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Synthesis and Evaluation of Pyrazole Derivatives as Potent Antinemic Agents

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Abstract—Pyrazole derivatives were synthesized by bromination of pyrazole, followed by N-alkylation of 4-bromopyrazole. The synthesized derivatives were characterized by microanalytical data and IR and ^{1}H and ^{13}C NMR spectra and were evaluated for their nematicidal activity against the root knot nematode *Meloidogyne incognita*. The compounds were screened for their egg hatch inhibition and mortality potential, and they showed significant nematicidal activity as compared to the control. 1*H*-Pyrazol-5(4*H*)-one was found to be most effective in egg hatch inhibition, and 4-bromopyrazole was found to be most effective in juvenile mortality.

Keywords: pyrazole derivatives, nematicidal activity, *Meloidogyne incognita*, egg hatch inhibition, juvenile mortality.

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Nitrogen heterocycles have attracted substantial attention in fundamental organic and medicinal chemistry around the world. The intrinsic synthetic versatility of this potent class of compounds has made them attractive precursors for their extensive use in organic synthesis [1, 2]. The structural diversity of these compounds has led to their promising biological activities [3, 4]. Due to the low mammalian and phytotoxicity, these heterocyclic fragments have marked their presence in various agricultural as well as medical practices [5]. Among various heterocyclic compounds, considerable attention has been focused on pyrazole derivatives. Pyrazoles belong to a class of diazoles that are building blocks in pharmaceutical and agrochemical industries [6]. Pyrazole is a five-membered doubly unsaturated heterocycle with two adjacent nitrogen atoms and three

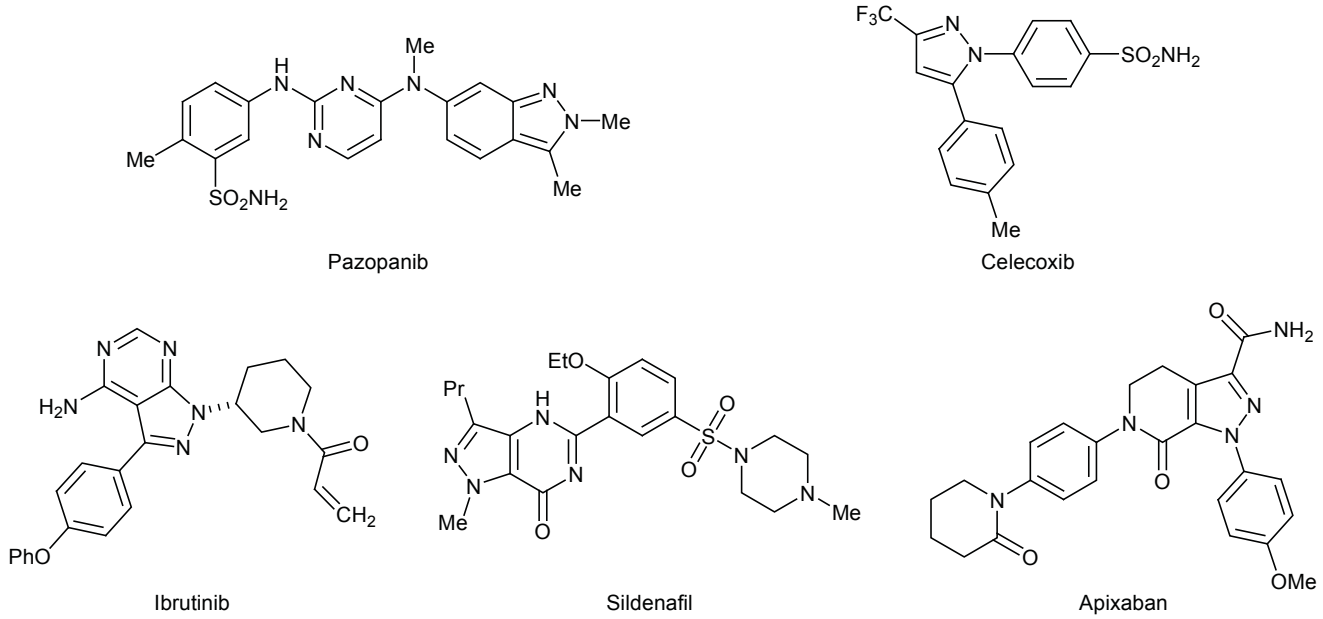


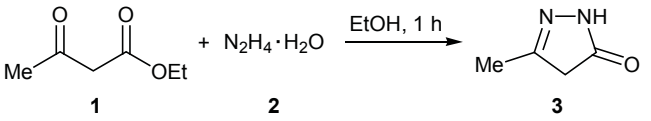
Fig. 1. Structures of some pyrazole-derived drugs.

