



# Anti-inflammatory Potential of a Novel Imidazole Containing Murrayanine Based Chalcone



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## Abstract

Murrayanine is an active carbazole compound present in the Indian Curry tree, known as *Murraya koenigii* L. belonging to the family Rutaceae. Traditionally, it is known to exhibit anti-anemic, febrifuge, carminative, stomachic, purgative, astringent, and anthelmintic. The present research involved the synthesis of (*E*)-3-(4-(1*H*-imidazol-1-yl)phenyl)-1-(1-methoxy-9*H*-carbazol-3-yl)prop-2-en-1-one from murrayanine and 4-(imidazol-1-yl)acetophenone and exploring the anti-inflammatory activity of the fabricated hybrid. The current effort involved screening the significance of imidazole function present in the ring-B of the murrayanine-chalcone scaffold and their further optimization thereof with emphasis on structural aspects. A moderate edema reducing potential has been seen in the newly developed compound (3). As compared with the indomethacin, the standard drug, the chalcone exhibited impressive anti-inflammation effect after 3hrs. The activity may be mediated by inhibiting the pro-inflammatory constituents like cyclooxygenase-2 (COX-2) and lipoxygenase (5-LOX) which may be due to the imidazole group and benzylidene acetophenone scaffold. This study will open new avenues of research by promoting the development of more potent natural product based hybrid compounds with a high level of safety. In successive studies, more derivatives may be prepared to rationally study the structural influence over the activity and to derive information which will be of applied interest.

**Keywords:** Murrayanine; *Murraya koenigii*; Imidazole; Chalcone; Inflammation; Synthesis

**Abbreviations:** COX-2: Cyclooxygenase-2; LOX: Lipoxygenase; DEC: Department Ethical Committee; TMS: Tetra Methyl Silane

## Introduction

Murrayanine is an active carbazole compound present in the Indian Curry tree, known as *Murraya koenigii* L. belonging to the family Rutaceae [1]. In general, the extract comprises of murrayanine, eucrestine B, mahaninebine, mahanine, bismahanine, koenimbine, O-methylmahanine, bispyrayafoline, mahaninebicine, O-methylmurrayanine A, isomahanine, bismurrayafoline, etc [2]. Traditionally, it is known to exhibit anti-anemic, febrifuge, carminative, stomachic, purgative, astringent, and anthelmintic [3]. Murrayanine is the extremely investigated molecule due to the simplicity of the chemical characteristics, an application template promoting semi-synthesis, facilitates substitution at multiple sites, and its resultant therapeutic aspects, etc [4]. Mother Nature has all the solution for all the prevailing ailments, and therefore nature-based scaffold/skeleton will definitely lead to the development of potent inhibitor molecules [5].

In our previous research, murrayanine was explored exhaustively for developing several promising semi-synthetic derivatives or hybrid compounds rationally with enhanced pharmacological effect, reduced toxicity, and better target modulator perspective. The hybrids of thiazole, oxazole,

hydantoin, thiazole, pyrimidine, pyrrole, isoxazole, benzodiazepine, benzothiazepine, benzoxazepine, phthalimide, etc. were fabricated which demonstrated better therapeutic potentials like anti-bacterial, anti-fungal, anti-oxidant, anti-inflammatory, anti-diabetic, anti-anxiety, anti-convulsant, etc [6-14]. The present research involved the synthesis of (*E*)-3-(4-(1*H*-imidazol-1-yl)phenyl)-1-(1-methoxy-9*H*-carbazol-3-yl)prop-2-en-1-one from murrayanine and 4-(imidazol-1-yl)acetophenone and exploring the anti-inflammatory activity of the fabricated hybrid. The current effort involved screening the significance of imidazole function present in the ring-B of the murrayanine-chalcone scaffold and their further optimization thereof with emphasis on structural aspects.

## Materials and Methods

### Chemicals and instrumentation

The starting compound, murrayanine was procured by extraction from *Murraya koenigii* L. by the soxhlation process as previously reported by our group [15]. The reactant 4-(imidazol-1-yl)acetophenone was purchased from Sigma-Aldrich, Germany. The analytical grade reagents and solvents used during synthesis

were purchased from HiMedia Ltd., Mumbai, India. The progress of the reaction was monitored by Merck pre-coated TLC plates of Silica Gel-G. The FT-IR study was performed in Shimadzu® IRAffinity-1 (KBr system). The <sup>1</sup>H-NMR was obtained on Bruker Avance-II instrument employing tetramethylsilane (TMS) as the internal standard. The mass spectra were recorded on MICROMASS Q-TOF instrument. The PerkinElmer 2400 model Elemental Analyzer was utilized for CHN analyses.

