Synthesis of some new Furyl, Thiophenyl-3-Oxopropyl Quinoline-2-(1H) one and their corresponding Pyrazole derivatives under microwave irradiation.

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Abstract

New series of chalcones (5-8) and their corresponding pyrazoles (9-12) were synthesized starting from *m*-toluidine (1) which was treated with phosphoric acid to form the corresponding amide (2). The amide was then converted into 2- chloro-7-methylquinoline-3-carbaldehyde (3) via the Vilsmeier reaction using $POCl_3$ in DMF. Subsequently, the formed aldehyde was treated with concentrated acetic acid to form 7- methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (4) which was irradiated with substituted acetylfuran or acetylthiophene in DCE using Amberlyst 15 resin as a catalyst forming chalcones (5-8). These chalcones were then treated with hydrazine monohydrate under microwave irradiation condition forming pyrazoles (9-12).

Key words: chalcone, pyrazole, Amberlyst 15 resin.

1. Introduction

In the last decade, the chemistry of chalcones and their derivatives has become an increasingly interesting field for many research groups due to the vital biological activities of these compounds. Licochalcone A, for instance, is one of the natural chalcones which was isolated from the roots of *Glycyrrhiza inflate* (Licorice) and has shown anti-leishmanial activity[1] and anti-malarial activity[2] both *in vivo* and *in vitro*. A variety of synthetic chalcones were also reported as anti-leishmanial agents[3], anti-microbial[4], anti-inflammatory[5], analgesic[6], anti-ulcerative[7], anti-proliferative [8], anti-hyperglycemic[9], antiviral[10] anti-oxidant[11] and anti-tubercular activities.[12] On the other hand, a variety of other compounds can be also linked or hybridized

with chalcones to exhibit more potent therapeutic properties such as anticancer[13-15] and anti HIV.[16] Furthermore, chalcones and their derivatives become one of the interesting compounds that show high activity in reducing PrP^{Sc} levels, some of which are natural products.[17] A large number of natural products containing the quinoline moiety in their skeletons were found to posses different biological activities.[18] 3-substituted quinolone-2-one is one of the interesting moieties which can be found in many compounds with interesting anti-tumor activities.[19] Moreover, quinolone derivatives were reported to be the most effective compounds in the cell culture assays and inhibit the aggregation of prion protein *in vitro*[20,21,22-24] . On the other hand, Pyrazolines were also found to have a broad spectrum of biological activities such as anti-inflammatory, pesticidal, antidepressant , antiviral and antiarthritic.[25-32] In view of the various biological activities of chalcones and pyrazolines, it is worth to synthesize new series of chalcones and their corresponding pyrazolines containing the quinoline moiety and furan, thiophene ring in their structure using microwave method as a green and efficient method which is environmentally and economically desirable which might have valuable value in antimicrobial activities and anti prion agents.

2. Experimental

All reagents were purchased from Sigma-Aldrich, PubChem and used without further purification. Microwave reactions were carried out via Smith Creator™ Optimiser EXP reaction (Personal Chemistry, Inc.). Melting points were recorded on a Gallenkamp machine. $^{1}H/^{13}C$ NMR spectra were measured using a Bruker AV-1400 model NMR instrument at 400 MHz. Accurate masses measurements were achieved using a Water-Micromass LCT electrospray mass spectrometer. All reactions and measurements were accomplished at the chemistry department, university of Sheffield, United kingdom. Aldehyde (4) was synthesized following the published procedure.[33] The structure of all compounds were confirmed based on their analytical and spectral NMR, mass & IR data and are well discussed.

2.1 Microwave synthesis of chalcones 5-8.

In a 20 mL microwave vial packed with Amberlyst 15 resin and equimolar quantities of aldehyde (4) and substituted acetylfuran or acetylthiophene dissolved in 10 mL DCE were heated to 80 ^{o}C (16 bar) via microwave irradiation for 10 minutes. The mixture was then allowed to cool to room temperature and then filtrated. The filtrate was evaporated by vacuum evaporator. The residue was purified by column chromatography using ethyl acetate and petroleum ether as a solvent system at a ratio of 1:2. The physical and spectral data were presented in the following article.

