Research Article

Synthesis and biological evaluation of some novel heterocyclic Chalcone derivatives

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Abstract

Objective: The chemistry of chalcones has generated intensive scientific studies throughout the world. In recent years, a variety of chalconilides have been reviewed for their cycotoxic, anticancer chemopreventive and mutagenic as well as antiviral, insecticidal and enzyme inhibitory properties. Condensation of aromatic aldehydes and aryl anilides in presence of suitable condensing agents gave chalcone derivatives. These types of chalcones are called chalconoids. **Materials and methods:** Heteroatoms such as N and O containing chalconoids have exhibited anti-inflammatory, antioxidant, analgesic, antitubercular and antibacterial activities etc. Therefore an attempt has been made to synthesize chalcones by the condensation of N-phenyl acetanilides with substituted Indole-3-carbaldehydes. The resulting chalcones (A1) after purification have been converted into substituted pyrazole derivatives (A2 & A3) by reaction with hydrazine hydrate and isonicotinylhydrazide. All these compounds were characterized and confirmed by TLC, elemental analysis, IR, ^{1}H and ^{13}C NMR. All these compounds were screened for their potential antimicrobial activity. **Results:** These novel compounds showed optimum activities at 25, 50, 75 and 100 µl concentrations against antibacterial gram positive *Staphylococcus aureus* and *Bacillus subtilis*, gram negative *Escherichia coli* and *Enterobacter microbes*, antifungal *Aspergillus niger* and *Candela albicans*. **Conclusion:** These compounds containing N-phenyl acetanilide group were found to show potent analgesic and antimicrobial activities. These findings prompted us to synthesize these chalconalides which are found to be the potential antimicrobial agents.

Keywords: Chalcone, acetanilide, isonicotinylhydrazide, antimicrobial activities.

Introduction

Chalcones are α, β-unsaturated Ketones containing the reactive ketoethylenic group CO-CH=CH. The name "Chalcones" was known by Kostanecki and Tambor (Pareek, et al., 2013). Chalcones are also identified as benzylideneacetophones or phenyl steryl ketones. Chalcones exist as either E or Z isomers. E isomer is one of the most stable form and consequently majority of chalcones are isolated in E isomeric form (Nowakowska et al., 2008). Flavanoids derived form chalcones are found similar to natural flavanoids (Dhar, 1981; Roger, 1988; Bent, 2002). The presence of a reactive α,β-unsaturated ketonic group in chalcone is the major cause for their antimicrobial activity (Daniela et al., 2009).

These types of chalconoids, also known as chalcones, form the fundamental core for a variety of significant biological compounds like aurones, isoxazolines, anthocynins, pyrazolines, pyrimidines, flavones, flavanols, quinoxalines, benzalcoumaranones. Some chalconoids were verified with the ability to block voltage-dependent potassium channels. Chalcones are also natural aromatize inhibitors. Chalcones are used as parent compounds in the synthesis of heterocyclic compounds containing di nitrogen atoms which are named as "di aze" (Patneedi et al., 2015).

Nowadays several heteroatom containing chalcones have been reported to posses various chemotherapeutic activities (Nabila et al., 2012). They show wide range of biological activities such as antibacterial (Indubhushan et al., 2014), antifungal (Reddy et al., 2008), anti-inflammatory (Won et al., 2005), antitumor (Mukherjee et al., 2001), anticancer (Syam et al., 2012), antidiabetics (Soliman et al., 1987) and antiproliferative (Cui Li et al., 2017) activities.

Materials and methods

The chemicals and solvents were obtained from Sigma-

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Aldrich and purified. All materials used for this experiment are analytical grade. Melting points of the products were determined in open capillaries and are uncorrected. The purity of compounds was ascertained by Thin Layer Chromatography using Silica gel G plates and Chloroform: Methanol: Benzene 5:1:1 as the mobile phase. The spots were visualized in iodine chamber. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III 500 MHz (AV 500) instrument using $CDCl_3$ or DMSO-*d*6 solvent with TMS as an internal standard. Infrared spectra were recorded in Shimadzu FT-IR spectrophotometer in KBr pellets. Elemental analyses (C, H and N) were performed using a LECO CHNS 932 elemental analyser. The newly synthesized compounds were prepared under Claisen-Schimidt condensation as well as cyclisation process. The compounds were recrystallised using ethanol.

Synthesis of chalconoids

1. Preparation of (2*E*)-3-(1*H*-indol-2-yl)-*N*-phenylprop-2-enamide (A1)

A mixture of N-phenylacetamide (0.01 mol) and Indole-2-carbaldehyde (0.01 mol) was stirred in ethanol (30ml). To this aqueous solution of NaOH was added drop wise after 30 minutes stirring and continued for 4 hrs. The mixture was kept overnight at room temperature and then it was poured into crushed ice and acidified with HCl. The solid separated was filtered and crystallized from ethanol.

