International Journal of Agricultural and Life Sciences

ISSN: 2454-6127(Online) Journal homepage: http://www.skyfox.co

Anti-microbial Perspective of a Chalcone, (*E*)-1-(1-methoxy-9*H*-carbazol-3-yl)-3-(4-(methylsulfonyl) phenyl)prop-2-en-1-one: Fabrication of a Hybrid by Unification of a Natural Product with a Synthetic Component

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To cite this article : Mahapatra, D. K., & Shivhare, R. S. (2018). Anti-microbial Perspective of a Chalcone, (*E*)-1-(1-methoxy-9*H*-carbazol-3-yl)-3-(4-(methylsulfonyl) phenyl)prop-2-en-1-one: Fabrication of a Hybrid by Unification of a Natural Product with a Synthetic Component. Int J Agr Life Sci, 4(2), 236-240. doi: 10.22573/spg.ijals.018.s12200090

To link to this article : https://doi.org/10.22573/spg.ijals.018.s12200090

Data Availability Statement : All relevant data are within the paper and its Supporting Information files.

Funding : The author(s) received no specific funding for this work.

Competing Interests : The authors have declared that no competing interests exist.

Published online: 30 June 2018.

International Journal of Agricultural and Life Sciences- IJALS (2018), Volume 4 (2) pp.236-240
http://dx.doi.org/10.22573/spg.ijals.018.s12200090
Available online at http://www.skyfox.co
ISSN: 2454-6127

RESEARCH ARTICLE

Anti-microbial Perspective of a Chalcone, (*E*)-1-(1-methoxy-9*H*-carbazol-3-yl)-3-(4-(methylsulfonyl) phenyl)prop-2-en-1-one: Fabrication of a Hybrid by Unification of a Natural Product with a Synthetic Component

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Received: May 2018 / Accepted: June 2018/ Published: June 2018

ABSTRACT: *Murraya koenigii* L. has been explored exhaustively and is known to possess more than 20 different carbazole-based alkaloids having multifarious therapeutic perception of this class of alkaloids, murrayanine is the highest explored alkaloid and is known to have (ethno)-pharmacological perspectives of purgative, astringent, febrifuge, anti-helminthic, anti-oxidant, anti-ulcerogenic, immunomodulation, etc. As murrayanine possess multiple sites for substituting wide-range of electron-donating / -withdrawing groups by semi-synthetic approach, in the present research, a chalcone; (*E*)-1-(1-methoxy-9*H*-carbazol-3-yl)-3-(4-(methylsulfonyl)phenyl)prop-2-en-1-one was fabricated rationally by incorporating a natural portion (murrayanine) in the A-ring and a synthetic component (4-methylsulfonyl group) 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 rationally designed chalcone demonstrated noteworthy anti-microbial activity. The fabricated chalcone was observed to be a better anti-bacterial agent as compared to its anti-fungal potentials. As compared to the standard drugs, the experimental molecule does hold well against pathogenic challenges. The present research therefore opened new avenues of judiciously developing a natural scaffold having an active methylsulfonyl group, which will inspire life science researchers across the globe in developing inhibitors with pronounced biological activity as compared with the parent compounds.
Keywords: *Murraya koenigii*, murrayanine, chalcone, methylsulfonyl, antimicrobial, antibacterial

INTRODUCTION

Murrayanine is a natural product obtained from *Murraya koenigii* L. (Rutaceae) (Mahapatra *et al*., 2018). It is a carbazole alkaloid known to have (ethno)-pharmacological perspectives of purgative, astringent, febrifuge, anti-helminthic, anti-oxidant, anti-ulcerogenic, immunomodulation, etc (Mahapatra *et al*., 2018a). *Murraya koenigii* L. has been explored exhaustively and is known to possess more than 20 different carbazole-based alkaloids having multifarious therapeutic perception (Shivhare *et al*., 2016) of this class of alkaloids, murrayanine is the highest explored and utilized component that finds its imperative role in the pharmacotherapeutics owing to diverse attributes like multiple sites for substituting wide-range of electron-donating / -withdrawing groups by semi-synthetic approaches, simple chemistry, and several other key factors (Mahapatra *et al*., 2018b). Over the years, a number of heterocyclic hybrids have been reported by our research group. Murrayanine based therapeutically active heterocycles like oxazole, pyrimidine, thiazole, pyrazole, hydantoin, thiadiazole, phthalimide, isoxazole, benzodiazepine, benzoxazepine, and benzothiazepine have been fabricated which demonstrated tremendous potentials (Mahapatra *et al*., 2018c; Mahapatra *et al*., 2018d; Mahapatra *et al*., 2017; Mahapatra *et al*., 2017a; Mahapatra *et al*., 2017b; Mahapatra *et al*., 2017c).

