,3-c]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (3g): Orange solid, m.p. 162-163 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.42 (s, 1H), 8.26 (s, 1H), 8.07 (d, *J* = 5.4 Hz, 1H), 7.85 (d, *J* = 3.3 Hz, 1H), 7.61-7.52 (m, 5H), 7.49-7.42 (m, 2H), 7.04 (td, *J* = 7.6, 0.6 Hz, 1H), 6.88 (d, *J* = 3.1 Hz, 1H), 6.56 (t, *J* = 7.5 Hz, 1H), 5.97 (d, *J* = 8.1 Hz, 1H), 3.94 (s, 3H); EI-MS: 419 [M + 1]$^+$.

3-(1-Methyl-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo-[2,3-b]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (3h): Orange solid, m.p. 199-200 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.05 (dd, *J* = 7.8, 1.5 Hz, 1H), 8.00 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.74 (d, *J* = 3.7 Hz, 1H), 7.59-7.50 (m, 4H), 7.48-7.44 (m, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.08-7.02 (m, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 3.7 Hz, 1H), 6.52 (t, *J* = 7.7 Hz, 1H), 5.90 (d, *J* = 8.1 Hz, 1H), 3.91 (s, 3H); EI-MS: 419 [M + 1]$^+$.

3-(1*H*-Benzo[d]imidazol-1-yl)-4-(1-methyl-1*H*-indol-3-yl)-1-phenyl-1*H*-pyrrole-2,5-dione (3i): Red solid, m.p. 200-201 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.29 (s, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.63-7.51 (m, 4H), 7.51-7.43 (m, 2H), 7.30-7.16 (m, 2H), 7.14-7.03 (m, 2H), 6.61 (t, *J* = 7.4 Hz, 1H), 6.08 (d, *J* = 7.9 Hz, 1H), 3.94 (s, 3H); EI-MS: 419 [M + 1]$^+$.

3-(1-Methyl-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-1,2,4-triazol-1-yl)-1*H*-pyrrole-2,5-dione (3j): Orange solid, m.p. 174-176 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.28 (s, 2H), 7.60-7.53 (m, 3H), 7.53-7.44 (m, 3H), 7.23 (t, *J* = 7.5 Hz, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.22 (d, *J* = 8.0 Hz, 1H), 3.95 (s, 3H); EI-MS: 370 [M + 1]$^+$.

General procedure for the synthesis of 4a-4j: A mixture of compound **3** (0.1 mmol) and ammonium acetate (1.39 g, 18 mmol) was heated by microwave irradiation at 140 °C for 20 min. After cooling, the resulted reaction mixture was poured into water (50 mL), adjusted to weak alkalinity with Na_2CO_3 and extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with brine (3 × 150 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using ethyl acetate/petroleum ether (2:1, v/v) as eluent to afford compound **4a-4i**.

3-(1-Methyl-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[3,2-c]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (4a): Orange solid, m.p. > 250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.30 (brs, 1H), 8.27 (dd, *J* = 4.6, 1.2 Hz, 1H), 8.17 (s, 1H), 7.84 (d, *J* = 3.5 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.90-6.85 (m, 2H), 6.52 (t, *J* = 7.5 Hz, 1H), 5.91 (d, *J* = 8.0 Hz, 1H), 3.90 (s, 3H); EI-MS: 343 [M + 1]$^+$.

3-(5-Chloro-1-methyl-1*H*-indol-3-yl)-4-(1*H*-pyrrolo-[3,2-c]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (4b): Orange solid, m.p. > 250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.33 (brs, 1H), 8.29 (dd, *J* = 4.6, 1.3 Hz, 1H), 8.19 (s, 1H), 7.86 (d, *J* = 3.5 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.02 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.92 (d, *J* = 3.5 Hz, 1H), 6.90-6.86 (m, 1H), 5.80 (d, *J* = 20 Hz, 1H), 3.91 (s, 3H); EI-MS: 377 [M + 1]$^+$.