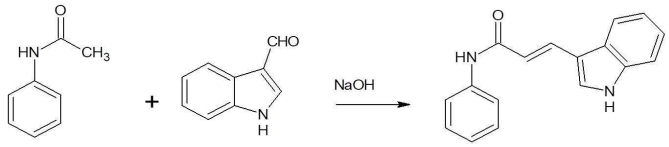

Figure 1. Synthesis of chalconoids (A1)

2. Preparation of 1-[3-anilino-5-(1*H*-indol-3-yl) - 4,5-dihydro-1*H*-pyrazol-1-yl]ethan-1-one (A2)

To the solution of (2*E*)-3-(1*H*-indol-3-yl)-*N*-phenylprop- 2-enamide (0.001 mol) (A1) in ethanol (30 ml) glacial acetic acid (2 ml) and 99 % hydrazine hydrate (0.002 mol) were added drop-wise and the reaction mixture was refluxed with stirring at 80° C for about 8 hours. The excess of solvent was distilled off and crude product poured into crushed ice. The solid obtained was washed with water and recrystallized from ethanol.

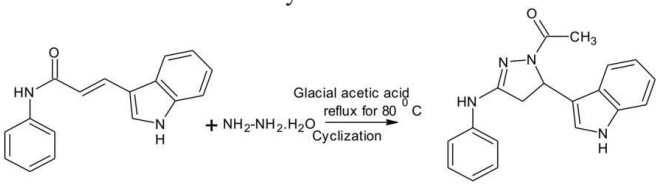

Figure 2. Synthesis of chalconoids (A2)

3. Preparation of [3-anilino-5-(1*H*-indol-3-yl)-4,5-dihydro-1*H*-pyrazol-1-yl](pyridin-4-yl) methanone (A3)

To a solution of (2*E*)-3-(1*H*-indol-3-yl)-*N*-phenylprop- 2-enamide (0.001 mol) (A1) in ethanol (30 ml) glacial acetic acid (2 ml) and isonicotinylhydrazide (0.002 mol) were added drop-wise and the reaction mixture was refluxed with stirring at 80° C for about 12 hours. The excess of solvent was distilled off and crude product was poured into crushed ice. The solid obtained was washed with water and recrystallized from ethanol. The purity of the product was checked on TLC by using mixture of acetone and petroleum ether as mobile phase.

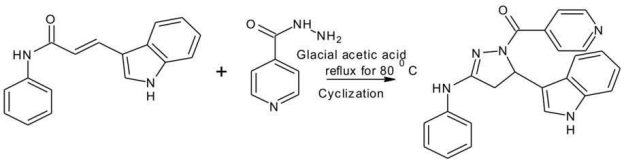

Figure 3. Synthesis of chalconoids (A3)

Results and discussion

All the synthesized compounds 1a, 2a, 3a have been characterized by their melting points, CHN analysis and spectroscopic methods such as IR, ^{1}H, ^{13}C, – NMR.

(2*E*)-3-(1*H*-indol-3-yl)-*N*-phenylprop-2-enamide (A1): M.F: $C_{17}H_{14}N_2O$, M.Wt: 262.3, m.p: 232ºC, Elemental analysis: C- 77.84%, H-5.38%, N-10.68%, IR: 1625 Cm^{-1} (C=O), 3530 Cm^{-1} (NH), 1460, 1550, 1668 Cm^{-1} (C=C), 1300 Cm^{-1} (C-N), ^{1}HNMR (300 MHz, DMSO) ppm: 7.8 (s, 1H, -NH-C=O), 6.81-7.54 (m, 15H, aromatic), 9.6 (s, 1H, indol proton), 7.2 (s, 1H, methine), ^{13}CNMR (300 MHz, DMSO) ppm: 162.3 (C=O), 112.3-124.1 (phenyl carbons), 137.5 (Ipso carbon), 139.2 (methine carbon).

1-[3-anilino-5-(1*H*-indol-3-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]ethan-1-one (A2): M.F: $C_{19}H_{18}N_4O$, M.Wt: 318.3, m.p: 254 ºC, Elemental analysis: C- 71.68%, H-5.70%, N-17.68%, IR: 1655 Cm^{-1} (C=O), 3320 Cm^{-1} (NH), 1480, 1450, 1568 Cm^{-1} (C=C), 1320 Cm^{-1} (C-N), ^{1}HNMR (300 MHz, DMSO) ppm: 3.8 (s, 1H, C-NH-C), 6.35-7.44 (m, 15H, aromatic), 9.4 (s, 1H, indol proton), 1.2 (s, 1H, methylene), ^{13}CNMR (300 MHz, DMSO) ppm: 160.3 (C=O), 120.3-123.9 (phenyl carbons), 137.5 (Ipso carbon), 40.2 (methine carbon).