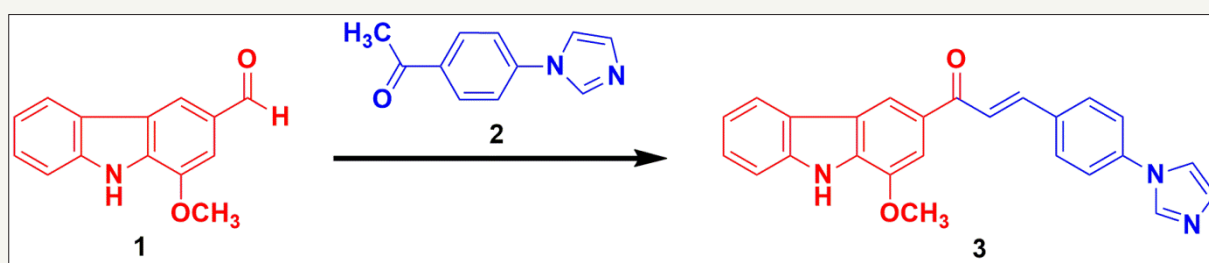
### Animals

Same-sex albino rats of 5-6 weeks age, having body weight range of 140-230g were taken for the experiment after getting permission from the Department Ethical Committee (DEC) as well as CPCSEA (1389/a/10/CPCSEA). The experimental animals were kept under hygienic conditions in the animal house under controlled environment (temp. 24-25°C/50-60% RH/and 12hr

light/dark shift). The rats were provided free access to standard rodent feed and water.

### Synthesis of target compounds

The imidazole containing murrayanine chalcone was synthesized from the starting carbazole material, murrayanine (1), extracted from the stem bark of *M. koenigii* L. The reaction involved reacting the -CHO portion (aldehyde) of murrayanine with the acetyl part (-COCH<sub>3</sub>) of the imidazole containing acetophenone (2) in the presence of the ethanolic NaOH solution. The plausible mechanism of chalcone formation was an aldol condensation which includes enolate ion reaction with the carbonyl function to derive a β-hydroxyketone followed by a dehydration to yield enone component (3). The (Figure 1) depicts the reaction for the synthesis of chalcone derivative.



**Figure 1:** Synthesis outline of novel imidazole containing murrayanine based chalcone.

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

Murrayanine (1) and 4-(imidazol-1-yl)acetophenone (2) were made to react in equimolar concentration (0.01M) in presence of an aqueous solution of sodium hydroxide (20mL) containing 90% ethanol (25mL). The content was made to reflux for the duration of 3hr and the reaction mixture was kept for the whole night. Following that, the content was poured over crushed ice and the content was separated in presence of dil. HCl (few drops). The precipitated solid product was washed thoroughly with water, filtered under vacuum using a Buchner funnel, and re-crystallized properly.

73% yield; FTIR(KBr) $\nu$ (cm<sup>-1</sup>): 3217(-NH, stretching), 3174(C-H, aromatic), 1701(C=O), 1649(C=N), 1663 (C=C, aromatic), 1568(-NH, bending), 1281(C-N), 1252(C-O); <sup>1</sup>H NMR( $\delta$ , ppm, CDCl<sub>3</sub>): 10.28(9, 1H), 7.1-8.6(Aromatic, 13H), 3.89(1, 3H). MS: M<sup>+</sup> 393. Anal. Calcd. for C<sub>25</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>: C, 76.32; H, 4.87; N, 10.68. Found: C, 76.17; H, 4.39; N, 10.23.

### Acute toxicity studies

According to the OECD guideline, the *in vivo* safety of the molecule in therapeutics/testing is an essential criterion. The acute toxicity study was performed to determine the highest therapeutic dose which will demonstrate no considerable mortality. The study involved progressively increasing doses of the experimental molecule from 25 to 500mg/kg. The therapeutic dose was decided based on LD<sub>50</sub> value [16].

