Acta Scientific Pharmaceutical Sciences

Volume 2 Issue 5 May 2018

Research Article

# Transforming Murrayanine-Chalcone into Corresponding 3*H*-benzo[b] [1,4] diazepine Derivatives: Accessing the Anti-Anxiety Effect by Inhibition of Locomotor Activity

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**Received:** March 21, 2018; **Published:** April 25, 2018

## Abstract

The numerous positive results and broad avenues of research on Murrayanine, a heterocyclic compound (carbazole) obtained from Indian curry plant *Murraya koenigii* L. (Rutaceae) have attracted us in developing semi-synthetic products with better pharmacodynamics and pharmacokinetic profiles. From our research group, various therapeutically active murrayanine based hybrid compounds have been developed where the extracted murrayanine was cyclized to various five/six-membered heterocyclic components such as isoxazole, thiazole, phthalimide, pyrazole, pyrimidine, hydantoin, Schiff's bases, etc. which demonstrated multifarious pharmacological activities like anti-oxidant, anti-convulsant, anti-bacterial, anti-fungal, anti-cancer, anti-diabetic, and anti-inflammatory. The present research aimed at developing several seven-membered heterocycle 3*H*-benzo[b][1,4]diazepine derivatives from Murrayanine-Chalcone, a hybrid compound previously reported by our research group by cyclization reaction and exploring the anti-anxiety or hypnotic effects of the fabricated molecule by evaluating locomotor inhibitory activity in Swiss albino rat. The study revealed the perspective to fabricate semi-synthetic heterocycles from murrayanine, which is a natural product and thus render desired safety and efficacy. The sophisticated analytical and spectroscopic tools revealed that the compounds were found to be in close agreement with that of the proposed structure. The influence of position, number, and the type of substituent were comprehensively studied where the lipophilic substituent containing scaffold **(3h)** presented the highest locomotor inhibition and therefore will translate anti-anxiety effect therapeutically. The study will open new avenues of research and will surely motivate the researchers in the rational development of safe and efficacious molecules in future from natural origin.

**Keywords:** Murrayanine; Chalcone; Benzodiazepine; Heterocycle; Locomotor; *Murraya koenigii*

## Introduction

Murrayanine, a heterocyclic compound (carbazole) obtained from Indian curry plant *Murraya koenigii* L. belonging to the family Ruta¬ceae [1]. The literature reported that hydroalcoholic, aqueous, and ethanol extracts of the root, leaf, and stem bark of *M. koenigii* L. have been reported to exhibit anti-oxidant, anti-tumor, anti-trichomal, anti-stress, analgesic, anti-inflammatory, anti-microbial, anti-ulcerogenic, anti-diabetic, anti-fungal, immunomodulatory, etc [2,3]. Ethnopharmacologically, the plant is known to promote appetite and digestion, applied externally to bruises, burn, and eruption. It is used internally as a potent stomachic, astringent, carminative, anti-helminthic, purgative, febrifuge, anti-anemic, antiperiodic, leucoderma, and blood disorders. Old texts of Ayurvedic System have described its utility for strengthening gums and teeth, bitter, acrid, cooling, analgesic, inflammation and itching [4,5].

The numerous positive results and broad avenues of research have attracted us in developing semi-synthetic products with better pharmacodynamics and pharmacokinetic profiles. Very recently, from our research group, various therapeutically active murrayanine based hybrid compounds have been developed. The extracted murrayanine was transformed into chalcone and was cyclized to various five/six-membered heterocyclic components such as isoxazole, thiazole, phthalimide, pyrazole, pyrimidine, hydantoin, Schiff's bases, etc. which demonstrated multifarious pharmacological activities like anti-oxidant, anti-convulsant, anti-bacterial, anti-fungal, anti-cancer, anti-diabetic, and anti-inflammatory [6-13].

The present research aimed at developing several seven-membered heterocycle 3*H*-benzo[b][1,4]diazepine derivatives from Murrayanine-Chalcone, a hybrid compound previously reported by our research group by cyclization reaction and exploring the anti-anxiety or hypnotic effects of the fabricated molecule by evaluating locomotor inhibitory activity in Swiss albino rat.

