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Novel Schiff's Base Containing Murrayanine-1,3,4-Thiadiazole Hybrids as Potential Anti-Inflammatory Agents

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Abstract

Murrayanine is the most highly explored molecule from *Murraya koenigii* L., known popularly as Indian curry plant (family Rutaceae) which demonstrates carminative, astringent, stomachic, purgative, febrifuge, anti-anemic, and anthelminthic. Thiadiazole is a scaffold of prime importance in medicinal chemistry. It has often been observed that thiadiazoles on hybridization with other heterocyclic scaffolds, demonstrates synergistic activity. Based on this fact, a hybrid of 1,3,4-thiadiazole was planned to fabricate with murrayanine and also to explore its synergistic potentials in a specific direction based on the available text information. The present study involved the synthesis of murrayanine-thiadiazole hybrids using a previously reported starting material (*E*)-2-((1-methoxy-9*H*-carbazol-3-yl)methylene)thiosemicarbazide and exploring the anti-inflammatory activity of the produced novel compounds. The compound 4c, containing 3-OCH_3 and 4-OH substituents displayed the highest edema reducing activity after 3 hrs. The enhanced activity may be due to the interaction of the hydrophilic moiety, via oxygen moiety with the active site of the inflammation causing elements like Cyclooxygenase (COX) and Lipoxygenase (LOX). We tried to establish a crystal clear structure-activity relationship, but due to mixed results, a true relationship cannot be predicted. Rather, an assumption was made based on the available interacting groups with the active sites of the chemical mediator. This research will definitely motivate global researchers in rationally designing of natural product-based heterocyclic hybrids which will have great perspective as therapeutic agents in future with reduced side-effects.

Keywords: Hybrid, Inflammation, Murrayanine, *Murraya koenigii*, Schiff's Base, Thiadiazole

1. Introduction

Thiadiazole is a scaffold of prime importance in medicinal chemistry. This class of heterocycles has predominant relevance in the present era and several derivatives are already present in the market after successful clinical trials[1]. The privileged scaffold finds application in the fields and sub-fields of anti-microbial[2], anti-diabetic[3], anti-hypertensive[4], anti-cancer[5], anti-inflammatory[6], anti-tubercular[7], anti-depressant[8], anti-leishmanial[9], anti-ulcer[10], anti-viral[11], anti-arrhythmic[12], anti-nociceptive[13], anti-retroviral1[4], anti-trypanosomal[15], etc.

Murraya koenigii L., known popularly as Indian curry plant is a plant of Asian origin, belonging to the family Rutaceae[16]. The leaves find abundant use as a condiment in traditional Indian food habits and are believed

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to have several ethnopharmacological perspectives such as carminative, astringent, stomachic, purgative, febrifuge, anti-anemic, and anthelminthic[17,18]. Murrayanine is the most highly explored molecules owing to its simple chemistry, a research-friendly template for rapid semi-synthesis, multiple sites facilitating substitution, multifarious therapeutic applications, etc[19]. In our previous research, we have already reported numerous murrayanine hybrids as budding therapeutic agents which act by modulating various molecular targets[20–27].

It has often been observed that thiadiazoles on hybridization with other heterocyclic scaffolds, demonstrates synergistic activity[28]. Based on this fact, a hybrid of 1,3,4-thiadiazole was planned to fabricate with murrayanine and also to explore its synergistic potentials in a specific direction based on the available text information. The present study involved the synthesis of murrayanine-thiadiazole hybrids using a previously reported starting material (*E*)-2-((1-methoxy-9*H*-carbazol-3-yl)methylene) thiosemicarbazide and exploring the anti-inflammatory activity of the produced novel compounds.

2. Materials and Methods

2.1 Chemicals and Instrumentation

From a previously reported starting material (*E*)-2-((1-methoxy-9*H*-carbazol-3-yl)methylene) hydrazinecarbothioamide, the synthesis was commenced[20]. The required chemicals, solvents, and materials were of analytical grade and purchased from well-known companies; Sigma-Aldrich, HiMedia, and Merck. The spectroscopic analyses were performed on KBr based Shimadzu® IRAffinity-1 (for FT-IR study) and Bruker Avance-II using the tetramethylsilane (TMS) (for proton-NMR study). The mass spectra were obtained on MICROMASS Q-TOF instrument. The chemical reaction progress was monitored by Merck pre-coated silica gel-G TLC plates. The CHN analyses were carried out on PerkinElmer 2400 model Elemental Analyzer.

