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A Convenient One-Pot Synthesis of Bis(indolyl)methane Derivatives and Evaluation of Their Nematicidal Activity against the Root Knot Nematode *Meloidogyne incognita*

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Abstract—Seven arylbis(indolyl)methanes were synthesized by electrophilic substitution reaction of aromatic aldehydes on indole using glacial acetic acid as catalyst in aqueous media under ultrasonic irradiation. The synthesized bis-indole derivatives were characterized using elemental analysis, ^{1}H and ^{13}C NMR, FT-IR spectroscopy, and mass spectrometry and were screened for their nematicidal activity against the root knot nematode *Meloidogyne incognita*. The efficiency of the synthesized compounds was evaluated in vitro by egg hatching and mortality tests. All tested compounds showed significant nematicidal potential, and the nitro substituted derivative, 3,3′-[(4-nitrophenyl)methylene]di(1*H*-indole), exhibited the highest activity.

Keywords: indole, glacial acetic acid, bis(indolyl)methanes, aromatic aldehydes, nematicidal activity, *Meloidogyne incognita*

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INTRODUCTION

Heterocycles constitute a wide class of organic compounds which contribute significantly in every facet of pure and applied chemistry [1]. Heterocyclic compounds have played an important role in biochemical industries as they are present in large proportion in biomolecules like vitamins, enzymes, biologically active compounds, and natural products [2]. Indole derivatives have attracted considerable attention [3] due to the broad range of their biological properties such as antiviral [4], antibacterial [5], anticancer [6], antidepressant [7], and antifungal activities [8].

Derivatives of indole have a variety of medicinal uses as antihypertensive and antiparasitic agents, antidepressants, as well as in cardiology, neurology, and endocrinology [9]. One of the indole alkaloids is delavirdine which prevents human immunodeficiency virus (HIV) from proliferating in human body [10]. Arbidol is an antiviral agent which is used for the treatment of influenza viruses, and it also acts as an efficient inhibitor of SARS-CoV-2 virus [11]. Rhopaladin

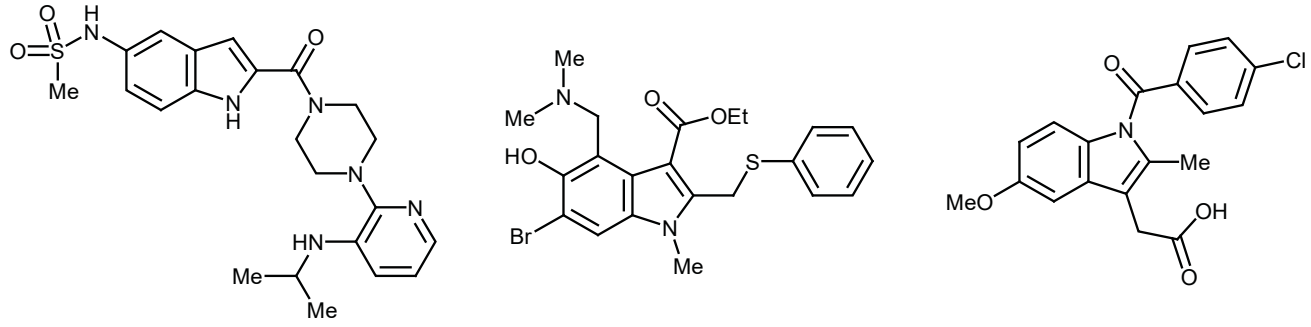
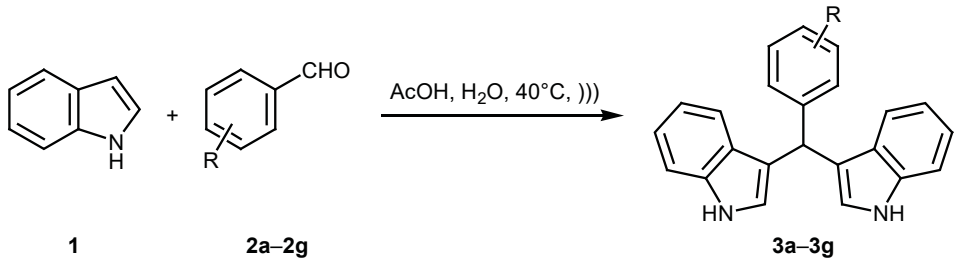


Fig. 1. Structures of some indole-containing drugs.