## Materials and Methods

### Chemical and Instrumentation

The starting material was obtained from our previous reports work, where a hybrid compound referred as "Murrayanine-Chalcone" was utilized. The chemical reagents for reaction and analytical grade solvents were procured were of Sigma-Aldrich, HiMedia, and Merck companies, from a local vendor. Pre-coated silica gel G TLC plates from Merck were utilized to monitor the progress of the chemical reaction. Using KBr methods, the IR spectra were

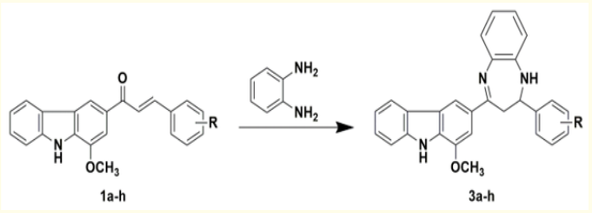
recorded using infrared spectrometer of Shimadzu® IRAffinity$^{-1}$. The obtained absorption frequencies were reported in cm$^{-1}$. MICROMASS Q-TOF instrument was employed for recording the mass spectra. PerkinElmer 2400 model Elemental Analyzer was used for CHN analysis. Employing tetramethylsilane (TMS), the internal standard, $^1$H NMR was recorded using Bruker Avance-II instrument. The chemical shifts were described in ppm relative to the internal standard.

## Animals

After getting proper approval from the Department Ethical Committee (DEC) and CPCSEA (1389/a/10/CPCSEA), the experiment was carried out on Swiss albino rat (6 in number) of age 5-6 weeks, having the body weight in the range of 160 - 290g. For carrying out the protocol, the rats were housed under a good hygienic state in the animal house where controlled temperature (24 - 25ºC temperature, humidity 50 - 60%, 12 hr light and dark). The rats were allowed to feed standard rodent pellets and were given free access to water.

## Synthesis of target compounds

The reaction involved a rational transformation of "murrayanine-chalcone" **(1a-h)**, the class of compound reported by our research group into corresponding 3*H*-benzo[b][1,4]diazepine derivatives by using ortho-phenylenediamine **(2)** which facilitates instantaneous alteration of the carbonyl portion into closed ring benzodiazepine form. The Scheme 1 illustrates the outline of chemical reaction.




1a-h 3a-h

**Scheme 1:** The chemical reaction for the synthesis of benzodiazepine derivatives from the murrayanine-chalcones.

## Synthetic protocol for (*E*)-3-(4-(substituted)-4,5-dihydro-3*H*-benzo[b][1,4]diazepin-2-yl)-1-methoxy-9*H*-carbazole (3a-h)

The murrayanine-chalcone derivatives **(1a-h)** (0.1 M) were made to react with ortho-phenylenediamine **(2)** in DMF in the presence of few drops of piperidine by refluxing 8-10 hrs. The reaction progress was scrutinized by using TLC. After confirming the completion of the reaction, the mixture was distilled to eliminate the excess solvent and crushed ice was added into it to obtain the crude solid product. The acquire product was filtered using Buchner's funnel, washed thoroughly with cold water and recrystallized from raw ethanol to attain pure products in good yields [14].

## (*E*)-3-(4-(2-fluorophenyl)-4,5-dihydro-3*H*-benzo[b][1,4]diazepin-2-yl)-1-methoxy-9*H*-carbazole (3a)

54% yield; FTIR (KBr) υ (cm$^{-1}$): 3220 (-NH), 3141 (C-H, aromatic), 1657 (C=N, aromatic), 1628 (C=C, aromatic), 1562 (-NH, bending), 1302 (C-N), 1277 (C-O), 1146 (C-F); $^1$H NMR (δ, ppm, $CDCl_3$): 10.23 (9, 1H), 6.7 - 7.9 (Aromatic, 14H), 3.97 (1, 3H), 2.12 (12, 1H); MS: M$^+$ 435. Anal. Calcd. for $C_{28}H_{22}FN_3O$: C, 77.22; H, 5.09; N, 9.65. Found: C, 76.66; H, 4.85; N, 9.49.

## (*E*)-3-(4-(4-fluorophenyl)-4,5-dihydro-3*H*-benzo[b][1,4]diazepin-2-yl)-1-methoxy-9*H*-carbazole (3b)

61% yield; FTIR (KBr) υ (cm$^{-1}$): 3234 (-NH), 3121 (C-H, aromatic), 1633 (C=N, aromatic), 1606 (C=C, aromatic), 1551 (-NH, bending), 1299 (C-N), 1252 (C-O), 1127 (C-F); $^1$H NMR (δ, ppm, $CDCl_3$): 10.28 (9, 1H), 6.9 - 7.7 (Aromatic, 14H), 3.71 (1, 3H), 2.23 (12, 1H); MS: M$^+$ 435. Anal. Calcd. for $C_{28}H_{22}FN_3O$: C, 77.22; H, 5.09; N, 9.65. Found: C, 76.52; H, 4.88; N, 9.53.