2.2 Animals

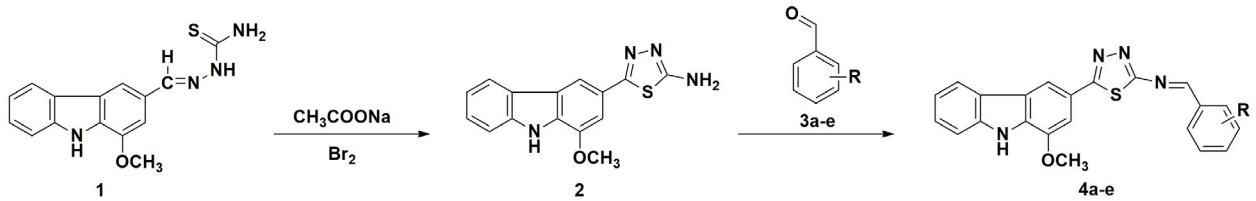
For the anti-inflammatory study, about 5-6 weeks aged albino rats (same sex) of body weight 160-270 g were used after receiving approval from the Department Ethical Committee (DEC) and CPCSEA (1389/a/10/CPCSEA). The rats were kept in the hygienic animal house under controlled environment of 24-25 °C temperature, humidity 50–60 %, and 12 hr light and dark. They were given free access to water and standard rodent pellet feed.

2.3 Synthesis of Target Compounds

The murrayanine-thiadiazole (**4a-e**) were designed rationally by utilizing (*E*)-2-((1-methoxy-9*H*-carbazol-3-yl) methylene)thiosemicarbazide **(1)** as the starting material. The thiosemicarbazide portion was cyclized to thiadiazole moiety **(2)** using sodium acetate and bromine. The produced amine-containing thiadiazole was further made to react with respective aldehydes; benzaldehyde **(3a)**, cuminaldehyde **(3b)**, vanillin **(3c)**, veratraldehyde **(3d)**, and syringaldehyde **(3e)** to yield corresponding Schiff's base analogs by employing glacial acetic acid. The **Scheme 1** portrays the reaction scheme of the novel murrayanine-thiadiazole hybrids.

Synthetic protocol for 5-(1-methoxy-9H-carbazol-3-yl)-1,3,4-thiadiazol-2-amine **(2)**

(*E*)-2-((1-methoxy-9*H*-carbazol-3-yl)methylene)thiosemicarbazide **(1)** (0.01 M) and sodium acetate (0.02 M) were dissolved in 50 mL of glacial acetic acid in a round bottom flask containing magnetic stirrer. Bromine (1 mL in 5 mL of glacial acetic acid) was added drop wise under constant stirring. After 1 hr of stirring, crushed ice was added to the reaction mixture. The solid product gets



Scheme 1. The outline for the synthesis of novel murrayanine-thiadiazole hybrids.

separated in precipitate form, which was separated, thoroughly dried, and recrystallized from raw ethanol.

51% yield; FTIR (KBr) υ (cm^{-1}): 3376 (-NH_2), 3266 (-NH, stretching), 3193 (C-H, aromatic), 1609 (C=C, aromatic), 1581 (-NH, bending), 1299 (C-N), 1264 (C-O); ^{1}H NMR (δ, ppm, $CDCl_3$): 10.18 (9, 1H), 8.33 (11, 2H), 7.1-7.9 (Aromatic, 6H), 3.72 (1, 3H). MS: M^+ 296. Anal. Calcd. for $C_{15}H_{12}N_4OS$: C, 60.79; H, 4.08; N, 18.91. Found: C, 59.12; H, 3.71; N, 18.33

Synthetic protocol for (E)-5-(1-methoxy-9H-carbazol-3-yl)-N-(substituted-benzylidene)-1,3,4-thiadiazol-2-amine **(4a-e)**

To the methanol-ethanol solution of 5-(1-methoxy-9*H*-carbazol-3-yl)-1,3,4-thiadiazol-2-amine **(2)** (0.01 M), substituted benzaldehydes **(3a-e)** (0.01 M) were added with continuous stirring and the reaction mixture was refluxed for 8 hrs in the presence of a few drops of glacial acetic acid. The progress of the reaction was monitored by TLC technique. The content was poured onto crushed ice, the obtained precipitate was filtered off using Whatman filter paper and recrystallized using the ethanolic solution.