Scheme 1.



1 **2a–2g** **3a–3g**

R = 4-NO_2 (**a**), 3-NO_2 (**b**), 4-F (**c**), 3,4-$(MeO)_2$ (**d**), 4-MeO (**e**), 3-MeO-4-HO (**f**), 4-OH (**g**).

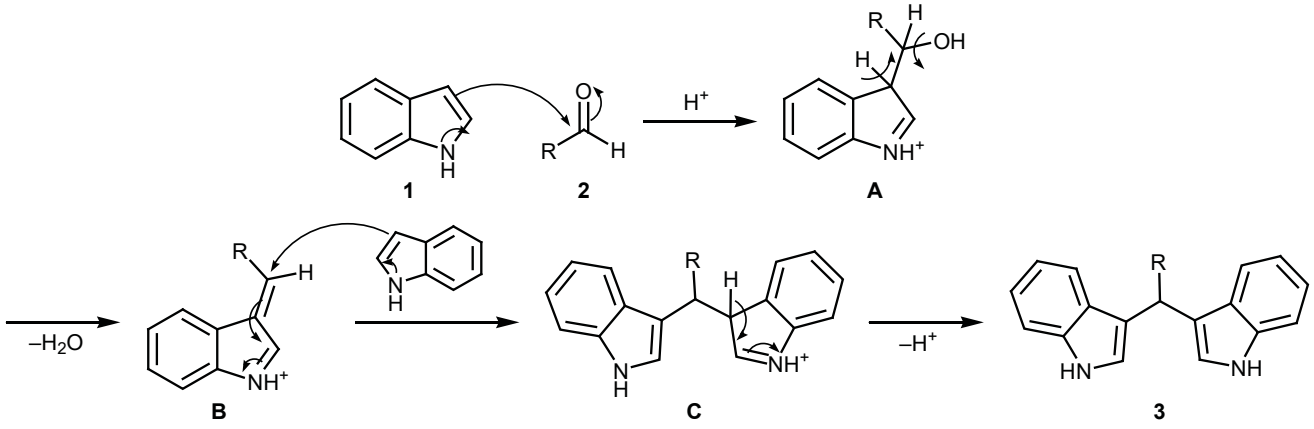
is a marine indole alkaloid which showed repressive activity against c-ErbB-2 kinase and cyclin-dependent kinase 4 [12] (Fig. 1). Indole derivatives such as tadalafil, chaetoindolone A, eudistomin C, streptochlorin analogs [13], etc., have also been evaluated for the effective control of plant pathogens. Plant pathogens cause damage to flora, fauna, and microorganisms [14]. Nowadays, the major threat to agriculture is the root-knot nematode of the *Meloidogyne* genus [15] out of which *Meloidogyne incognita* species majorly cause yield loss in different crops like tomato, brinjal, turmeric, melon, etc. [16] which damage crops worth $125 billion with a yield loss of 14% all over the world [17]. In India, annual loss in 30 crops caused by nematodes is in crores each year. Therefore, efforts have been made for the prevention of infectious nematodes.

Various reagents have been used for the synthesis of indole dimers. The reagents commonly used for the substitution reaction of indole with aromatic aldehydes are mineral acids like HCl, H_2SO_4, and HF, but these are listed as hazardous catalysts [18]. Herein, we report a convenient one-step reaction for the synthesis of bisindolyl methanes using glacial acetic acid under ultrasonication conditions as it has emerged as a new lead in green organic synthesis [19]. Also, the use of glacial acetic acid offers many advantages such as cost effectiveness, easy availability, lower toxicity, air stability, and easy separation of products by simple filtration, thereby eradicating the necessity of purification protocols such as chromatography and liquid–liquid extractions which are very time-consuming [20]. As far as nematicidal activity [21] is concerned, only limited information is available in this regard. To bridge this gap, bis(indolyl)methanes have been synthesized from indole and aromatic aldehydes and examined for their nematicidal activity against the root knot nematode *M. incognita* [22].