3-(5-Bromo-1-methyl-1*H*-indol-3-yl)-4-(1*H*-pyrrolo-[3,2-c]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (4c): Yellow solid, m.p. > 250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.33 (brs, 1H), 8.29 (dd, *J* = 4.6, 1.3 Hz, 1H), 8.17 (s, 1H), 7.85 (d, *J* = 3.5 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.13 (dd, *J* = 8.7, 1.8 Hz, 1H), 6.92 (d, *J* = 3.2 Hz, 1H), 6.90-6.86 (m, 1H), 5.94 (d, *J* = 1.8 Hz, 1H), 3.89 (s, 3H); EI-MS:322 [M + 1]$^+$.

3-(5-Methoxy-1-methyl-1*H*-indol-3-yl)-4-(1*H*-pyrrolo-[3,2-c]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (4d): Orange solid, m.p. > 250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.28 (s, 1H), 8.27 (dd, *J* = 4.5, 1.0 Hz, 1H), 8.03 (s, 1H), 7.80 (d, *J* = 3.4 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 6.93-6.88 (m, 1H), 6.84 (d, *J* = 3.3 Hz, 1H), 6.69 (d, *J* = 7.2 Hz, 1H), 6.35 (t, *J* = 7.6 Hz, 1H), 5.79 (d, *J* = 8.1 Hz, 1H), 4.16 (s, 3H), 2.66 (s, 3H); EI-MS: 357 [M + 1]$^+$.

3-(1,7-Dimethyl-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[3,2-c]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (4e): Orange solid, m.p. > 250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.28 (s, 1H), 8.32 (dd, *J* = 4.6, 1.3 Hz, 1H), 8.15 (s, 1H), 7.82 (d, *J* = 3.4 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.30 (d, *J* = 8.9 Hz, 1H), 6.98 - 6.94 (m, 1H), 6.84 (d, *J* = 3.8 Hz, 1H), 6.60 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.40 (d, *J* = 2.4 Hz, 1H), 3.88 (s, 3H), 2.95 (s, 3H); EI-MS: 373 [M + 1]$^+$.

3-(1-Methyl-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[3,2-b]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (4f): Orange solid, m.p. > 250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.30 (brs, 1H), 8.27 (d, *J* = 4.1 Hz, 1H), 8.17 (s, 1H), 7.84 (d, *J* = 3.3 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.91-6.85 (m, 2H), 6.52 (t, *J* = 7.6 Hz, 1H), 5.91 (d, *J* = 8.0 Hz, 1H), 3.90 (s, 3H); EI-MS: 343 [M + 1]$^+$.

3-(1-Methyl-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[2,3-c]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (4g): Orange solid, m.p. > 250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.32 (brs, 1H), 8.27 (s, 1H), 8.19 (s, 1H), 8.03 (d, *J* = 5.3 Hz, 1H), 7.81 (d, *J* = 3.2 Hz, 1H), 7.55 (d, *J* = 5.2 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 3.1 Hz, 1H), 6.51 (t, *J* = 7.6 Hz, 1H), 5.88 (d, *J* = 8.1 Hz, 1H), 3.92 (s, 3H); EI-MS: 343 [M + 1]$^+$.

3-(1-Methyl-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[2,3-b]-pyridin-1-yl)-1*H*-pyrrole-2,5-dione (4h): Orange solid, m.p. > 250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.28 (brs, 1H), 8.23 (s, 1H), 8.03 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.98 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.67 (d, *J* = 3.6 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.08-7.04 (m, 1H), 7.00 (t, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 3.6 Hz, 1H), 6.48 (t, *J* = 7.5 Hz, 1H), 5.83 (d, *J* = 8.1 Hz, 1H), 3.88 (s, 3H); EI-MS: 343 [M + 1]$^+$.

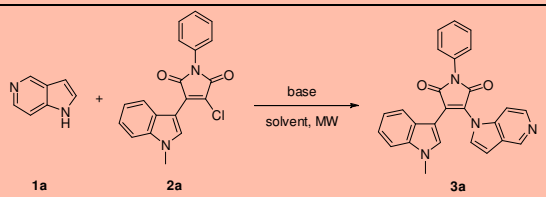
3-(1*H*-Benzo[d]imidazol-1-yl)-4-(1-methyl-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (4i): Brown solid, m.p. > 250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.41 (brs, 1H), 8.42 (s, 1H), 8.22 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.17 (m, *J* = 7.20-7.15 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.06-7.01 (m, 2H), 6.56 (t, *J* = 7.5 Hz, 1H), 5.99 (d, *J* = 8.0 Hz, 1H), 3.91 (s, 3H); EI-MS: 343.2 [M + 1]$^+$.