### Anti-inflammatory screening

The *in vivo* anti-inflammatory activity of the fabricated molecule was studied by carrageenan-induced paw edema method. The experimental protocol was performed in overnight fasted rats to reduce any inconsistency of edema. The rats in the control group received the saline solution containing a few drops of solubilizer (Tween 80). Before initiation of protocol, 5mL of distilled water was administered by oral route, individually. The inflammation was created by introducing 1% carrageenan solution at the right hind paw via the subcutaneous route. The edema reducing potential was screened at a dose of 100mg/kg b.w. The compound was initially suspended in saline solution and administered 1hr previous to the commencement of the study. The edema was measured using mercury digital micrometer for 3hrs duration with an interval of 1hr. The difference in the dimension of the width of injected and non-injected paws was computed to determine the edema reducing the ability of the experimental compound. The acquired results were expressed as the Mean $\pm$ SEM [17].

### Statistical treatment

The experimentally generated data were analyzed by one-way ANOVA method followed by treatment with Dunnett's multiple comparison test. The value of P<0.01 was considered to be statistically significant.

## Results and Discussion

### Chemistry

The spectroscopy and elemental analysis studies supported the formation of the compound (3). The disappearance of (-CHO) component and the appearance of C=O at 1701cm<sup>-1</sup> confirmed the formation of the chalcone. The C=N component at 1649cm<sup>-1</sup> substantiates the presence of five-membered imidazole portion. The key FT-IR spectral data have been highlighted in the experimental section. The <sup>1</sup>H-NMR spectra represented few key aspects. The spectral range of 7.1-8.4ppm emphasizes the presence of protons in the compound. Additionally, the -NH and -OCH<sub>3</sub> aspects were located at 10.28ppm and 3.89ppm, respectively. Furthermore, the mass spectra presented exactly the same molecular weight of the fabricated molecule in the base peak. In addition to that, the fragment peaks (m/z 100-200) also appeared. Finally, the observed ratio(s) of the elements (C, H, and N) of the produced derivative was found to be of immense support.

### Acute toxicity study results

The compound (3) did not show any sign of toxicity with the escalated dose and was seen as a safe compound. The anti-inflammatory was screened at a dose of 100mg/kg b.w.

### Anti-inflammatory screening

**Table 1:** In vivo anti-inflammatory potential of (*E*)-3-(4-(1*H*-imidazol-1-yl)phenyl)-1-(1-methoxy-9*H*-carbazol-3-yl)prop-2-en-1-one.

Compound	Percentage (%) Inhibition of Edema		
	1hr	2hr	3hr
3	20.54**±2.19	29.24*±2.32	40.13*±2.77
Indomethacin	46.17**±1.42	59.66*±1.81	73.91**±1.34

n=6; ED<sub>50</sub> of 100mg/kg bw in male adult albino mice; \*\*P<0.01; \*P<0.05

A moderate edema reducing potential has been seen in the newly developed compound (3). As compared with the indomethacin, the standard drug, the chalcone exhibited impressive anti-inflammation effect after 3hrs. The activity may be mediated by inhibiting the pro-inflammatory constituents like cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) which may be due to the imidazole group and benzylideneacetophenone scaffold [18]. However, it may be predicted that rationally substituting the murrayanine portion (Ring-A) and the imidazole part (Ring-B) by electron-withdrawing/donating group may lead to enhanced pharmacological activity, which was awfully missing in this study. The substitution by different moieties comprising of active oxygen and nitrogen atoms may facilitate the binding with the active site of the inflammation mediating targets [19]. Moreover, it may be envisaged that due to the lack of lipophilic groups, the compound (3) did not penetrate

or cross the biological membrane to mediate the effect. Therefore, the lipophilic group may play an imperative role in promoting the anti-inflammatory activity (Table 1).

### Conclusion

The research presented a semi-synthetic approach for the fabricating of imidazole containing chalcone molecule which demonstrated noteworthy anti-inflammatory activity as compared with the standard drug, indomethacin. However, it may be stated that substitution by electron-withdrawing/donating group at both the rings may facilitate better edema reducing activity due to the oxygen and nitrogen atoms which will promote strong binding with the inflammation mediating targets like COX-2 and LOX. This study will open new avenues of research by promoting the development of more potent natural product based hybrid compounds with a high level of safety. In successive studies, more derivatives may be prepared to rationally study the structural influence over the activity and to derive information which will be of applied interest.

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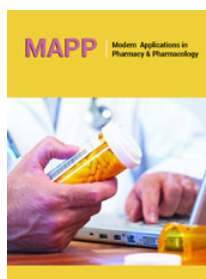
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