RESULTS AND DISCUSSION

Bis(indolyl)methane derivatives **3a**–**3g** were synthesized as shown in Scheme 1 by the reaction of indole (**1**) with aromatic aldehydes **2a**–**2g** in water in the presence of acetic acid as catalyst at 40°C under ultrasonic irradiation. The crude products were recrystallized from ethanol to afford pure compounds **3a**–**3g** in good yields. The structure of the synthesized compounds was confirmed by using various spectroscopic techniques, including ^1H and ^{13}C NMR, FT-IR spectroscopy, and mass spectrometry. Compounds **3a**–**3g**

Scheme 2.



are colored crystalline solids that are stable in air and readily soluble in dimethyl sulfoxide, methylene chloride, chloroform, and other polar solvents.

The proposed mechanism of indole dimerization with aromatic aldehydes involves electrophilic substitution at the 3-position of indole by the aldehyde carbonyl carbon atom in acidic environment to give intermediate **A** which is converted to another intermediate **B** via elimination of water molecule. The addition of the second indole molecule to **B** produces protonated bis(indolyl)methane **C** whose deprotonation affords final product **3** (Scheme 2).

Indole (**1**) and its derivatives **3a**–**3g** were evaluated for their nematicidal activity against *Meloidogyne incognita* at different concentrations (1500, 1000, 750, 500, 250, and 100 ppm) after exposure for 24, 48, 72, 96, and 120 h. The efficiency of compounds **1** and **3a**–**3g** on the egg hatch inhibition of *M. incognita* at different concentrations and durations are shown in Figs. 2 and 3 (see also Supplementary Materials). The highest percent egg hatch inhibition was exhibited by the compounds at the maximum concentration (1500 ppm), and their efficiency declined as the concentration decreased (Fig. 2). Similarly, the maximum egg hatch inhibition was observed after 120 h of duration, followed by 96, 72, 48, and 24 h (Fig. 3).

Figures 4 and 5 illustrate the effect of indole (**1**) and its derivatives **3a**–**3g** on the percent mortality of second stage juveniles (J_2) of *M. incognita* at different concentrations and durations. The observed pattern was similar to that of percent egg hatch inhibition, i.e., the percent mortality decreased with decrease in the concentration and exposure time (Supplementary Table 2).

The maximum percent mortality against second stage juvenile of *M. incognita* was seen after 120 h duration, followed by 96, 72, 48, and 24 h of exposure (Fig. 5). Thus, all the compounds showed both concentration and duration dependent manner for both percent egg hatch inhibition and percent mortality of root knot nematodes. 3,3′-[(4-Nitrophenyl)methyl]di(1*H*-indole) (**3a**) exhibited the highest percent egg hatch inhibition potential (96.83%) and maximum percent mortality potential (100.00%). For percent egg hatch inhibition, the order of efficiency was as follows: **3a** > **3b** > **3c** > **3d** > **3e** > **3f** > **1** > **3g** which showed that **3a** was the most effective and that **3g** was the least effective. The same order was observed for percent mortality. Thus, the compounds having electron-withdrawing groups showed better nematicidal activity [23, 24].

EXPERIMENTAL

The melting points were measured in open-end capillaries with a Nutronics digital melting point apparatus. The reactions were carried out using a Helix Biosciences Ultra Sonicator (220 V, 700 W) from the Central Instrumentation Laboratory (Punjab Agricul-