carbon atoms [7]. The synthetic versatility of pyrazole moiety has stemmed from the interest in the biological and pharmaceutical properties of its derivatives. It exhibits various biological activities such as hypoglycemic [8, 9], anti-inflammatory, anticonvulsant [10], antipyretic [11], anticancer [12], antibacterial [13], analgesic [14] and antitubercular [15]. This encourages chemists to synthesize novel pyrazole derivatives that could dramatically enhance or alter the pharmacophoric profile of pyrazole. Pyrazole has been used as a core scaffold in a number of medicinal drugs, in particular Pazopanib, Celecoxib, Sildenafil, Ibrutinib and Apixaban (Fig. 1). Pazopanib has been used as a signaling molecule in oncology [16], and Celecoxib is a dominant cyclooxygenase (COX-2) inhibitor [17]. Ibrutinib (Imbruvica) and Sildenafil are used for the treatment of erectile dysfunction [18], while Apixaban is an anticoagulant.

The main task in agriculture is to improve the crop growth and productivity under extreme conditions of biotic and abiotic stress. Root knot nematodes are invisible plant parasitic microscopic worms known to attack host plants and subsequently decrease crop production. These hidden pests are highly toxic to some staple cereal crops and industrial crops. *Meloidogyne incognita*, also known as southern root knot nematode, is the most common among root knot nematodes. Overlooked damage induced by tiny nematodes because of their hidden nature and resemblance with other pathogens has caused enormous loss of $150.7 billion worldwide [19]. Nodulation, yellowing of plants, and gall formation are the most common symptoms of plants infected with nematodes [20–22]. Therefore, in order to limit the damage caused by nematodes, various methods such as the use of chemical nematicides, green manures, biofumigants, biological control agents, crop rotation, and soil solarization [23] have been employed. But management of root knot nematode is a challenging task due to its wide host range, high reproductive potential, and short life cycle [24]. Nowadays, synthetic nematicides are the most commonly used weapons for phytonematode control [25]. Therefore, present focus of researchers is to search for newer low-molecular-weight chemicals to achieve the effective control of nematodes. Thus, in the present study, pyrazole derivatives were synthesized and screened for their nematicidal efficacy against *M. incognita*.

Herein we report methods for the synthesis of 3-methyl-1*H*-pyrazol-5(4*H*)-one (**3**), 4-bromopyrazole (**6**), and N^1-substituted 4-bromopyrazole derivatives **9a**–**9c**. Pyrazole ring formation via cyclization of ethyl acetoacetate (**1**) and hydrazine hydrate (**2**) in the presence of ethanol to afford 3-methyl-1*H*-pyrazol-5(4*H*)-one (**3**) has been carried out conveniently in a single step as shown in Scheme 1. It has advantages over other reported methods such as easy analysis of the reaction progress, shorter time, and cost effectiveness.

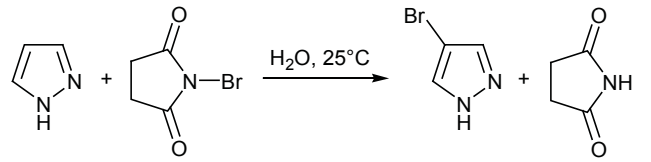
Scheme 1.



1 **2** **3**

Halogenation of pyrazole **4** with *N*-bromosuccinimide (**5**, NBS) in the presence of water at room temperature without any catalyst or nitrogen atmosphere was carried out as shown in Scheme 2. The reaction involved formation of succinimide (**7**) as by-product which can be easily separated by filtration, and product **6** was extracted from the filtrate and recrystallized from chloroform. This method avoids the use of dangerous brominating agents such as elemental bromine or HBr and involves simple reaction conditions with easy workup procedure. In addition, the bromination of pyrazole in water as green solvent has many advantages such as high yield and shorter reaction time [26].

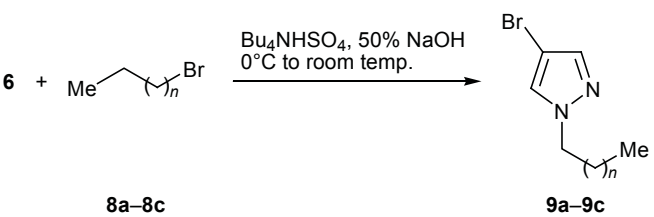
Scheme 2.