(*E*)-*N*-benzylidene-5-(1-methoxy-9*H*-carbazol-3-yl)-1,3,4-thiadiazol-2-amine **(4a)**

66% yield; FTIR (KBr) υ (cm^{-1}): 3247 (-NH, stretching), 3165 (C-H, aromatic), 1642 (Azomethine, C=N), 1636 (C=C, aromatic), 1554 (-NH, bending), 1291 (C-N), 1211 (C-O); ^{1}H NMR (δ, ppm, $CDCl_3$): 10.12 (9, 1H), 8.52 (Azomethine, 1H), 7.2-8.6 (Aromatic, 11H), 3.85 (1, 3H). MS: M^+ 384. Anal. Calcd. for $C_{22}H_{16}N_4OS$: C, 68.73; H, 4.19; N, 14.57. Found: C, 68.11; H, 3.80; N, 14.19

(*E*)-*N*-(4-isopropylbenzylidene)-5-(1-methoxy-9*H*-carbazol-3-yl)-1,3,4-thiadiazol-2-amine **(4b)**

41% yield; FTIR (KBr) υ (cm^{-1}): 3256 (-NH, stretching), 3148 (C-H, aromatic), 1619 (Azomethine, C=N), 1617 (C=C, aromatic), 1576 (-NH, bending), 1267 (C-N), 1232 (C-O); ^{1}H NMR (δ, ppm, $CDCl_3$): 10.17 (9, 1H), 8.47 (Azomethine, 1H), 7.3-8.1 (Aromatic, 10H), 3.81 (1, 3H), 1.29 (17, 6H). MS: M^+ 426. Anal. Calcd. for $C_{25}H_{22}N_4OS$: C, 70.40; H, 5.20; N, 13.14. Found: C, 69.23; H, 4.87; N, 12.68

(*E*)-2-methoxy-4-(((5-(1-methoxy-9*H*-carbazol-3-yl)-1,3,4-thiadiazol-2-yl)imino)methyl)phenol **(4c)**

53% yield; FTIR (KBr) υ (cm^{-1}): 3401 (-OH), 3214 (-NH, stretching), 3156 (C-H, aromatic), 1658 (Azomethine, C=N), 1641 (C=C, aromatic), 1590 (-NH, bending), 1288 (C-N), 1249 (C-O); ^{1}H NMR (δ, ppm, $CDCl_3$): 10.21 (9, 1H), 8.54 (Azomethine, 1H), 7.2-8.0 (Aromatic, 9H), 5.11 (16, 1H), 3.79 (1, 3H). MS: M^+ 430. Anal. Calcd. for $C_{23}H_{18}N_4O_3S$: C, 64.17; H, 4.21; N, 13.01. Found: C, 63.32; H, 3.98; N, 12.63

(*E*)-*N*-(3,4-dimethoxybenzylidene)-5-(1-methoxy-9*H*-carbazol-3-yl)-1,3,4-thiadiazol-2-amine **(4d)**

72% yield; FTIR (KBr) υ (cm^{-1}): 3222 (-NH, stretching), 3173 (C-H, aromatic), 1635 (Azomethine, C=N), 1624 (C=C, aromatic), 1568 (-NH, bending), 1276 (C-N), 1227 (C-O); ^{1}H NMR (δ, ppm, $CDCl_3$): 10.15 (9, 1H), 8.49 (Azomethine, 1H), 6.9-7.6 (Aromatic, 9H), 3.83 (1, 9H). MS: M^+ 444. Anal. Calcd. for $C_{24}H_{20}N_4O_3S$: C, 64.85; H, 4.54; N, 12.60. Found: C, 64.22; H, 4.17; N, 12.15