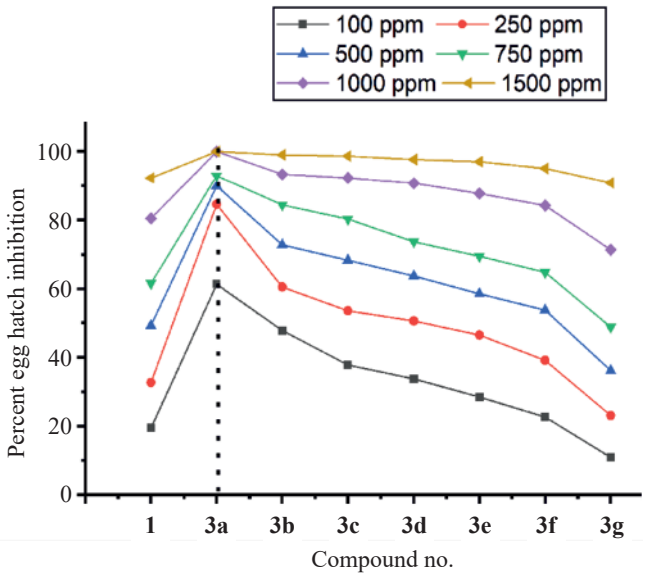


Fig. 2. Effect of indole (**1**) and its derivatives **3a**–**3g** on percent egg hatch inhibition of *M. incognita* at different concentrations.

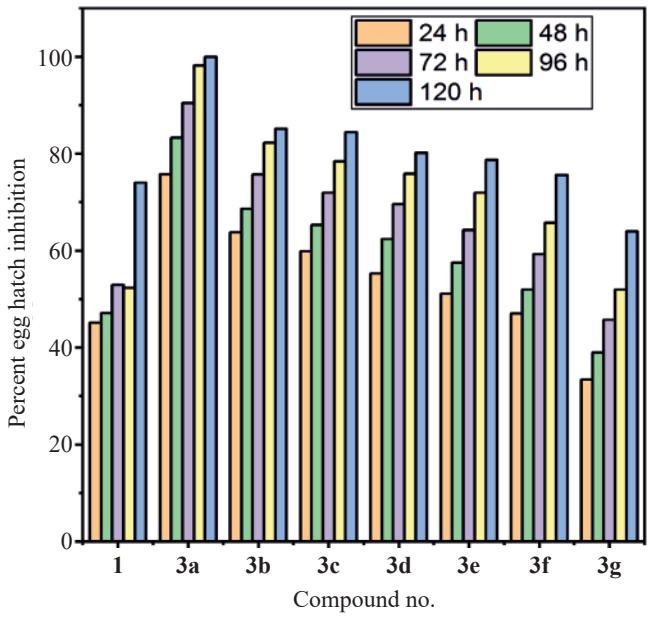


Fig. 3. Effect of indole (**1**) and its derivatives **3a**–**3g** on percent egg hatch inhibition of *M. incognita* at different durations.

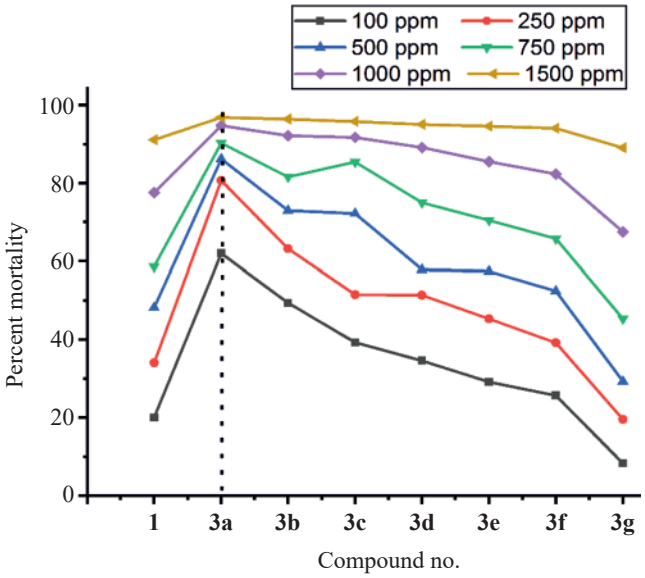


Fig. 4. Effect of indole (**1**) and its derivatives **3a**–**3g** on percent mortality of second stage juveniles of *M. incognita* at different concentrations.