## (*E*)-3-(4-(2-iodophenyl)-4,5-dihydro-3*H*-benzo[b][1,4]diazepin-2-yl)-1-methoxy-9*H*-carbazole (3c)

43% yield; FTIR (KBr) υ (cm$^{-1}$): 3263 (-NH), 3108 (C-H, aromatic), 1666 (C=N, aromatic), 1637 (C=C, aromatic), 1522 (-NH, bending), 1325 (C-N), 1287 (C-O), 689 (C-I); $^1$H NMR (δ, ppm, $CDCl_3$): 10.19 (9, 1H), 7.1 - 8.9 (Aromatic, 14H), 3.84 (1, 3H), 2.19 (12, 1H); MS: M$^+$ 543. Anal. Calcd. for $C_{28}H_{22}IN_3O$: C, 61.89; H, 4.08; N, 7.73. Found: C, 60.17; H, 3.80; N, 7.54.

## (*E*)-3-(4-(4-iodophenyl)-4,5-dihydro-3*H*-benzo[b][1,4]diazepin-2-yl)-1-methoxy-9*H*-carbazole (3d)

39% yield; FTIR (KBr) υ (cm$^{-1}$): 3199 (-NH), 3136 (C-H, aromatic), 1651 (C=N, aromatic), 1623 (C=C, aromatic), 1535 (-NH, bending), 1314 (C-N), 1249 (C-O), 698 (C-I); $^1$H NMR (δ, ppm, $CDCl_3$): 10.26 (9, 1H), 7.1 - 8.5 (Aromatic, 14H), 3.79 (1, 3H), 2.16 (12, 1H); MS: M$^+$ 543. $C_{28}H_{22}IN_3O$: C, 61.89; H, 4.08; N, 7.73. Found: C, 61.02; H, 3.83; N, 7.61.

## (*E*)-3-(4-(4-bromophenyl)-4,5-dihydro-3*H*-benzo[b][1,4]diazepin-2-yl)-1-methoxy-9*H*-carbazole (3e)

48% yield; FTIR (KBr) υ (cm$^{-1}$): 3223 (-NH), 3181 (C-H, aromatic), 1644 (C=N, aromatic), 1607 (C=C, aromatic), 1558 (-NH, bending), 1347 (C-N), 1265 (C-O), 653 (C-Br); $^1$H NMR (δ, ppm, $CDCl_3$): 10.17 (9, 1H), 7.2 - 8.4 (Aromatic, 14H), 3.84 (1, 3H), 2.11 (12, 1H); MS: M$^+$ 495, M+2 497. Anal. Calcd. for $C_{28}H_{22}BrN_3O$: C, 67.75; H, 4.47; N, 8.47. Found: C, 67.11; H, 4.12; N, 8.19.

## (*E*)-1-methoxy-3-(4-(2-(trifluoromethyl)phenyl)-4,5-dihydro-3*H*-benzo[b][1,4]diazepin-2-yl)-9*H*-carbazole (3f)

66% yield; FTIR (KBr) υ (cm$^{-1}$): 3249 (-NH), 3118 (C-H, aromatic), 1630 (C=N, aromatic), 1639 (C=C, aromatic), 1535 (-NH, bending), 1324 (C-N), 1226 (C-O), 1172 (C-F); $^1$H NMR (δ, ppm, $CDCl_3$): 10.15 (9, 1H), 7.3 - 8.6 (Aromatic, 14H), 3.88 (1, 3H), 2.14 (12, 1H); MS: M$^+$ 485. Anal. Calcd. for $C_{29}H_{22}F_3N_3O$: C, 71.74; H, 4.57; N, 8.66. Found: C, 71.43; H, 4.09; N, 8.35.