3-(1-methyl-1*H*-indol-3-yl)-4-(1*H*-1,2,4-triazol-1-yl)-1*H*-pyrrole-2,5-dione (4j): Dark red solid, m.p. 232-234 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.22 (brs, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.46-7.42 (m, 2H), 7.19-7.16 (m, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 6.69 (brs, 2H), 3.81 (s, 3H); EI-MS: 294.1 [M + 1]$^+$.

RESULTS AND DISCUSSION

To get a good yield for the synthesis of **3**, the condensation of **1a** with **2a** to afford **3a** was selected as a model reaction to survey the reaction condition. In a mild reaction environment, different solvents were first investigated (Table-1, Entry 1-5, 7-9). Polar solvents such as DMF or MeCN afforded a

TABLE-1
SYNTHESIS OF **3a**[a]



1a **2a** **3a**

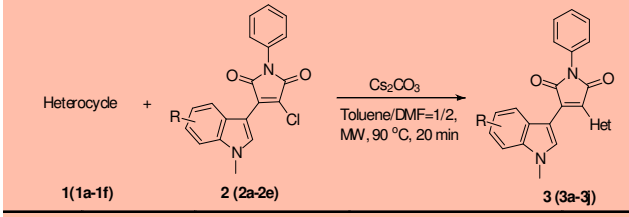
Entry	Heat method	Solvent	Base	Temp. (°C)	Time (min)	Yield of **3a** (%)[b]
1	MW	DMF	Cs_2CO_3	90	20	49
2	MW	MeCN	Cs_2CO_3	90	20	57
3	MW	Toluene	Cs_2CO_3	90	20	Trace
4	MW	Toluene/MeCN = 1/1[c]	Cs_2CO_3	90	20	55
5	MW	Toluene/DMF = 1/1	Cs_2CO_3	90	20	73
6	Oil bath	Toluene/DMF = 1/1	Cs_2CO_3	90	120	32
7	MW	Toluene/DMF = 2/1	Cs_2CO_3	90	20	52
8	MW	Toluene/DMF = 1/2	Cs_2CO_3	90	20	80
9	MW	Toluene/DMF = 1/5	Cs_2CO_3	90	20	68
10	MW	Toluene/DMF = 1/2	K_2CO_3	90	20	42
11	MW	Toluene/DMF = 1/2	t-BuOK	90	20	50
12	MW	Toluene/DMF = 1/2	LiHMDS	90	20	19
13	MW	Toluene/DMF = 1/2	DBU	90	20	6
14	MW	Toluene/DMF = 1/2	Et_3N	90	20	3
15	MW	Toluene/DMF = 1/2	Cs_2CO_3	120	20	68
16	MW	Toluene/DMF = 1/2	Cs_2CO_3	60	20	79

[a]Reactions were run using 0.12 mmol of **1a**, 0.1 mmol of **2a**, and 0.2 mmol of base in 2.0 mL of solvent. [b]Isolated yields. [c]The solvent was mixed in volume ratio, and the total volume was 2 mL.