Similarly, an effort has been made in rational designing of a natural scaffold "chalcone" by unifying the natural product 'murrayanine' with a synthetic component '4-methylsulfonyl'. Thereby, combining a natural portion with a synthetic part to yield a component which itself is of a natural constitution (Figure 1). In the majority of the cases, it has been observed that substituting an active synthetic group often enhances the biological activity (Mahapatra *et al*., 2017d). In the upcoming research, several hybrids of natural products are evidenced which have demonstrated superior activity than the parent moieties from which they have derived (Mahapatra *et al*., 2017e). The methylsulfonyl group finds its significance in compounds exhibiting anti-inflammatory (Lim *et al*., 2017), anti-allergic (Guda *et al*., 2013), anti-bacterial, anti-fungal, and anti-cancer activity (Lad *et al*., 2017). As a result of these, the methylsulfonyl group was included in our fabricated product with an expectation of pronounced biological activity.

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ISSN: 2454-6127

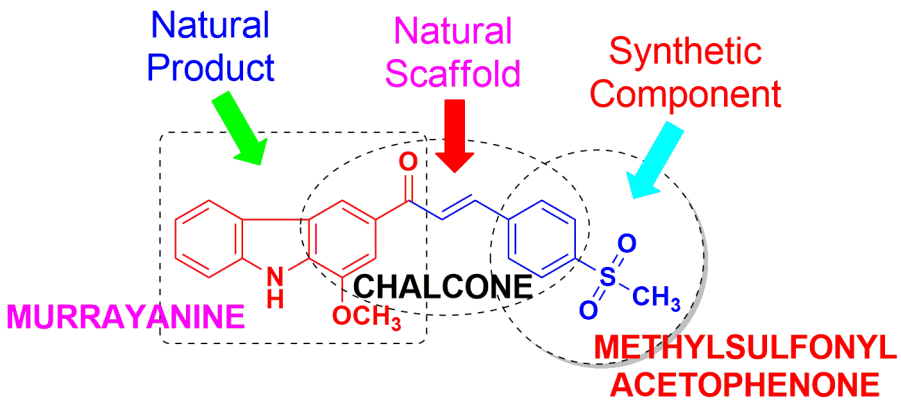


Figure 1. The rationale for the development of (*E*)-1-(1-methoxy-9*H*-carbazol-3-yl)-3-(4-(methylsulfonyl)phenyl)prop-2-en-1-one

Chalcone or benzylideneacetophenone or 1,3-diphenyl-2*E*-propene-1-one is an open chain intermediate in the synthesis of aurones of the flavones pathway and subsist in numerous conjugated forms as the originator of many flavonoids and isoflavonoids compounds (Mahapatra & Bharti, 2016). They have been reported to exhibit anti-hypertensive, anti-arrhythmic, anti-obesity, anti-platelet, hypolipidemic (Mahapatra *et al*., 2016), anti-histaminic, anti-gout, anti-ulcer, anti-inflammatory (Mahapatra *et al*., 2017f), anti-filarial, anti-malarial, anti-tubercular, anti-fungal, anti-retroviral, anti-bacterial, anti-protozoal (Mahapatra *et al*., 2015), anti-neoplastic, anti-oxidant, anti-angiogenic (Mahapatra *et al*., 2015a), anti-diabetic (Mahapatra *et al*., 2015b), etc. The methylsulfonyl containing chalcone gained prime attention on account of anti-oxidant, anti-bacterial, anti-fungal (Kamble *et al*., 2011), anti-inflammatory, anti-nociceptive (Razmi *et al*., 2013), and anti-cancer activity (Ismail *et al*., 2013).

In the present research, a chalcone was fabricated rationally by incorporating a natural portion (murrayanine) in the A-ring and a synthetic component (4-methylsulfonyl group) in the B-ring and screened against two bacterial and two fungal species.