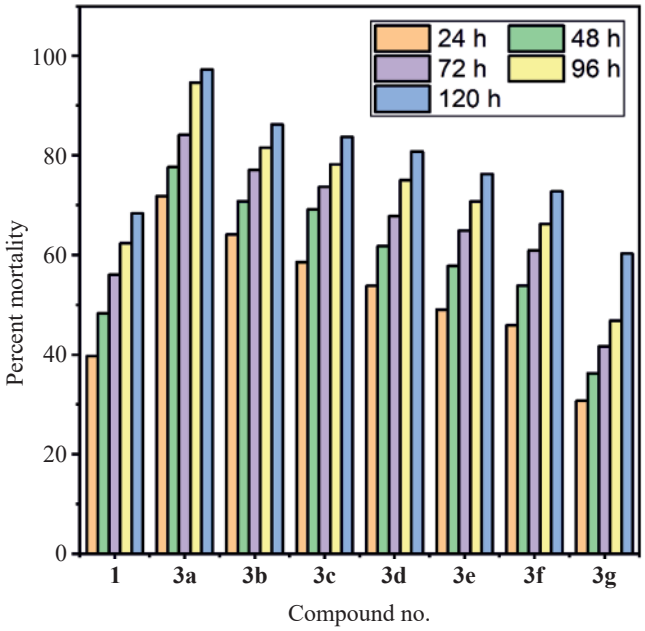


Fig. 5. Effect of indole (**1**) and its derivatives **3a**–**3g** on percent mortality of second stage juveniles of *M. incognita* at different durations.

tural University, Ludhiana). The ^{1}H and ^{13}C NMR spectra were recorded at 25°C on a Bruker Avance II spectrometer (500 and 125 MHz, respectively) using $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard. The IR spectra (400–4000 cm^{-1}) were recorded on a Perkin Elmer Spectrum Two FT-IR spectrometer from samples prepared as KBr pellets. Elemental analyses were obtained on a Thermo Scientific instrument (Department of Chemistry, Guru Nanak Dev University, Amritsar).

General procedure for the synthesis of 3,3′-(arylmethylene)di(1*H*-indoles) 3a–3g. A solution of indole (**1**, 0.138 mol, 0.162 g) in acetonitrile (5.0 mL) was added dropwise at room temperature to a solution of aromatic aldehyde **2a**–**2e** (0.039 mol) in acetonitrile (5.0 mL). Water (20.0 mL) and a catalytic amount of acetic acid (0.5 mol %) were then added, and the mixture was irradiated at 40°C in an ultrasonicator. After completion of the reaction (2–8 h; TLC), the mixture was poured onto crushed ice, and the solid product was filtered off and recrystallized from hot methylene chloride.

3,3′-[(4-Nitrophenyl)methylene]di(1*H*-indole) (3a). Yield 78%, yellow crystalline solid, mp 220–222°C (from CH_2Cl_2), R_f 0.52 (EtOAc–hexane, 20:80). IR spectrum, ν, cm^{-1}: 1219 (C–N), 1344 (NO_2), 1515 (NO_2), 1554 (C=C$_{arom}$), 2858 (C–H), 3023 (C–H$_{arom}$), 3397 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.92 s (1H, CH), 6.62 d (2H, J = 1.7 Hz, H$_{arom}$), 6.94–6.98 m (2H, H$_{arom}$), 7.11–7.14 m (2H, H$_{arom}$), 7.28 d (2H, J = 7.95 Hz, H$_{arom}$), 7.31 d (2H, J = 8.15 Hz, H$_{arom}$), 7.36–7.39 q (1H, J = 7.9 Hz, H$_{arom}$), 7.62 d (1H, J = 7.65 Hz, H$_{arom}$), 7.94 s (2H, NH, D_2O exchangeable), 8.01 d.d (1H, J = 1.3, 1.45 Hz, H$_{arom}$), 8.14 t (1H, J = 1.7 Hz, H$_{arom}$). ^{13}C NMR spectrum ($CDCl_3$), δ$_C$, ppm: 111.26, 118.23, 119.55, 121.51, 122.34, 123.63, 123.67, 126.65, 129.13, 134.87, 136.75, 146.38, 148.51. Mass spectrum: *m*/*z* 368.09 [M + 1]$^+$. Found, %: C 75.19; H 4.66; N 11.44; O 8.71. $C_{23}H_{17}N_3O_2$. Calculated, %: C 74.09; H 4.26; N 11.34; O 8.21. M 367.13.