[3-anilino-5-(1*H*-indol-3-yl)-4,5-dihydro-1*H*-pyrazol-1-yl](pyridin-4-yl)methanone (A3): M.F: $C_{23}H_{19}N_5O$, M.Wt: 262.3, m.p: 295 ºC, Elemental analysis: C- 72.42%, H-5.02%, N-18.36%, IR: 1565 Cm^{-1} (C=O), 3580 Cm^{-1} (NH), 1450, 1490, 1568 Cm^{-1} (C=C), 1340 Cm^{-1} (C-N), ^{1}HNMR (300 MHz, DMSO) ppm: 3.6 (s, 1H, -NH-C), 6.41-7.64 (m, 15, aromatic), 9.4 (s, 1H, indol proton), 1.4 (s, 1H, methylene), ^{13}CNMR (300 MHz, DMSO) ppm: 165.3 (C=O), 112.3-128.1 (phenyl carbons), 147.5, 142.3 (Ipso carbons), 41.2 (methine carbon).

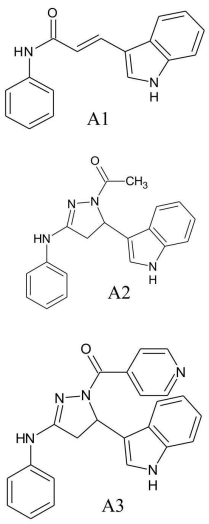

Figure 4. Structure of synthesized compounds A1, A2 and A3

Antimicrobial activity

All the three newly synthesized compounds were screened for in-vitro antibacterial activity and antifungal activity. The antimicrobial activity was evaluated against 24 h culture of different bacterial strains such as *Staphylococcus aureus* and *Bacillus subtilis* (gram positive), *Escherichia coli* and *Enterobacter* (gram negative), fungal strains such as *Aspergillus niger* and *Candela albicans*. Minimum inhibitory concentration (MIC, µg/mL) of synthesized compounds were determined using broth dilution methods.

Erythromycin was used as a standard drug for the comparison of antibacterial activity. Amphotericin were used as standard drugs for the comparison of antifungal activity.

Table 1. Antimicrobial activity of compound (2*E*)-3-(1*H*-indol-2-yl)-*N*-phenylprop-2-enamide (A1)

Organisms		Zone of inhibition (mm/µL)				
		25 µL	50 µL	75 µL	100 µL	Control
Bacterial Strain	*Staphylococcus Auresus*	19	20	22	25	17
	Bacillus subtilis	22	24	27	29	21
	Escherichia coli	21	23	25	27	19
	Enterobacter	18	20	22	25	17
Fungi Strain	*Aspergillus niger*	25	27	24	30	23
	Candida albicans	17	19	21	24	15

Table 2. Antimicrobial activity of compound 1-[3-anilino-5-(1*H*-indol-3-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]ethan-1-one (A2)

Organisms		Zone of inhibition (mm/µL)				
		25 µL	50 µL	75 µL	100 µL	Control
Bacterial Strain	*Staphylococcus Auresus*	18	21	23	27	15
	Bacillus subtilis	21	24	28	25	20
	Escherichia coli	26	19	22	24	18
	Enterobacter	23	26	24	28	21
Fungi	*Aspergillus niger*	27	29	25	28	24
Strain	*Candida albicans*	19	21	23	26	17

Table 3. Antimicrobial activity of compound 3-anilino-5-(1*H*-indol-3-yl)-4,5-dihydro-1*H*-pyrazol-1-yl](pyridin-4-yl)methanone (A3)

Organisms		Zone of inhibition (mm/µL)				
		25 µL	50 µL	75 µL	100 µL	Control
Bacterial Strain	*Staphylococcus Auresus*	15	17	19	21	13
	Bacillus subtilis	21	23	26	24	19
	Escherichia coli	25	27	29	31	22
	Enterobacter	19	21	25	27	17
Fungi	*Aspergillus niger*	26	29	31	33	24
Strain	*Candida albicans*	25	29	27	30	23

Conclusion

In the present work, we synthesized the chalconoids (2*E*)-3-(1*H*-indol-3-yl)-*N*-phenylprop-2-enamide (A1) and pyrazole derivatives 1-[3-anilino-5-(1*H*-indol-3-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]ethan-1-one(A2) and 3-anilino-5-(1*H*-indol-3-yl)-4,5-dihydro-1*H*-pyrazol-1-yl](pyridin-4-yl)methanone (A3). The newly synthesized compounds were obtained in good yields and confirmed their structures on the basis of spectral and elemental analysis data. Erythromycin and Amphotericin are used as standard for antibacterial and antifungal activity. The antimicrobial activity of synthesized compounds reveals that they are showing optimum activity compared to standard drug.

Conflict of interest

There is no conflict of interest in the present study.

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