2.2 Microwave synthesis of pyrazoles 9-12.

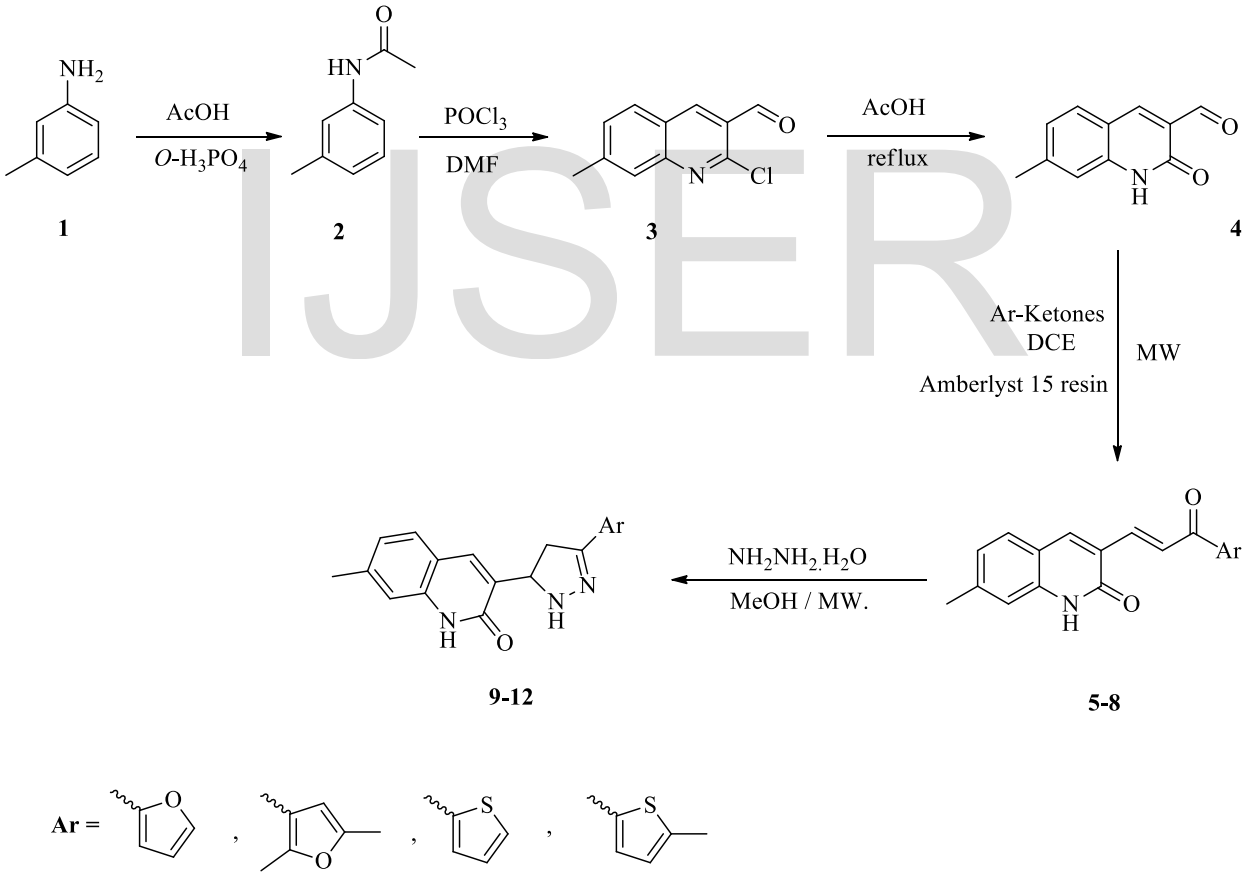
In a 20 mL microwave vial 1.0 mmol of chalcone **5-8** and 3.0 mmol (80%) hydrazine monohydrate in 10 mL methanol were heated to 70 ^{o}C (16 bar) via microwave irradiation for 5 minutes. The mixture was then allowed to cool to room temperature and then an ice cold water was added. The product was precipitated out, filtered and washed with water several times to obtain the pure product with 96-98 % yield as a white powder without further purification. The physical and spectral data were presented in the following article.

3. Results and discussion

In continuation of our interest in the development of green organic synthesis, a microwave protocol was used to synthesis this new series of chalcones and their corresponding pyrazoles[34] . The aromatic aldehyde containing quinoline moiety was synthesized in three steps starting from *m*-toluidine (1) which was treated with phosphoric acid to form the corresponding amide (2) (Scheme 1). The amide was then converted into 2- chloro-7-methylquinoline-3-carbaldehyde (3) via the Vilsmeier reaction using $POCl_3$ in DMF. Subsequently, the formed aldehyde was treated with concentrated acetic acid to form 7- methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (4) which was irradiated for 10 minutes at 80 ^{o}C (16 bar) with substituted acetylfuran or acetylthiophene in DCE using Amberlyst 15 resin as a catalyst forming

chalcones (5-8). The greatest advantage of using the solid catalyst for synthesizing these compounds is that it can be used several times without any significant loss in efficiency in each single reaction. Furthermore, this type of catalyst is cheaper than other conventional catalysts and hence reduces the cost of synthesizing these types of chalcones.