3,3′-[(3-Nitrophenyl)methylene]di(1*H*-indole) (3b). Yield 82%, yellow crystalline solid, mp 218–220°C (from CH_2Cl_2), R_f 0.40 (EtOAc–hexane, 20:80). IR spectrum, ν, cm^{-1}: 1232 (C–N), 1338 (NO_2), 1522 (NO_2), 1551 (C=C$_{arom}$), 2856 (C–H), 3019 (C–H$_{arom}$), 3356 (N–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.03 s (1H, H$_{arom}$), 6.87–6.90 m (4H, H$_{arom}$), 7.04–7.07 m (2H, H$_{arom}$), 7.29 d (2H, J = 7.95 Hz, H$_{arom}$), 7.37 d (2H, J = 8.1 Hz, H$_{arom}$), 7.61 d (2H, J = 8.7 Hz, H$_{arom}$), 8.15 d.d (2H, J = 1.85, 1.32 Hz, H$_{arom}$), 10.92 d (2H, J = 1.4 Hz, NH, D_2O exchangeable). ^{13}C NMR spectrum (DMSO-d_6), δ$_C$, ppm: 111.46, 116.55, 118.29, 118.79, 120.97, 123.30, 123.73, 126.24, 129.33, 136.47, 145.64, 153.02. Mass spectrum: *m*/*z* 368.23 [M + 1]$^+$. Found, %: C 75.19; H 4.66; N 11.44; O 8.71.

$C_{23}H_{17}N_3O_2$. Calculated, %: C 75.02; H 4.45; N 11.21; O 8.11. *M* 367.13.

3,3′-[(4-Fluorophenyl)methylene]di(1*H*-indole) (3c). Yield 75%, light brown crystalline solid, mp 78–80°C (from CH_2Cl_2), R_f 0.34 (EtOAc–hexane, 20:80). IR spectrum, ν, cm^{-1}: 1224 (C–N), 1332 (C–F), 1521 (C=C_{arom}), 2860 (C–H), 3013 (C–H_{arom}), 3448 (N–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 5.93 s (1H, CH), 6.61 d (2H, *J* = 2.2 Hz, H_{arom}), 6.93–6.98 m (2H, H_{arom}), 7.11–7.15 m (2H, H_{arom}), 7.27 d (2H, *J* = 5.90 Hz, H_{arom}), 7.32 d (2H, *J* = 12.3 Hz, H_{arom}), 7.37 q (1H, *J* = 12.9 Hz, H_{arom}), 7.63 d (1H, *J* = 7.60 Hz, H_{arom}), 7.94 s (2H, NH, D_2O exchangeable), 8.02 d.d (1H, *J* = 3.8, 0.54 Hz, H_{arom}), 8.15 t (1H, *J* = 3.15 Hz, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 112.26, 118.35, 119.75, 119.91, 121.13, 122.34, 123.75, 124.93, 126.15, 129.56, 134.67, 136.65, 146.68, 148.15. Mass spectrum: *m*/*z* 341.23 $[M + 1]^+$. Found, %: C 81.16; H 5.03; F 5.58; N 8.23. $C_{23}H_{17}FN_2$. Calculated, %: C 80.86; H 4.91; F 5.28; N 8.13. *M* 340.39.