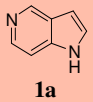
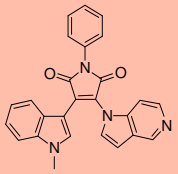
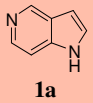
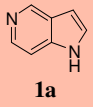
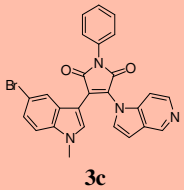
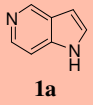
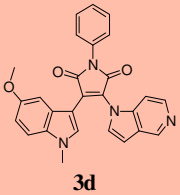
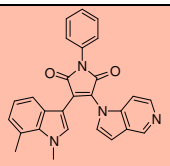
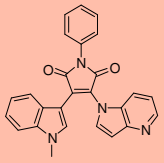
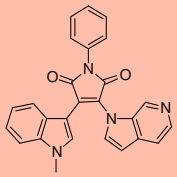
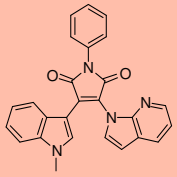
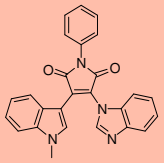
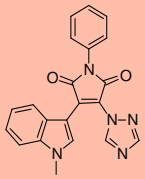
moderate yield (50 %). However, only trace of **3a** could be found when nonpolar toluene was used as the solvent. The yield was improved by using a mixed solution of DMF and toluene and the best yield (80 %) was obtained when the volume of DMF was 2 times of toluene. We next shifted our focus to other bases such as K_2CO_3, *t*-BuOK, LiHMDS, DBU and Et_3N (Table-1, Entry 10-14). However, no better yields were obtained. Finally, different reaction temperatures were studied. When the reaction temperature was increased to 120 °C or decreased to 60 °C, it was not helpful to increase the yield (Table-1, Entry 15-16). As compared to using a conventional reaction condition (entry 6), the microwave irradiation displayed extreme efficiency, which promoted the reaction to completion in 20 min and also in high yield (entry 5). Therefore, optimized conditions involved microwave assisted condensation of **1a** (1.2 equiv) with **2b** (1.0 equiv) at 90 °C in a mixed solution (DMF: toluene = 2:1 v:v), using Cs_2CO_3 (2 equiv) as the base, which gave **3a** in 80 % yield.

To investigate the scope of the microwave assisted condensation reaction, several N-containing heterocycles **1a-1f** were selected to react with different substituted monochloromaleimides **2** and the results were listed in Table-2.

TABLE-2
SYNTHESIS OF **3** (**3a-3j**)



1(1a-1f) 2 (2a-2e) 3 (3a-3j)

Entry	1 (1a-1f)	2 (2a-2e)	Product 3 (3a-3j)	Yield (%)[a]
1	 **1a**	**2a**: R = H	 **3a**	80
2	 **1a**	**2b**: R = 5-Cl	 **3b**	60
3	 **1a**	**2c**: R = 5-Br	 **3c**	71
4	 **1a**	**2d**: R = 5-OMe	 **3d**	70
5	 **1a**	**2e**: R = 7-Me	 **3e**	75
6	 **1b**	**2a**: R = H	 **3f**	76
7	 **1c**	**2a**: R = H	 **3g**	81
8	 **1d**	**2a**: R = H	 **3h**	43
9	 **1e**	**2a**: R = H	 **3i**	61
10	 **1f**	**2a**: R = H	 **3j**	39

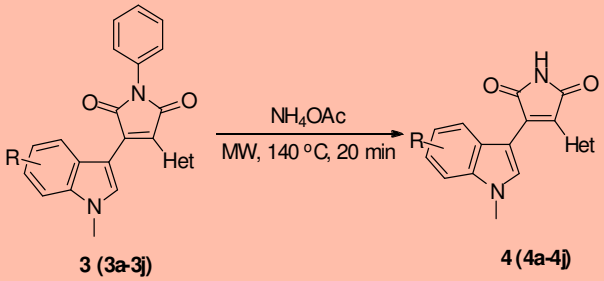
[a]Reactions were carried out using 0.15 mmol of **2**, 0.18 mmol of **1** and 0.3 mmol of cesium carbonate in mixed solvent of DMF (2 mL) and Toluene (1.0 mL); isolated yields

It is observed that the azaindoles, benzoimidazole and 1,3,4-trizazole are all able to react with different substituted monochloromaleimide to get the target products and the yields were affected to some extent by the structure of heterocycle and monochloromaleimide. When 4-azaindole, 5-azaindole or 6-azaindole was employed in the microwave assisted condensation, the yield was relatively high (Table-2, Entry 1, 6, 7). However, using 7-azaindole or 1,3,4-triazole in the reaction was unfavorable for the yield (Table 2, Entry 8, 10). All the synthesized **3a-3j** can be converted to potential GSK-3 inhibitors **4a-4j** easily by a microwave assisted ammonolysis in yield 55-98 % (Table-3) and the microwave irradiation was also superior to the conventional reaction condition.