MATERIALS AND METHODS

Chemicals and Instrumentation

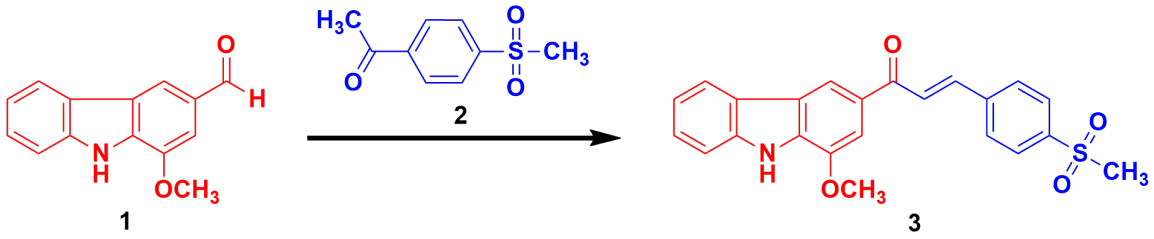
4′-(methylsulfonyl) acetophenone, the reactant, was purchased from Sigma Aldrich, Germany. The reagents and chemicals employed for the extraction of murrayanine and for experimental studies were of analytical grade and procured from HiMedia Ltd., India. The spectral data were obtained using the following: FT-IR study (KBr based Shimadzu® IRAffinity-1 instrument); ^{1}H-NMR study (Bruker Avance-II instrument, calibrated using the internal standard tetramethylsilane); and mass study (MICROMASS Q-TOF instrument). The progress of the reaction was detected by pre-coated TLC plates of silica gel-G (Merck, India). CHN analysis was performed on PerkinElmer 2400 model Elemental Analyzer.

Extraction of murrayanine

The starting compound murrayanine **(1)** was isolated based on our previous reports (Mahapatra *et al*., 2017). The powdered *M. koenigii* stem bark was extracted with n-hexane employing silica gel-based column chromatography and the obtained hexane fractions (B_{21}-B_{37}) were inspected by thin layer chromatography. The product was further concentrated using the vacuum rotary evaporator.

Synthesis of target compounds

The semi-synthesis involved reaction of –CHO portion (aldehyde) of murrayanine **(1)** with the acetyl part (-$COCH_3$) of the methylsulfonyl containing acetophenone **(2)** in the presence of the ethanolic NaOH solution to form a benzylideneacetophenone (chalcone) scaffold **(3)** comprising of a carbonyl function (β-hydroxyketone) by aldol condensation based mechanism (Mahapatra *et al*., 2017e). The **Scheme 1** describes the semi-synthetic route of chalcone compound.



Scheme 1. Semi-synthetic approach for the fabrication of chalcone based compound.

Synthetic protocol for (*E*)-1-(1-methoxy-9*H*-carbazol-3-yl)-3-(4-(methylsulfonyl) phenyl) prop-2-en-1-one (3)

In the presence of an aqueous solution of sodium hydroxide (20 mL) containing 90% ethanol (25 mL), an equal concentration (0.01 M) of murrayanine **(1)** and 4′-(methylsulfonyl) acetophenone **(2)** were reacted in reflux system for the period of 3 hr. For overnight, the reaction content was made to stand and the

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mixture was added over the ice (containing a few drops of dilute HCl) with stirring to precipitate out the solid product. The obtained chalcone **(3)** was filtered, washed properly, and recrystallized suitably.

61% yield; FTIR (KBr) υ (cm^{-1}): 3199 (-NH, stretching), 3121 (C-H, aromatic), 1686 (C=O), 1619 (C=C, aromatic), 1573 (-NH, bending), 1304 (C-N), 1248 (C-O), 1056 (S=O); ^{1}H NMR (δ, ppm, $CDCl_3$): 10.14 (9, 1H), 7.2-8.5 (Aromatic, 10H), 3.77 (1, 3H), 3.29 (17, 3H). MS: M^+ 405. Anal. Calcd. for $C_{23}H_{19}NO_4S$: C, 68.13; H, 4.72; N, 3.45. Found: C, 67.88; H, 4.29; N, 3.14.