4 **5** **6** **7**

N-Alkylation of 4-bromopyrazole (**6**) to afford *N*-alkyl-4-bromopyrazole derivatives **9a**–**9c** was carried out using tetrabutylammonium hydrogen sulfate (TBAHS) as a catalyst under solvent-free conditions in the presence of sodium hydroxide as shown in Scheme 3 [27]. By this method, the reaction occurred in a smooth fashion and required easy workup, and C_3–C_6 carbon chain was successfully appended at the N^1-position of

Scheme 3.



8a–8c **9a–9c**

n = 1 (**a**), 2 (**b**), 4 (**c**).

Table 1. Percent egg hatch inhibition of root knot nematode by pyrazole derivatives **3**, **6**, and **9a**–**9c** at different concentrations

Compound no.	Duration, h	Egg hatch inhibition at different concentrations, %					
		50 ppm	125 ppm	250 ppm	500 ppm	750 ppm	1500 ppm
3	24	38.33 (38.21)	52.48 (46.42)	57.86 (49.55)	62.39 (52.22)	77.77 (62.32)	85.57 (68.42)
	48	44.83 (41.99)	57.48 (49.33)	62.61 (52.35)	68.09 (55.65)	81.50 (65.10)	86.80 (69.27)
	72	50.25 (45.13)	60.59 (51.18)	65.09 (53.82)	69.42 (56.49)	84.55 (67.72)	89.83 (75.11)
	96	52.32 (46.31)	61.41 (51.65)	73.33 (58.90)	78.15 (62.12)	88.55 (70.85)	91.83 (76.85)
6	24	29.75 (32.85)	53.92 (47.27)	62.60 (52.33)	75.48 (60.32)	79.53 (63.12)	89.35 (70.95)
	48	35.24 (36.35)	60.27 (50.98)	68.96 (56.20)	78.10 (62.09)	83.41 (66.04)	92.52 (74.14)
	72	39.67 (38.96)	63.71 (53.10)	73.22 (58.89)	80.65 (63.92)	87.55 (69.36)	94.92 (77.23)
	96	45.91 (42.63)	72.08 (58.14)	78.22 (62.16)	84.14 (66.69)	91.84 (73.51)	99.62 (87.93)
9a	24	27.30 (31.40)	51.78 (46.01)	64.24 (53.30)	72.92 (58.70)	86.73 (68.89)	91.62 (73.44)
	48	37.28 (37.53)	55.66 (48.24)	68.99 (56.16)	77.18 (61.54)	87.96 (69.95)	92.76 (74.77)
	72	39.90 (39.09)	58.13 (49.67)	72.12 (58.13)	79.09 (62.89)	89.58 (71.36)	94.50 (76.64)
	96	41.92 (40.31)	60.32 (50.94)	73.48 (58.98)	80.88 (64.13)	91.21 (73.05)	96.44 (79.21)
9b	24	42.12 (40.43)	60.44 (51.06)	65.49 (54.04)	70.20 (56.97)	79.58 (63.12)	86.57 (68.63)
	48	49.08 (44.44)	64.93 (53.74)	68.58 (55.94)	73.41 (59.09)	82.32 (65.12)	87.23 (69.17)
	72	49.33 (44.59)	67.06 (55.05)	72.25 (58.21)	76.17 (60.85)	83.38 (65.95)	89.08 (70.88)
	96	56.49 (48.75)	69.37 (56.47)	73.82 (59.22)	81.90 (64.83)	86.64 (68.53)	92.60 (72.01)
9c	24	16.24 (23.49)	33.48 (35.08)	57.01 (49.02)	66.20 (54.53)	74.77 (59.83)	81.80 (65.09)
	48	28.22 (32.06)	41.41 (39.98)	60.75 (51.20)	67.41 (55.30)	77.29 (61.59)	85.00 (67.67)
	72	31.93 (34.37)	47.21 (43.37)	63.77 (53.00)	71.51 (57.83)	78.57 (62.42)	86.89 (69.32)
	96	32.41 (34.65)	52.18 (46.23)	72.15 (58.19)	75.84(60.60)	83.62 (66.15)	90.60 (74.50)

Table 2. Percent mortality of root knot nematode caused by pyrazole derivatives **3**, **6**, and **9a**–**9c** at different concentrations