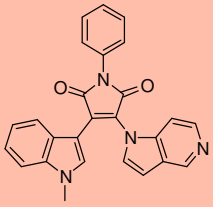
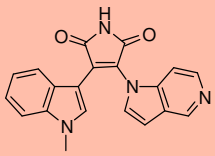
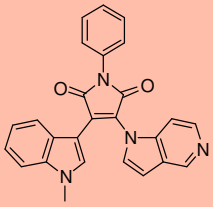
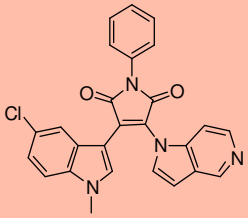
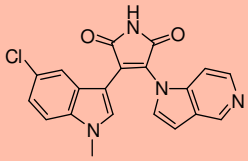
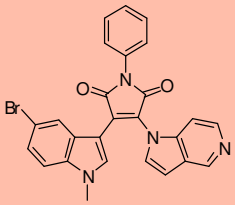
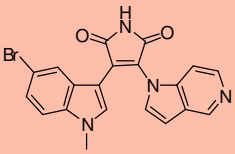
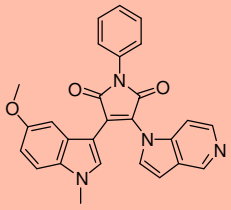
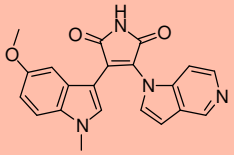
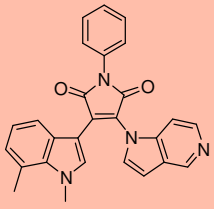
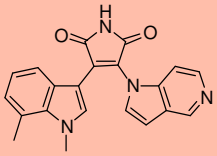
Conclusion

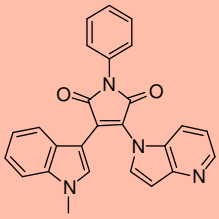
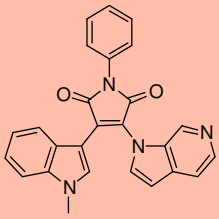
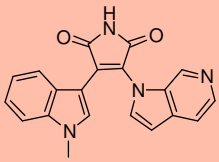
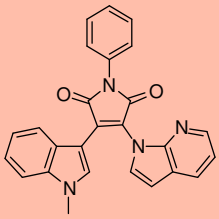
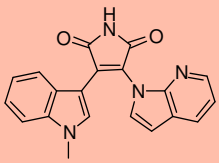
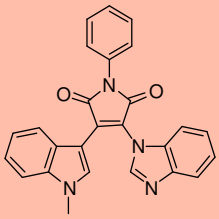
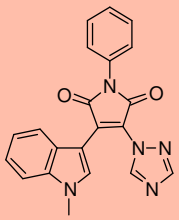
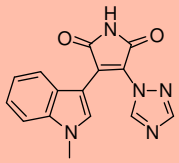
We have reported a convenient, simple and efficient synthesis of some new monoindolylmaleimides *via* microwave assisted condensation of substituted monochloro-maleimides

TABLE-3
SYNTHESIS OF **4 (4a-4j)**



3 (3a-3j) **4 (4a-4j)**

Entry	**3**	Heat method	Product 4	Yield (%) [a]
1.	 **3a**	MW	 **4a**	98
2[b]	 **3a**	Oil bath	 **4a**	85
3	 **3b**	MW	 **4b**	91
4	 **3c**	MW	 **4c**	82
5	 **3d**	MW	 **4d**	98
6	 **3e**	MW	 **4e**	90

7	 **3f**	MW	 **4f**	99
8	 **3g**	MW	 **4g**	72
9	 **3h**	MW	 **4h**	55
10	 **3i**	MW	 **4i**	89
11	 **3j**	MW	 **4j**	69

[a]Reactions were carried out using 0.1 mmol of **3** and 240 mmol ammonium acetate for 20 min; isolated yields. [b]Reaction was carried out for 4 h

with N-containing heterocycles followed by ammonolysis. Further studies of the scope of the reaction and the pharmacological activity of the new monoindolylmaleimides are currently in progress.

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