3,3′-[(3,4-Dimethoxyphenyl)methylene]di(1*H*-indole) (3d). Yield 90%, light pink crystalline solid, mp 198–200°C (from CH_2Cl_2), R_f 0.53 (EtOAc–hexane, 20:80). IR spectrum, ν, cm^{-1}: 1084 (C–O), 1198 (C–N) 1539 (C=C_{arom}), 2831 (C–H), 3008 (C–H_{arom}), 3240 (N–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.74 s (3H, OMe), 3.83 s (3H, OMe), 5.82 s (1H, CH), 6.63 t (2H, *J* = 1.4 Hz, H_{arom}), 6.75 d (1H, *J* = 8.25 Hz, H_{arom}), 6.82 d.d (1H, *J* = 3.40 Hz, H_{arom}), 6.92 d (1H, *J* = 1.95 Hz, H_{arom}), 6.98–7.01 m (2H, H_{arom}), 7.14–7.17 m (2H, H_{arom}), 7.33 d (2H, *J* = 8.2 Hz, H_{arom}), 7.39 d (2H, *J* = 7.95 Hz, H_{arom}), 7.88 s (2H, NH, D_2O exchangeable). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 55.82, 55.85, 110.94, 111.04, 112.27, 119.23, 119.93, 119.97, 120.61, 121.93, 123.55, 127.10, 136.73, 136.75, 147.33, 148.71. Mass spectrum: *m*/*z* 383.29 $[M + 1]^+$. Found, %: C 78.51; H 5.80; N 7.32; O 8.37. $C_{25}H_{22}N_2O_2$. Calculated, %: C 78.13; H 5.49; N 7.22; O 8.24. calculated: *M* 382.45.

3,3′-[(4-Methoxyphenyl)methylene]di(1*H*-indole) (3e). Yield 94%, light red crystalline solid, mp 180–182°C (from CH_2Cl_2), R_f 0.50 (EtOAc–hexane, 20:80). IR spectrum, ν, cm^{-1}: 1029 (C–O), 1147 (C–N), 1488 (C=C_{arom}), 2689 (C–H), 3051 (C–H_{arom}), 3197 (N–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.83 s (3H, OMe), 5.82 s (1H, CH), 6.62 t (2H, *J* = 2.85 Hz, H_{arom}), 6.75 d (1H, *J* = 8.30 Hz, H_{arom}), 6.82 d.d (1H, *J* = 1.95, 0.76 Hz, H_{arom}), 6.93 d (1H, *J* = 7.05 Hz, H_{arom}), 6.93–7.04 m (2H, H_{arom}), 7.14–7.17 m (2H, H_{arom}), 7.32 d (2H, *J* = 9.95 Hz, H_{arom}), 7.38 d (2H, *J* = 4.20 Hz, H_{arom}), 7.88 s (2H, NH, D_2O exchangeable). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 55.84, 110.47, 111.49, 113.67, 119.22, 119.39, 119.91, 121.61, 122.13, 124.75, 127.90, 137.63, 137.65, 147.13, 148.53. Mass spectrum: *m*/*z* 353.41 $[M + 1]^+$. Found, %: C 81.79; H 5.72; N 7.95; O 4.54. $C_{24}H_{20}N_2O$. Calculated, %: C 81.87; H 5.65; N 7.45; O 4.41. *M* 352.43.

4-[Di(1*H*-indol-3-yl)methyl]-2-methoxyphenol (3f). Yield 88%, grey crystalline solid, mp 111–113°C (from CH_2Cl_2), R_f 0.43 (EtOAc–hexane, 20:80). IR spectrum, ν, cm^{-1}: 1134 (C–O), 1214 (C–N), 1545 (C=C_{arom}), 2899 (C–H), 3112 (C–H_{arom}), 3342 (N–H), 3365 (O–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.86 s (3H, OMe), 5.52 s (1H, CH), 5.79 s (1H, OH, D_2O exchangeable), 6.68 d (2H, *J* = 1.50 Hz, H_{arom}), 6.76 d (1H, *J* = 8.25 Hz, H_{arom}), 6.84 d.d (1H, *J* = 2.05, 0.71 Hz, H_{arom}), 6.92 d (1H, *J* = 2.05 Hz, H_{arom}), 6.70 t (2H, *J* = 7.20 Hz, H_{arom}), 7.14–7.17 m (2H, H_{arom}), 7.34 d (2H, *J* = 8.15 Hz, H_{arom}), 7.40 d (2H, *J* = 8.15 Hz, H_{arom}), 7.90 s (2H, NH, D_2O exchangeable). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 55.93, 110.37, 110.96, 115.07, 119.18, 119.91, 119.96, 120.11, 121.87, 123.46, 127.10, 136.71, 144.93, 145.30. Mass spectrum: *m*/*z* 369.19 $[M + 1]^+$. Found, %: C 78.24; H 5.47; N 7.60; O 8.69. $C_{24}H_{20}N_2O_2$. Calculated, %: C 78.14; H 5.24; N 7.57; O 8.45. *M* 368.43.