Compound no.	Duration, h	Mortality of second stage juveniles of root knot nematode, %					
		50 ppm	125 ppm	250 ppm	500 ppm	750 ppm	1500 ppm
3	24	19.91 (26.37)	45.60 (42.44)	45.74 (42.49)	53.92 (47.23)	60.21 (50.88)	77.20 (61.51)
	48	25.53 (30.13)	50.59 (45.32)	53.49 (46.99)	62.59 (52.31)	66.46 (54.63)	82.51 (65.26)
	72	30.85 (33.58)	56.06 (48.49)	63.60 (53.04)	64.86 (53.66)	72.99 (58.85)	86.2 (68.21)
	96	31.93 (34.24)	61.31 (51.56)	66.76 (54.18)	68.24 (55.69)	77.50 (61.88)	90.00 (71.68)
6	24	23.15 (28.38)	27.63 (31.68)	48.98 (44.39)	55.58 (48.19)	64.34 (53.98)	66.25 (54.57)
	48	26.77 (30.96)	35.02 (36.24)	52.42 (46.36)	62.38 (52.18)	72.95 (58.65)	80.71 (64.16)
	72	28.53 (32.06)	50.48 (45.25)	59.57 (50.51)	72.40 (58.40)	81.44 (64.54)	100.00 (89.96)
	96	32.11 (34.41)	55.79 (48.34)	64.05 (53.15)	79.52 (63.25)	93.05 (74.87)	100.00 (89.96)
9a	24	9.80 (18.19)	35.34 (36.41)	51.66 (45.96)	65.36 (53.95)	73.36 (58.91)	78.04 (62.05)
	48	12.10 (20.32)	50.40 (45.18)	57.45 (49.29)	71.61 (57.91)	75.41 (60.30)	81.80 (64.74)
	72	20.33 (26.60)	52.56 (46.46)	66.70 (54.77)	72.83 (58.68)	81.06 (64.53)	83.33 (65.88)
	96	25.42 (30.18)	54.33 (47.49)	67.60 (55.32)	76.13 (60.88)	85.40 (67.66)	88.90 (70.64)
9b	24	9.09 (17.40)	16.93 (23.80)	35.56 (36.53)	48.03 (43.79)	54.95 (47.90)	56.58 (48.80)
	48	23.86 (28.88)	25.96 (30.39)	46.89 (43.20)	52.28 (46.41)	61.79 (51.87)	65.69 (54.23)
	72	25.22 (29.79)	33.76 (35.42)	60.5 (51.08)	70.85 (57.78)	76.47 (61.03)	82.05 (65.02)
	96	30.23 (33.30)	36.97 (37.43)	66.49 (54.61)	81.83 (65.08)	83.30 (65.88)	85.22 (67.65)
9c	24	13.70 (21.50)	17.96 (25.03)	24.29 (29.46)	47.42 (43.37)	58.40 (49.82)	79.99 (63.41)
	48	17.76 (24.87)	27.49 (31.60)	39.22 (38.75)	45.63 (42.47)	63.14 (52.60)	81.54 (64.60)
	72	20.53 (26.93)	37.72 (37.87)	53.29 (46.87)	57.59 (49.36)	74.25 (59.55)	82.73 (65.46)
	96	22.16 (28.06)	40.08 (39.25)	61.41 (51.62)	69.66 (56.55)	78.19 (62.25)	85.00 (67.95)

Table 3. Comparative efficacy of pyrazole derivatives **3**, **6**, and **9a**–**9c** in egg hatch inhibition and mortality of second stage juveniles of root knot nematode

Compound no.	Egg hatch inhibition, %	Second stage juvenile mortality, %
3	68.38	58.92
6	72.69	60.19
9a	70.50	59.87
9b	71.90	51.27
9c	60.59	49.99

4-bromopyrazole. Long-chain alkyl halides reacted slowly as compared to short-chain alkyl halides.

Pyrazole derivatives **3**, **6**, and **9a**–**9c** were evaluated for their nematicidal activity against *M. incognita* at different concentrations (1500, 750, 500, 250, 125, and 50 ppm) after different durations of exposure (24, 48, 72, and 96 h). The results were statistically processed. Table 1 shows the effect of pyrazoles **3**, **6**, and **9a**–**9c** on percent egg hatch inhibition of *M. incognita*. The maximum percent egg hatch inhibition was shown by the compounds at the highest concentration (1500 ppm), and all the compounds showed reduced egg hatch inhibition as their concentration decreased. Similarly, maximum inhibition in egg hatching was shown by the compounds after 96 h of exposure, followed by 72, 48, and 24 h of exposure. Thus, egg hatch inhibition is both concentration and time dependent.