(*E*)-2,6-dimethoxy-4-(((5-(1-methoxy-9*H*-carbazol-3-yl)-1,3,4-thiadiazol-2-yl)imino)methyl)phenol **(4e)**

44% yield; FTIR (KBr) υ (cm^{-1}): 3467 (-OH), 3282 (-NH, stretching), 3144 (C-H, aromatic), 1628 (Azomethine, C=N), 1613 (C=C, aromatic), 1551 (-NH, bending), 1264 (C-N), 1218 (C-O); ^{1}H NMR (δ, ppm, $CDCl_3$): 10.12 (9, 1H), 8.59 (Azomethine, 1H), 7.2-8.5 (Aromatic, 8H), 5.28 (16, 1H), 3.87 (1, 9H). MS: M^+ 460. Anal. Calcd. for $C_{24}H_{20}N_4O_4S$: C, 62.60; H, 4.38; N, 12.71. Found: C, 62.14; H, 3.94; N, 12.27

2.4 Acute Toxicity Studies

Acute toxicity study is a mandatory protocol for assessment of *in vivo* safety as per the OECD guidelines to evaluate the level of maximum therapeutic effect with no significant mortality. The study procedure involved the introduction of steadily rising doses of the molecules from 25 mg/kg to 500 mg/kg. The therapeutic dose was calculated based on 50% death of the rats.

2.5 Anti-Inflammatory Screening

Employing the standard carrageenan-induced paw edema method, the *in vivo* anti-inflammatory activity of the fabricated molecules was assessed. The rats were fasted overnight before the initiation of the protocol so as to decrease the discrepancy of edema. Previous to the starting of the experimentation, by oral route 5 mL of distilled

water was administered individually. The control group rats received the saline solution containing a few drops of Tween 80 (solubilizer). The experimental molecules at a dose of 100 mg/kg b.w. were suspended firstly in the saline solution and administered orally 1 hr before the initiation of inflammation. The inflammation was produced in the right hind paw of rats (subplanter region) by injecting 1% carrageenan solution via the subcutaneous route. The mercury digital micrometer was utilized to determine the edema where the thickness of each rat paw was measured for the duration of 3 hrs with an interval of 1 hr. The ability of the experimental compounds in reducing the edema was measured by the difference between the width of injected and non-injected paws. The obtained results were expressed as the Mean±SEM.

2.6 Statistical Treatment

The data were statistically analyzed by one-way ANOVA approach followed by Dunnett's multiple comparison test. The $P<0.01$ value was considered to be the most statistically significant.

3. Result and Discussion

3.1 Chemistry

The data obtained from the spectroscopic analysis supported the formation of the targeted molecules. The formation of the compound **(2)** was proved from the FT-IR spectra by the disappearance of the Schiff's base of compound **(1)** in the range of 1540-1680 cm^{-1}. The fabrication of the molecules **(4a-e)** was predominantly confirmed as a result of the disappearance of NH_2 group from the FT-IR spectra of the molecule **(2)** and the emergence of Schiff's base formation in the range of 1619-1658 cm^{-1}. The final step of conversion was guaranteed by studying the FT-IR spectra of the individual compounds very thoroughly. The molecules (**4c** and **4e**) were easily as certained by the appearance of the hydroxyl group (-OH) at 3401 and 3467 cm^{-1}, respectively. The aromatic rings were found out from the C=C and C-H absorption frequencies in FT-IR spectra which emerged in 1613-1641 cm^{-1} and 3144-3173 cm^{-1}, respectively. Furthermore, the existence of five-membered scaffold was indeed acknowledged by the –NH stretching and bending at 3214-3282 and 1554-1590 cm^{-1}, correspondingly.