4-[Di(1*H*-indol-3-yl)methyl]phenol (3f). Yield 78%, pink crystalline solid, mp 118–120°C (from CH_2Cl_2), R_f 0.47 (EtOAc–hexane, 20:80). IR spectrum, ν, cm^{-1}: 1221 (C–N), 1322 (C–O), 1524 (C=C_{arom}), 2864 (C–H), 3054 (C–H_{arom}), 3247 (N–H), 3373 (O–H). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 5.71 s (1H, CH), 6.66 d.d (2H, *J* = 8.55, 5.9 Hz, H_{arom}), 6.78 d (2H, *J* = 1.80 Hz, H_{arom}), 6.84–6.87 m (2H, H_{arom}), 7.01–7.04 m (2H, H_{arom}), 7.14 d (2H, *J* = 8.45 Hz, H_{arom}), 7.26 d (2H, *J* = 8.11 Hz, H_{arom}), 7.33 d (2H, *J* = 8.10 Hz, H_{arom}), 9.11 s (1H, OH, D_2O exchangeable), 10.75 d (2H, *J* = 1.65 Hz, NH, D_2O exchangeable). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 111.25, 114.62, 117.92, 118.54, 119.04, 120.63, 123.24, 126.54, 128.99, 135.07, 136.46, 155.13. Mass spectrum: *m*/*z* 339.29 $[M + 1]^+$. Found, %: C 81.63; H 5.36; N 8.28; O 4.73. $C_{23}H_{18}N_2O$. Calculated, %: C 81.49; H 5.26; N 8.18; O 4.65. *M* 338.40.

Nematicidal activity. *a. Egg hatch inhibition assay*. A pure culture of root knot nematodes was raised on the crop of brinjal. Five egg masses were taken and placed in a solution of a tested compound in water (5 mL) with a concentration of 1500, 1000, 750, 500, 250, and 100 ppm. A small quantity of acetone was

added to dissolve the compounds in distilled water for preparing stock solutions which were then diluted to a required concentration. Distilled water with the same amount of acetone was used as control in each treatment, and three replications of each treatment were made. Egg hatching was observed after 24, 48, 72, 96, and 120 h, maintaining the temperature at 27±2°C. Statistical analysis was performed, and critical differences were calculated. The percent hatch inhibition was calculated as $(C - T)/C \times 100$, where C is the number of nematodes in the control sample, and T is the number of nematodes after treatment.

b. Second stage juvenile mortality assay. Freshly hatched second stage juveniles (J_2) were taken for the mortality test. An average of 20 stage two juveniles were placed in 1 mL of distilled water, and 5 mL of a solution of each test compound prepared as in the hatching test was added with 4 replications each together with control. For each concentration, the results were recorded after 24, 48, 72, 96, and 120 h of exposure, and the percent ratio of the number of dead nematodes to the total number of nematodes was determined.

CONCLUSIONS

Arylbis(indolyl)methanes were synthesized by a one-step procedure from aromatic aldehydes and indole under ultrasonic irradiation. The proposed procedure is relatively easy, less time consuming, and greener than those reported previously. 3,3′-[(4-Nitrophenyl)methylene]di(1*H*-indole) (**3a**) showed the best nematicidal activity against the root knot nematode *M. incognita* according to the egg hatch inhibition and second stage juvenile mortality assays. Arylbis(indolyl)methanes having electron-withdrawing groups were more effective.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY INFORMATION

The online version contains supplementary material available at https://doi.org/10.1134/S1070428022100219.

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