The effect of pyrazole derivatives **3**, **6**, and **9a**–**9c** on percent mortality of second stage juveniles of *M. incognita* was also evaluated (Table 2). The compounds showed similar trends as in egg hatch inhibition, i.e. the efficacy with respect to juvenile mortality was found to decrease with decrease in the concentration of the compounds and vice versa. Similarly, the maximum percent mortality of second stage juveniles of *M. incognita* was observed after 96 h of exposure, followed by 72, 48, and 24 h of exposure.

Thus, all the compounds exhibited both concentration and duration dependent behavior for both egg hatch inhibition and mortality of second stage juveniles of *M. incognita*. Table 3 compares the efficiency of pyrazole derivatives **3**, **6**, and **9a**–**9c** in egg hatch inhibition and mortality of second stage juveniles of the root knot nematode *M. incognita*. It is seen that 4-bromopyrazole (**6**) and 4-bromo-1-butyl-1*H*-pyrazole (**9b**) exhibited the highest percent egg hatch inhibition potential (72.69 and 71.90%, respectively) and that the maximum percent mortality potential (60.19%) was shown by compound **6**.

EXPERIMENTAL

The melting points were determined by using an Electronics India 934 digital melting point apparatus in open capillaries and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker Avance II 400 spectrometer at 400 and 100 MHz, respectively, at 25°C using tetramethylsilane as internal standard. The IR spectra were recorded in the range 400–4000 cm^{-1} on a Perkin Elmer Spectrum Two Fourier-transform spectrophotometer using KBr pellets. The elemental analyses were obtained with a Thermo Electron FLASH EA 112 CHN analyzer.

3-Methyl-1*H*-pyrazol-5(4*H*)-one (3). A solution of hydrazine hydrate (**2**) (0.2 mol) in ethanol (20 mL) was added dropwise with continuous stirring to ethyl acetoacetate (**1**), maintaining the temperature at 60°C. The completion of the reaction was monitored by TLC using ethyl acetate as eluent. The mixture was cooled in an ice bath, and the solid product was filtered off, washed with ice-cold ethanol, and recrystallized from methanol. Yield 84%, white crystalline solid, mp 156–157°C, R_f 0.6 (EtOAc–hexane, 8.5:1.5). IR spectrum, ν, cm^{-1}: 1609 (C=O), 1502 (C=N), 1248 (C–N). ^{1}H NMR spectrum, δ, ppm: 2.09 s (3H, CH_3), 5.23 s (2H, 4-H), 10.48 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 11.10, 88.89, 139.47, 161.08. Found, %: C 48.69; H 5.94; N 28.19; S 6.73. $C_4H_6N_2O$. Calculated, %: C 48.97; H 6.12; N 28.57.

4-Bromo-1*H*-pyrazole (6). Pyrazole (**4**, 0.01 mol) was dissolved in water (5 mL), and *N*-bromosuccinimide (**5**, 0.01 mol) was added over a period of 2 h with continuous stirring at room temperature. The progress of the reaction was monitored by TLC using ethyl acetate–hexane (1:1) as eluent. The precipitate of succinimide (**7**) was filtered off, the filtrate was extracted with ethyl acetate (3×60 mL), and the extract was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was recrystallized from

chloroform. Yield 80%, off-white solid, mp 98–100°C, R_f 0.7 (CH_2Cl_2–hexane, 8:2). IR spectrum, ν, cm^{-1}: 3158 (N–H), 3072 (C–H), 2966 (C–H), 1686 (C=C), 1433 (C=N), 1237 (C–N), 559 (C–Br). ^1H NMR spectrum, δ, ppm: 7.70 s (2H, CH), 13.13 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 91.71, 133.86. Found, %: C 24.23; H 1.91; N 18.57. $C_3H_3BrN_2$. Calculated, %: C 24.48; H 2.04; N 19.04.

1-Alkyl-4-bromo-1*H*-pyrazoles 9a–9c (*general procedure*). A mixture of 4-bromo-1*H*-pyrazole (**6**, 5.26 mmol), tetrabutylammonium hydrogen sulfate, and alkyl halide **8a**–**8c** (160 mmol) in a round-bottom flask was cooled to 0°C, and 50% aqueous sodium hydroxide (2.0 mL) was slowly added while stirring at 0°C. The mixture was stirred for 30 min at 0°C and allowed to warm up to room temperature. After completion of the reaction (TLC), the mixture was neutralized using 1.0 N aqueous HCl, and the product was isolated by extraction.

