Piperidine Containing Murrayanine-Chalcones as Emerging Bactericidal and Fungicidal Agents

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Abstract

Among the 20 other alkaloid molecules, murrayanine is the highest explored alkaloidal component present in the curry plant (Murraya koenigii L.). In the current research, a piperidine containing chalcone [(E)-1-(1-methoxy-9H-carbazol-3-yl)-3-(4-(piperidin-1-yl)phenyl)prop-2-en-1-one] was rationally developed by incorporating the natural portion (murrayanine) in the A-ring and a synthetic component (1-(4-(piperidin-1-yl)phenyl)ethanone, a piperidine containing acetophenone) in the B-ring and screened against two bacterial species (Escherichia coli and Staphylococcus aureus) and two fungal species (Candida albicans and Aspergillus niger) in the B-ring and screened against two bacterial species (Escherichia coli and Staphylococcus aureus) and two fungal species (Candida albicans and Aspergillus niger). The chalcone (1, 3-diphenyl-2E-propene-1-one) candidate expressed a better anti-bacterial activity than that of anti-fungal activity. The chalcone displayed the highest activity against E. coli followed by S. aureus, and lowest against C. albicans. Although, were found to have less activity and potency than that of the standard compounds (ciprofloxacin and fluconazole). The current study will open new avenues of research on hybrid heterocyclic chalcones and will motivate researchers to further developing highly active compounds based on benzylideneacetophenone scaffold.

Keywords: Murraya koenigii; Murrayanine; Chalcone; Piperidine; Antifungal; Antibacterial

Introduction

The benzylideneacetophenone or 1, 3-diphenyl-2E-propene-1-one or chalcone is one of the most emerging scaffolds which is present in nature abundantly. It is believed to be an open chain intermediate in aurone synthesis of flavones pathway and also play a pivotal role in the natural synthesis of is of lavonoids and flavonoids[1]. The molecules of chalcone scaffold have been reported to express anti-inflammatory, anti-diabetic, anti-gout, anti-hypertensive, anti-retroviral, anti-oxidant, anti-tubercular, anti-angiogenic, anti-malarial, anti-neoplastic, anti-protozoal, anti-bacterial, anti-arhythmic, anti-histaminic, anti-platelet, anti-fungal, anti-uler, anti-filarial, hypolipidemic, and anti-obesity[2-6]. Murrayanine is a carbazole containing natural product obtained from Murraya koenigii L. (Family: Rutaceae), having ethnopharmacological importance like immunomodulation, astringent, anti-oxidant, febrifuge, purgative, anti-helminthic, anti-ucrgerogenic, etc. In the modern studies related to Murraya koenigii and its carbazole containing active principles, activities such as anti-diabetic, anti-oxidant, anti-inflammatory, anti-infective, etc[7]. Among the 20 other alkaloid molecules, murrayanine is the highest explored alkaloidal component present in the curry plant. Very recently, we have explored the pharmacological perspectives of the semi-synthetic products of this molecule and rationally developed the heterocyclic hybrids of murrayanine such as benzodiazepine[8], benzothiazepine[9], benzoazepine[10], chalcone[11-14], hydantoin[15], imidazole[16], isoxazole[17], oxadiazole[18], phthalimide[19], pyrazole[20], pyrimidine[21], Schiff’s base analog[22], thiazole[23], thiazole[24], and uracil[25-27], and explored multifarious pharmacological activities such as anxiolytic, anti-cancer, anti-convulsant, anti-inflammatory, anti-microbial, anti-oxidant, etc. Likewise, in the current research, a piperidine containing chalcone was rationally developed by incorporating the natural portion (murrayanine) in the A-ring and a synthetic component (piperidine containing acetophenone) in the B-ring and screened against bacterial and fungal species.

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Materials and Methods

Chemicals and instrumentation: The reactant 1-(4-(piperidin-1-yl)phenyl)ethane was procured from Sigma Aldrich, Germany. The analytical grade chemicals, solvents, and reagents were purchased from HiMedia Ltd., India. The structural elucidation was performed on Fourier transformed Infrared Spectroscopy (Shimadzu® IR-Affinity-1), Mass Spectroscopy (MICROMASS Q-TOF), and 1H-NMR Spectroscopy (Bruker CDCl3): 10.22 (9, 1H), 6.8-8.2 (Aromatic, 10H), 3.99 (1, 3H).

Extraction of murrayanine: Murrayanine was extracted from the M. koenigii powdered stem bark as per our previously developed method[7]. The extraction was performed on a silica gel-based column by using n-hexane mobile phase. The obtained hexane fractions (B1-B12) were scrutinized by thin layer chromatography and concentrated further by the vacuum rotary evaporator.

Synthesis of target compounds: The synthesis of benzylideneacetophenone (chalcone) scaffold (3) comprising the β-hydroxyketone function involved an aldol condensation mechanism where the –CHO (aldehyde) portion of the starting material murrayanine (1) reacts with the –COCH3 (acetyl) part of the piperidine containing acetophenone (2) in the presence of ethanolic NaOH solution (Scheme 1).