Anti-microbial screening

The fabricated chalcone **(3)** was screened both for anti-bacterial studies against *Escherichia coli* (*E. coli*, MTCC 2961) and *Staphylococcus aureus* (*S. aureus,* MTCC 3160), and also for anti-fungal studies against *Candida albicans* (*C. albicans*, MTCC 227) and *Aspergillus niger* (*A. niger*, MTCC 277). The study was performed by disc diffusion method against these pathogens by employing Muller Hinton Agar medium (for anti-bacterial) / Potato dextrose agar medium (for anti-fungal). Initially, the species were cultured in the nutrient broth environment followed by incubation at 37°C for 24 hr. Subsequently, the cultured microbial cells were transferred onto the specific agar plates under a laminar flow cabinet. The experimental compound was dissolved in dimethylsulfoxide (DMSO), soaked over Whatman filter paper, kept over the bacterial plates, and incubated at 37°C for 24 hrs (for anti-bacterial) / 28±2°C for 72 hrs (for anti-fungal). The anti-microbial potential was measured from the zone of inhibition diameter (in mm) using ciprofloxacin (for anti-bacterial) / fluconazole (for anti-fungal) as the positive control and DMSO as the negative control (Telrandhe *et al*., 2017). The minimum inhibitory concentration (MIC) was determined by the agar streak dilution method which involved the preparation of microbial suspension containing 10^5 CFU/mL (approximately) and applied to the petridish with serial dilution in DMSO. The required quantity of the suspension containing the test sample was transferred at a temperature of40-50°C into a petridish, up to 4-5 mm depth and permitted to set aside. The microbial content was incubated at 37±1°C. The MIC values were measured in triplicate manner and their average was taken. Ciprofloxacin (for anti-bacterial) / fluconazole (for anti-fungal) was employed as the positive control and DMSO as the negative control (Kamble *et al*., 2017).

RESULTS AND DISCUSSION

Chemistry

The FT-IR spectra revealed several crucial aspects which aided in the structure determination. The vanishing of respective aldehydes peak in the spectra of the starting material murrayanine **(1)** and evolution of a new peak of the C=O at 1686 cm^{-1} in IR-spectra supported the formation of chalcone **(3)**. The determined ratios of carbon, hydrogen, and nitrogen by the elemental analysis further supported the fabrication of the new compound. The ^{1}H-NMR spectra helped to obtain vital structural information. The observed range of 7.2-8.5 ppm presented the existence of 10 aromatic protons. The methyl protons of the methylsulfonyl group were chiefly noticed at 3.29 ppm, confirming the unification of the synthetic component at ring-B of the chalcone. Additionally, the protons of the methoxy group were chiefly located at 3.77 ppm. The –NH section of the murrayanine was principally seen at 10.14 ppm, thereby, further confirming the presence of natural portion in the ring-A of the chalcone. Besides the obtained data, the mass spectra finally confirmed the formation of the proposed compound due to the appearance of the base peak corresponding with the molecular weight of the chalcone **(3)**. The fragment peaks (m/z 100-175) represented the fragmentation of the molecule into respective aromatic fragments.

Anti-microbial study

The formed product **(3)** expressed noteworthy anti-microbial activity. The fabricated chalcone was observed to be a better anti-bacterial agent as compared to its anti-fungal potentials. The molecule exhibited the best growth inhibition of *E. coli* as compared to *S. aureus*. The anti-fungal activity of the compound was displayed best against *A. niger* than *C. albicans* (**Table 1**). However, a marked difference in the inter- and intra-variability was not observed. As compared to the standard drugs, the experimental molecule does hold well against pathogenic challenges. Therefore, from this study, an anti-infective perspective was found for the novel chalcone.

CONCLUSION

The rationally designed chalcone; (*E*)-1-(1-methoxy-9*H*-carbazol-3-yl)-3-(4-(methylsulfonyl) phenyl) prop-2-en-1-one, comprising of both natural (murrayanine) and synthetic (4-methylsulfonyl) components demonstrated noteworthy anti-microbial activity. The fabricated chalcone was observed to be a better anti-bacterial agent as compared to its anti-fungal potentials. As compared to the standard drugs, the experimental molecule does hold well against pathogenic challenges. The present research, therefore, opened new avenues of judiciously developing a natural scaffold having an active methylsulfonyl group, which will inspire life science researchers across the globe in developing inhibitors with pronounced biological activity as compared with the parent compounds.

ACKNOWLEDGMENT

Authors are highly thankful to Savitribai Phule Pune University, Pune, Maharashtra, India for providing research grants (Grant No. 13PHM000126).

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Table 1. Anti-microbial activity of the synthesized chalcone.

Compounds	*E. coli*	*S. aureus*	*C. albicans*	*A. niger*
3	24.11±0.94 (25)	26.34±1.12 (25)	20.57±1.24 (25)	21.44±0.89 (25)
Ciprofloxacin	33.73±1.76 (6.25)	31.28±1.69 (6.25)	-	-
Fluconazole	-	-	31.83±1.81 (6.25)	32.54±1.37 (6.25)

Zone of inhibition in millimeter, SD = standard deviation.

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How to cite this article

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CONFLICTS OF INTEREST

"The authors declare no conflict of interest".