In the modern heterocyclic chemistry the major challenge is to discover a clean, economic and efficient protocol for synthesizing these types of compounds, therefore the same new protocol was used for synthesizing pyrazoles (9-12), (Scheme 1). These pyrazoles were obtained from the irradiation of chalcones (5-8) with hydrazine monohydrate using methanol as a reaction media affording an excellent percentage yield of pure products.



Scheme 1

(E)-3-(3-(furan-2-yl)-3-oxoprop-1-en-1-yl)-7-methylquinolin-2(1H)-one. (5)

White solid, MP: 119 ºC, 91 %. ^{1}H NMR (DMSO 400 MHz): δ 12.09 (bs, 1H, NH), 8.6-7.35 (m, 7 Ar-H), 7.13 (d 1H, *J* = 15.0 Hz, CH) 7.09 (d 1H, *J* = 15.5 Hz, CH), 2.40 (s, 3H, CH_3). ^{13}C NMR (DMSO 100 MHz): δ 182.2 , 161.5 , 145.8 , 142.9 , 141.6 , 139.7 , 138.8 , 133.5 , 129.4 , 129.0 , 125.1 , 124.4 , 123.7 , 117.4 , 115.3 , 22.1 . υ $_{max}$ (ATR) cm^{-1} 3249 (N-H), 1661 (C=O), 1572(C=C). LRMS m/z (ES): 280 (100%), $[M + H]^+$.

(E)-3-(3-(2,5-dimethylfuran-3-yl)-3-oxoprop-1-en-1-yl)-7-methylquinolin-2(1H)-one. (6)

White solid, MP: 127 ºC, 94 %. ^{1}H NMR (DMSO 400 MHz): δ 12.0 (bs, 1H, NH), 8.5-6.1 (m, 5 Ar-H), 7.5 (d 1H, *J* = 15.1 Hz, CH) 7.05 (d 1H, *J* = 15.5 Hz, CH), 2.40 (s, 3H, CH_3), 2.30 (s, 3H, CH_3). ^{13}C NMR (DMSO 100 MHz): δ 185.6 , 161.5 , 157.4 , 150.3 , 142.7 , 141.4 , 139.5 , 137.9 , 128.9 , 126.3 , 125.2 , 124.3 , 122.8 , 117.5 , 115.2 , 106.4 , 22.0 , 14.5 , 13.3. υ $_{max}$ (ATR) cm^{-1} 3148 (N-H), 1659 (C=O), 1581(C=C). LRMS m/z (ES): 308 (100%), $[M + H]^+$.

(E)-7-methyl-3-(3-oxo-3-(thiophen-2-yl)prop-1-en-1-yl)quinolin-2(1H)-one. (7)

Pale yellow solid, M.P: 131 ºC, 96 %. ^{1}H NMR (DMSO 400 MHz): δ 12.01 (bs, 1H, NH), 8.60-7.09 (m, 7 Ar-H), 7.6 (d 1H, *J* = 15.0 Hz, CH) 7.08 (d 1H, *J* = 15.5 Hz, CH), 2.40 (s, 3H, CH_3). ^{13}C NMR (DMSO 100 MHz): δ 182.2 , 161.5 , 145.8 , 142.9 , 141.6 , 139.7 , 138.8 , 135.9 , 133.5 , 129.4 , 129.0 , 125.1 , 124.4 , 123.7 , 117.4 , 115.3, 22.1. υ $_{max}$ (ATR) cm^{-1} 3145 (N-H), 1651 (C=O), 1581 (C=C). LRMS m/z (ES): 296 (100%), $[M + H]^+$.

(E)-7-methyl-3-(3-(5-methylthiophen-2-yl)-3-oxoprop-1-en-1-yl)quinolin-2(1H)-one. (8)

Pale yellow solid, MP: 142, 96 %. ^{1}H NMR (DMSO 400 MHz): δ 12.0 (bs, 1H, NH), 8.5-6.49 (m, 6 Ar-H), 7.1 (d 1H, *J* = 15.0 Hz, CH) 7.08 (d 1H, *J* = 15.5 Hz, CH), 2.42 (s, 3H, CH_3), 2.41

(s, 3H, CH_3). ^{13}C NMR (DMSO 100 MHz): δ 176.7 , 161.4 , 158.8 , 152.5 , 142.8 , 141.4 , 139.6 , 138.0 , 129.0 , 125.2 , 124.4 , 123.7 , 121.1 , 117.4 , 115.2 , 110.1, 22.1 , 14.2. υ_{max} (ATR) cm^{-1} 3209 (N-H), 1661 (C=O), 1578 (C=C). LRMS m/z (ES): 310 (100%), $[M + H]^+$.