## (*E*)-3-(4-(3,5-bis(trifluoromethyl)phenyl)-4,5-dihydro-3*H*-benzo[b][1,4]diazepin-2-yl)-1-methoxy-9*H*-carbazole (3g)

69% yield; FTIR (KBr) υ (cm$^{-1}$): 3272 (-NH), 3184 (C-H, aromatic), 1665 (C=N, aromatic), 1646 (C=C, aromatic), 1597 (-NH, bending), 1331 (C-N), 1273 (C-O), 1202 (C-F); $^1$H NMR (δ, ppm, $CDCl_3$): 10.18 (9, 1H), 7.1 - 8.5 (Aromatic, 13H), 3.83 (1, 3H), 2.17 (12, 1H); MS: M$^+$ 553. Anal. Calcd. for $C_{30}H_{21}F_6N_3O$: C, 65.10; H, 3.82; N, 7.59. Found: C, 64.43; H, 3.41; N, 7.24.

### (*E*)-3-(4-(2,4-dichloro-5-fluorophenyl)-4,5-dihydro-3*H*-benzo[b][1,4]diazepin-2-yl)-1-methoxy-9*H*-carbazole (3h)

47% yield; FTIR (KBr) υ ($cm^{-1}$): 3292 (-NH), 3142 (C-H, aromatic), 1634 (C=N, aromatic), 1625 (C=C, aromatic), 1573 (-NH, bending), 1319 (C-N), 1286 (C-O), 1238 (C-F), 709 (C-Cl); $^1$H NMR (δ, ppm, $CDCl_3$): 10.18 (9, 1H), 7.2-8.4 (Aromatic, 12H), 3.92 (1, 3H), 2.22 (12, 1H); MS: $M^+$ 503, M+2 505. Anal. Calcd. for $C_{28}H_{20}Cl_2N_3O$: C, 66.68; H, 4.00; N, 8.33. Found: C, 65.21; H, 3.77; N, 7.89.

### Acute toxicity studies

The acute toxicity studies were done to estimate the dose which will demonstrate highest possible biological activity with no appearance of any toxic symptoms, a key parameter for the determination of *in vivo* safety profile of the experimental molecule. The molecules of interest were injected to approximate the lethal dose ($LD_{50}$) at progressively increasing dose ranging from 10 mg/kg to 100 mg/kg. The dose was calculated based on the death of 50% animals [15].

### Accessing anti-anxiety effect by inhibition of locomotor activity

The locomotor activity was studied by using an actophotometer with little modification. Each animal was located independently in the system and the basal activity score was computed comprehensively for each experimental animal after 10 and 20 min of drug administration. The activity on each rat was retested for 10 min. The disparity in the locomotor activity was documented in view of; before drug treatment values and after drug treatment values. At last, the percentage reduction in locomotor activity was determined and expressed in percentage [16].

### Statistical treatment

All the obtained results were expressed as Mean ± SEM and statistically analyzed by one-way ANOVA approach followed by Dunnett's multiple comparisons test. The data obtained were compared with the vehicle control group. The $P < 0.01$ value was judged to be most statistically significant.

## Results and Discussion

### Chemistry

The sophisticated analytical and spectroscopic tool investigation yields multiple imperative facts that supported the conversion of chalcone into the seven-membered heterocycle. The main evidence was the transformation of the ketonic C=O moiety of the chalcone, which initially appeared in its characteristic range of 1680 - 1760 $cm^{-1}$, but later disappeared, which strongly concluded the formation of the destination product. The aromatic rings displayed characteristic spectral information where primarily the C-H stretching (range 3118 - 3184 $cm^{-1}$) and C=C stretching (range 1606 - 1646 $cm^{-1}$). The amide (present in carbazole and benzodiazepine moiety) stretching and bending were noticed in the distinctive ranges of 3220 - 3292 $cm^{-1}$ and 1252-1347 $cm^{-1}$, respectively. The proton NMR studies highlighted the distinct features of the prepared benzodiazepine compound. The proton of carbazole nitrogen was chiefly scrutinized at 10 ppm. The protons of the heterocyclic scaffold were detected at 2 ppm. The aromatic ring protons were principally located in the spectral range of 6.7 - 8.9 ppm. On examining the mass spectra, it was seen that the base peaks compounds exactly matched with the theoretical molecular mass along with isotopic forms where molecular mass + 2 peaks were situated in the case of bromine and chlorine analogs. A number of fragment peaks were also perceived in the spectra in the range of m/z 100 - 200. These above personas confirmed the alteration of chalcones into the heterocycles. Ultimately, the ratios of elemental analysis (carbon, hydrogen, and nitrogen) composition of the derivatives certainly indicated the formation of molecules.