Anti-microbial screening: The developed piperidine containing chalcone was screened by using disc diffusion method against Staphylococcus aureus (S. aureus, MTCC 3160) and Escherichia coli (E. coli, MTCC 2961) [anti-bacterial, by utilizing Muller Hinton Agar medium and incubation at 37 ± 1°C for 24 hrs] and Aspergillus niger (A. niger, MTCC 277) and Candida albicans (C. albicans, MTCC 227) [anti-fungal, by utilizing Potato Dextrose Agar medium and incubation at 37 ± 1°C for 72 hrs]. The nutrient broth media was initially employed for culturing the microbial species at 37 ± 1°C for 24 hr, which was followed by specifically transferring them into the agar plates under laminar air flow. The chalcone in dimethyl sulfoxide (DMSO) was soaked over Whatman filter paper, carefully placed over the microbial plates and incubated. The ciprofloxacin was utilized as the positive control for anti-bacterial screening, the fluconazole served an analogous function for the anti-fungal screening, and DMSO was employed as the negative control[29]. The agar streak dilution method was employed for the estimation of MIC (Minimum Inhibitory Concentration). For the determination, a 105 CFU / mL microbial suspension was prepared and serial dilution was applied with DMSO. The test sample containing suspension in required quantity was transferred into the petri dish to 5 mm depth at 40 - 50°C temperature. The average of MIC value was taken into account. The ciprofloxacin was utilized as the positive control for anti-bacterial screening, the fluconazole served analogous function for the anti-fungal screening, and DMSO was employed as the negative control[29].

Results and Discussion

Chemistry: The spectroscopic studies helped in elucidating the structure of piperidine containing chalcone compound. The FT-IR spectra confirmed the formation of a new ketonic carbonyl group at 1727 cm⁻¹ and disappearance of the aldehydic carbonyl group which was earlier noticed at 1753 cm⁻¹. In addition to it, the proton-NMR focused on some imperative aspects of the structure. The aromatic protons were distinctly located in the range of 6.8 - 8.2 ppm. The methoxy protons were discerned from the peak at 3.99 ppm which furthermore substantiated the presence of heterocyclic carbazole moiety in the structure as well as the unification of the two aromatic sections in the molecule. The piperidine heterocycle was particularly distinguished from the peak at 3.99 ppm which furthermore substantiated the presence of heterocyclic carbazole moiety in the structure as well as the unification of the two aromatic sections in the molecule. The piperidine heterocycle was particularly distinguished by the peaks at 3.61 ppm (position 18) and 1.67 ppm (position 19). The fabrication of the chalcone derivative was ascertained from the mass spectra which revealed the emergence of the base peak corresponding with the molecular mass of the molecule along with some fragmented products with m/z of < 100. The ratios of CHN analysis demonstrated a close agreement with the theoretical values and certainly supported the formation of the prop-2-en-1-one compound.

Synthetic protocol for (E)-1-(1-methoxy-9H-carbazol-3-yl)-3-(4-piperidin-1-yl) phenyl) prop-2-en-1-one: An equimolar concentration (0.01 M) of the starting material murrayanine (1) and the reactant 1-(4-(piperidin-1-yl)phenyl)ethane (2) were made to reflux in the presence of 20 mL aqueous solution of sodium hydroxide containing 25 mL of 90 % ethanol. The reaction mixture was made to stand overnight. The content was poured over crushed ice containing dilute HCl (a few drops) and stirred vigorously using a glass rod. The obtained product (3) was separated by filtration, thoroughly washed, and suitably recrystallized.

45 % yield; FTIR (KBr) ν (cm⁻¹): 3260 (-NH, stretching), 3078 (C-H, aromatic), 1727 (C = O), 1622 (C = C, aromatic), 1601 (-NH, bending), 1319 (C-N), 1198 (C-O); 1H NMR (δ, ppm, CDCl3): 10.22 (9, 1H), 6.8-8.2 (Aromatic, 10H), 3.99 (1, 3H), 3.61 (18, 2H), 1.67 (19, 2H). MS: M⁺ 410. Anal. Calcd. For C27H26N2O2: C, 79.00; H, 6.38; N, 6.82. Found: C, 78.06; H, 6.09; N, 6.71.
difference and variability (Inter and Intra) were found to be quite minor. An anti-infective perspective of the fabricated heterocyclic containing chalcone was observed from this study.

Table 1: Anti-microbial perspectives of piperidine containing chalcone.

| Compounds       | E. coli         | S. aureus       | A. niger         | C. albicans     |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| 3               | 22.71 ±1.29 (25)| 20.52 ±1.88 (25)| 19.37 ±1.91 (25)| 16.89 ±1.46 (25)|
| Ciprofloxacin   | 33.16 ±1.63 (6.25)| 31.09 ±1.31 (6.25)| -                | -               |
| Fluconazole     | -               | -               | 33.84 ±1.33 (6.25)| 32.16 ±1.97 (6.25)|

Zone of inhibition in millimeter, SD = standard deviation.

**Conclusion**

The developed chalcone molecule; (E)-1-(1-methoxy-9H-carbazol-3-yl)-3-(4-(piperidin-1-yl)phenyl)prop-2-en-1-one comprising of a natural product murrayanine in ring-A and a heterocycle (piperidine) containing portion in ring-B, displayed noteworthy anti-microbial against E. coli, S. aureus, A. niger, and C. albicans. The chalcone candidate expressed a better anti-bacterial activity than that of anti-fungal activity. Although, were found to have less activity and potency than that of the standard compounds (ciprofloxacin and fluconazole). The current study will open new avenues of research on hybrid heterocyclic chalcones and will motivate researchers in further developing highly active compounds based on benzylideneacetophenone scaffold.

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**Conflict of Interest**

No conflict of interest declared.

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