3-(3-(furan-2-yl)-4,5-dihydro-1H-pyrazol-5-yl)-7-methylquinolin-2(1H)-one. (9)

Pale yellow solid, M.P: 148 ^oC. 96%. ^1H NMR (DMSO 400 MHz): δ 11.9 (bs, 1H, Ar-NH), 7.85-7.0 (m, 7 Ar-H and (s, 1H, N-NH), 4.91-4.83 (m, 1H, CH), 3.52-3.49 (dd, 1H, *J* = 14.5 and 11.0 Hz, CH_2), 2.87 (dd, 1H, *J* = 16.5 and 10.5 Hz, CH_2), 2.39 (s, 3H, CH_3).^{13}C NMR (DMSO 100 MHz): δ 161.2 , 145.8 , 140.3 , 138.5 , 137.4 , 134.5 , 133.0 , 128.1 , 127.9 , 126.7 , 126.6 , 123.8 , 117.3 , 115.0 , 58.9 , 40.4 , 21.8. υ_{max} (ATR) cm^{-1} 3213 (Ar-N-H), 3246 (N-H), 1558 (C=N). LRMS m/z (ES): 293 (100%), $[M + H]^+$.

3-(4-(2,5-dimethylfuran-3-yl)-2,3-dihydro-1H-pyrrol-2-yl)-7-methylquinolin-2(1H)-one. (10)

Pale yellow solid, M.P: 153 ^oC. 98% ^1H NMR (DMSO 400 MHz): δ 11.9 (bs, 1H, Ar-NH), 7.91-6.2 (m, 5 Ar-H and (s, 1H, N-NH), 4.90-4.82 (m, 1H, CH), 3.42-3.39 (dd, 1H, *J* = 14.5 and 11.0 Hz, CH_2), 2.77 (dd, 1H, *J* = 16.5 and 10.5 Hz, CH_2), 2.40 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.38 (s, 3H, CH_3).^{13}C NMR (DMSO 100 MHz): δ 162.2 , 149.7 , 148.0 , 145.2 , 140.2 , 138.4 , 134.4 , 133.4 , 128.0 , 123.7 , 117.3 , 115.7 , 115.0 , 106.3 , 58.2 , 21.8 , 13.7 , 13.4 υ_{max} (ATR) cm^{-1} 3305 (Ar-N-H), 3250 (N-H), 1566 (C=N). LRMS m/z (ES): 322 (100%), $[M + H]^+$.

7-methyl-3-(4-(thiophen-2-yl)-2,3-dihydro-1H-pyrrol-2-yl)quinolin-2(1H)-one. (11)

Pale yellow solid, M.P: 149 ^oC. 98% ^1H NMR (DMSO 400 MHz): δ 11.9 (bs, 1H, Ar-NH), 7.8-6.9 (m, 7 Ar-H and (s, 1H, N-NH), 4.92-4.84 (m, 1H, CH), 3.52-3.49 (dd, 1H, *J* = 14.5 and 11.0

Hz, CH_2), 2.87 (dd, 1H, *J* = 16.5 and 10.5 Hz, CH_2), 2.39 (s, 3H, CH_3).^{13}C NMR (DMSO 100 MHz): δ 162.1 , 145.8 , 140.3 , 138.5 , 137.4 , 134.5 , 133.0 , 128.1 , 127.9 , 126.7 , 126.6 , 123.8 , 117.3 , 115.0 , 58.9 , 21.8 . υ_{max} (ATR) cm^{-1} 3225 (Ar-N-H), 2962 (N-H), 1567 (C=N). LRMS m/z (ES): 310 (100%), $[M + H]^+$.

7-methyl-3-(4-(5-methylthiophen-2-yl)-2,3-dihydro-1H-pyrrol-2-yl)quinolin-2(1H)-one. (12)

Pale yellow solid, M.P: 156 ^oC. 96% ^{1}H NMR (DMSO 400 MHz): δ 11.8 (bs, 1H, Ar-NH), 7.83-6.19 (m, 6 Ar-H and (s, 1H, N-NH), 4.81-4.78 (m, 1H, CH), 3.45-3.33 (dd, 1H, *J* = 14.5 and 11.0 Hz, CH_2), 2.77 (dd, 1H, *J* = 16.5 and 10.5 Hz, CH_2), 2.40 (s, 3H, CH_3), 2.39 (s, 3H, CH_3).^{13}C NMR (DMSO 100 MHz): δ 162.1 , 152.8 , 147.3 , 141.7 , 140.3 , 138.5 , 134.4 , 132.9 , 128.1 , 123.8 , 117.3 , 115.0 , 110.9 , 108.2 , 58.3 , 21.8 , 13.8 . υ_{max} (ATR) cm^{-1} 3217 (Ar-N-H), 2915 (N-H), 1568 (C=N). LRMS m/z (ES): 324 (100%), $[M + H]^+$.

Acknowledgments

The authors would like to thank the chemistry department of Sheffield university in the United Kingdom for their cooperation and providing the facilities to do this work.

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