4-Bromo-1-propyl-1*H*-pyrazole (9a). Yield 65%, colorless liquid, R_f 0.6 (EtOAc–hexane, 8.5 : 1.5). IR spectrum, ν, cm^{-1}: 2955 (C–H), 2924 (C–H_{aliph}), 1464 (C=N), 1377 (C–N), 609 (C–Br). ^1H NMR spectrum, δ, ppm: 0.93 t (3H, CH_3, J = 7.32 Hz), 1.33 q (2H, CH_2, J = 7.32 Hz,), 1.52–1.60 m (2H, CH_2), 7.55 s (2H, 3-H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 13.48, 19.51, 23.74, 58.51, 92.43, 134.02. Found, %: C 37.92; H 4.55; N 14.56. $C_6H_9BrN_2$. Calculated, %: C 38.09; H 4.76; N 14.81.

4-Bromo-1-butyl-1*H*-pyrazole (9b). Yield 60%, colorless liquid, R_f 0.6 (EtOAc–hexane, 8.5 : 1.5). IR spectrum, ν, cm^{-1}: 3108 (C–H), 2961 (C–H_{aliph}), 1463 (C=N), 1372 (C–N), 608 (C–Br). ^1H NMR spectrum, δ, ppm: 0.93 t (3H, CH_3, J = 7.44 Hz), 1.32 q (2H, CH_2, J = 7.48 Hz), 1.77–1.84 m (2H, CH_2), 4.08 t (2H, CH_2, J = 7.20 Hz), 7.38 d (2H, 3-H, 5-H, J = 20.08 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.53, 19.68, 32.22, 52.55, 92.52, 129.04, 139.46. Found, %: C 40.98; H 5.03; N 13.53. $C_7H_{11}BrN_2$. Calculated, %: C 41.30; H 5.41; N 13.79.

4-Bromo-1-hexyl-1*H*-pyrazole (9c). Yield 62%, light yellow liquid, R_f 0.7 (EtOAc–hexane, 8.5:1.5). IR spectrum, ν, cm^{-1}: 3122 (C–H), 2927 (C–H_{aliph}), 1458 (C=N), 1311 (C–N), 608 (C–Br). ^1H NMR, δ, ppm: 0.86 t (3H, Me, J = 6.88 Hz), 1.27 s (6H, CH_2), 1.81 q (2H, CH_2, J = 7.24 Hz), 4.05 t (2H, CH_2, J = 7.12 Hz), 7.37 s and 7.42 s (1H each, 3-H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 13.88, 22.37, 26.08, 30.11, 31.17, 52.75, 92.43, 128.92, 139.32. Found, %: C 46.54; H 6.31; N 11.93. $C_9H_{15}BrN_2$. Calculated, %: C 46.75; H 6.49; N 12.12.

Nematicidal activity. Pyrazole derivatives **3**, **6**, and **9a**–**9c** were screened for their nematicidal activity, i.e., egg hatch inhibition and mortality of second stage juveniles of *Meloidogyne incognita*, at six different concentrations, 1500, 750, 500, 250, 125, and 50.00 ppm. The observations were recorded after 24, 48, 72, and 96 h.

a. *Egg hatch inhibition assay*. A pure culture of root knot nematodes was raised in brinjal crop. Five egg masses were taken and placed in a solution (5 mL) of **3**, **6**, or **9a**–**9c** at a concentration of 1500, 750, 500, 250, 125, or 50.00 ppm. A very small amount of acetone was used to dissolve the compounds in distilled water for making stock solution which was further diluted to a required concentration. Distilled water containing the same amount of acetone was used as control. Three replications of each treatment were made. Egg hatching after 24, 48, 72, and 96 h at 27±2°C was recorded [28, 29]. 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*. Freshly hatched stage two juveniles (j_2) were taken instead of egg masses for mortality test. The number of juveniles per milliliter of distilled water was counted which was found to be average of 20 juveniles. Solutions of the test compounds (5 mL) were prepared as described above for the egg hatch assay test with 3 replications each along with control. A juvenile suspension (1 mL) was placed in each solution with a concentration of 1500, 750, 500, 250, 125, and 50 ppm, and the results were recorded after 24, 48, 72, and 96 h [28, 29]. The percent juvenile mortality was calculated as the ratio of the number of dead nematodes to the total number of nematodes multiplied by 100%.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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