The proton NMR (^{1}H-NMR) certainly added more inputs to the available FT-IR spectra and presented a better vision for the verification. The protons present in the nitrogen of carbazole was principally located at 10 ppm. The spectral region of 6.9-8.6 ppm, indicated the hydrogens of the aromatic rings. The disappearance of NH_2 group of compound **(2)** which earlier appeared at 8.33 ppm in the proton-NMR spectra and appearance of new azomethine peaks in the range 8.47-8.59 ppm largely authenticate the formation of analogs (**4a-e**). The analog (**4b**) was confirmed by the presence of two bulky methyl group which appeared at 1.29 ppm, while the molecule (**4d** and **4e**) were verified by the hydroxyl moieties which emerge at 5.11 and 5.28 ppm, respectively. The peaks of the methoxy groups were noticed mainly at 3.8 ppm. The mass spectra of the derivatives demonstrated that the base peaks corresponds similarly or exactly the theoretical molecular weight. The mass spectra further confirmed the transformation of the starting material **(1)** into the heterocyclic form **(2)**. In addition, fragment peaks of m/z 100-200 were seen. Lastly, the ratio(s) of elements of the produced derivatives additional substantiate the formation of novel compounds.

3.2 Acute Toxicity Study Results

The prepared derivatives of murrayanine-thiadiazoles were found to be very safe in the treated dose range with no toxic effects or signs observed. The anti-inflammatory effect of thecompounds was explored at the dose of 100 mg/kg b.w.

3.3 Anti-Inflammatory Screening

The fabricated compounds exhibited remarkable anti-inflammatory potentials in carrageenan-induced paw edema model. The compound **4c**, containing 3-OCH_3 and 4-OH substituents displayed the highest edema reducing activity after 3 hrs. The enhanced activity may be due to the interaction of the hydrophilic moiety, via oxygen moiety with the active site of the inflammation causing elements like Cyclooxygenase (COX) and Lipoxygenase (LOX). The compound **4e** having three moieties; 3,5-OCH_3 and 4-OH expressed considerable anti-inflammatory activity (**Table 1**). Although, it was noticed that inspite of the three interacting groups, the compound did not present the highest activity, which may be explained or predicted similarly to the previously mentioned phenomenon, where the steric hindrance may be an accountable reason that prevented the access of the compound to the active site of the chemical mediators. The molecule **4b**

Table 1. Exploring *in vivo* anti-inflammatory effect of murrayanine thiadiazole molecules 4(a-e) in carrageenan-induced paw edema rat models

Group	R	Percentage (%) inhibition of edema		
		1 hr	2 hr	3 hr
4a	H	19.12** ± 3.07	24.76** ± 2.64	37.79* ± 2.81
4b	$CH(CH_3)_2$	14.79* ± 2.92	21.51** ± 3.03	31.99** ± 2.48
4c	3-OCH_3; 4-OH	31.96** ± 2.44	43.59** ± 2.23	59.88** ± 2.01
4d	3,4-OCH_3	26.35* ± 2.61	33.86** ± 2.42	47.71* ± 2.33
4e	3,5-OCH_3; 4-OH	24.57** ± 2.13	36.41** ± 2.68	54.27** ± 2.16
Indomethacin	-	43.55** ± 1.63	51.94** ± 1.26	70.62** ± 1.87

n = 6; ED_{50} of 100 mg/kg b.w. in male adult albino mice; **P < 0.01; *P< 0.05

articulated the least edema suppression potential as indicated by the obtained results. This may be explained as an inability of the molecule to bind to the active site of COX and LOX through the bulky methyl substituents. The aromatic ring containing (**4a**) demonstrated fairly good activity. The plausible reason may be the lipophilicity of the compound that facilitated easy crossing of the biological membranes and interact with the mediators. But, the activity was not comparable with the analogs (**4c** and **4e**). The other molecules (**4d**) showed a considerable inflammatory reducing potential.

4. Conclusion

The research certainly highlighted the potential of murrayanine-thiadiazole hybrids as anti-inflammatory candidates. The compound **4c**, containing 3-OCH_3 and 4-OH substituents displayed the highest edema reducing activity after 3 hrs. We tried to establish a crystal clear structure-activity relationship, but due to mixed results, a true relationship cannot be predicted. Rather, an assumption was made based on the available interacting groups with the active sites of the chemical mediator. This research will definitely motivate global researchers in rationally designing of natural product-based heterocyclic hybrids which will have a great perspective as therapeutic agents in future with reduced side-effects.

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