### Determination of $LD_{50}$ value

The acute toxicity study highlighted that the produced benzodiazepine derivatives were relatively safe in the administrated range of 10 - 100 mg/kg b.w. as no symptoms and signs of toxicity were observed. In this experiment, a fixed dose of 20 mg/kg b.w. was employed for accessing the inhibition of locomotor activity in experimental animals.

### Locomotor inhibitory activity

The data obtained from the animal studies revealed that the entire treated experimental molecule displayed inhibitory effect on CNS and therefore leads to compromised locomotor activity in the rats. In the obtained result, it was noticed that the position, number, and the type of substituent has a crucial role in exhibiting the biological activity. The compound **3h** displayed the highest inhibition of the locomotor activity. The probable reason may be the lipophilicity of the compound that has driven the component to cross the biological membranes and exert the pharmacological activity [17]. On the other half, substitution of two highly electronegative groups (-$CF_3$) (**3g**) leads to drastic fall in the activity due to the formation of micelles of the compounds or binding to the amino acid residues which may produce hindrance in crossing the biological barrier [18]. Another key phenomenon was observed that the highly lipophilic molecules do not produced a long-term activity, that may be due to a large distribution of the drug components in the adipose portion and stay for longer duration and not participated in the meantime biological activity [19]. In fluorine substituent (**3a** and **3b**), the ortho-position was found to be more prevalent for inducing the effect. In contrast, the event reverses for iodine (**3c** and **3d**), where the para-substituents dominated the locomotor activity. In the case of bromo-substituent (**3e**) and single tri-fluoro compound (**3f**), the activity was seen to be moderate. The reason may be the wide distribution in the body and low participation in the CNS interphase [20]. However, none of the compounds exhibited better pharmacological activity than the standard drug, benzodiazepine. The mode of action of the murrayanine based benzodiazepine analogs may be similar to that of the benzodiazepine (diazepam); i.e. by enhancing the effect of GABA neurotransmitter at GABAA receptor, thereby producing hypnosis and anxiolysis [21].

| Group | R | Photocell count in 10 minutes | % inhibition | Photocell count in 20 minutes | % inhibition |
|---|---|---|---|---|---|
| Control* | - | 387.33 ± 1.56 | - | 391.66 ± 1.12 | - |
| Standard# | - | 119.66 ± 1.33 | 69.11 | 108.33 ± 2.13 | 72.35 |
| 3a& | 2-F | 168.66 ± 1.04** | 56.35 | 162.66 ± 1.91** | 58.98 |
| 3b | 4-F | 213.66 ± 1.31 | 44.84 | 211.66 ± 1.18 | 45.96 |
| 3c | 2-I | 242.66 ± 1.78 | 37.35 | 238.66 ± 0.81 | 39.07 |
| 3d | 4-I | 182.33 ± 1.93** | 52.93 | 176.66 ± 2.05** | 54.90 |
| 3e | 4-Br | 197.33 ± 2.03 | 49.06 | 193.33 ± 1.41 | 50.64 |
| 3f | 2-$CF_3$ | 172.33 ± 0.94** | 55.51 | 169.66 ± 1.32** | 56.77 |
| 3g | 3,5-$CF_3$ | 155.33 ± 1.99** | 59.90 | 149.33 ± 1.82** | 61.88 |
| 3h | 2,4-Cl; 5-F | 151.33 ± 1.07** | 60.93 | 140.33 ± 1.49** | 64.18 |

**Table 1:** Locomotor inhibitory potential as anti-anxiety effect of some fabricated benzodiazepine derivatives.

*: 0.9% saline; #: Benzodiazepine – 3 mg/kg b.w.; &: Dose of 20 mg/kg b.w.; **P < 0.01; Values expressed as mean ± SEM, from 6 rats.

## Conclusion

The study revealed the perspective to fabricate semi-synthetic heterocycles from murrayanine, which is a natural product and thus render desired safety and efficacy. The sophisticated analytical and spectroscopic tools revealed that the compounds were found to be in close agreement with that of the proposed structure. The influence of position, number, and the type of substituent were comprehensively studied where the lipophilic substituent containing scaffold **(3h)** presented the highest locomotor inhibition and therefore will translate anti-anxiety effect therapeutically. The study will open new avenues of research and will surely motivate the researchers in the rational development of safe and efficacious molecules in future from natural origin.

## Acknowledgement

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

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