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REGULAR ARTICLE

Synthesis and herbicidal evaluation of N-cinnamoyl-N-substituted hydroxylamine and its derivatives.

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AK: Conceptualization; Experimental data collection; Data storage; Data analysis; Literature review; Manuscript revision; Supervision. SA: Conceptualization; Data storage; Data analysis; Literature review; Manuscript writing. SC: Experimental data collection; Manuscript writing. SK: Data storage; Manuscript revision. AG: Experimental data collection; Literature review; Manuscript writing.

Abstract

The group of cinnamon and hydroxylamine produces significant results in the field of agriculture. So, the combination of both groups in the compound performs effective results in numerous fields of the medicinal and chemical industry. Still, this type of moiety combination is not used in the agricultural field as an herbicide. The cost-effective plant that grows alongside crops develops resistance to current herbicides. To effectively combat undesirable herbs, new or modified groupings are needed. To investigate the prospect of discovering a new class of herbicide, the current work aims to synthesize derivatives of cinnamon hydroxamic acid and screen them for herbicidal activity. A cinnamo hydroxamic acid derivative was synthesized by a reaction of substituted cinnamic acids and hydroxylamine derivatives, and the final product was characterized by FTIR, ^{1}H NMR, and ^{13}C NMR spectroscopy. The final product was tested for herbicidal activity against Radish (*Raphanus sativus*) seeds at 50, 100 and 200 ppm concentrations and compared with standard pendimethalin. Amongst the tested compounds, 3-nitro cinnamo hydroxamic acid (A_2), o-tolyl-(3-bromo) cinnamo hydroxamic acid (B_1) and 2-bromo-(4-chloro) cinnamo hydroxamic acid) (C_1) exhibited activity at par with standard pendimethalin at a concentration of 200 ppm and In silico PASS studies also showed that it has excellent herbicidal properties.

Keywords

Cinnamo Hydroxamic Acid; NMR Spectroscopy; Unwanted Herbs; Raphanus sativus; Herbicidal Activity; Pendimethalin; PASS studies.

Introduction

The transport of iron by microbes is facilitated by naturally occurring hydroxamic acid derivatives (siderophores) (Köster et al., 2001). Antibiotics, antifungal medications, dietary additives, tumor inhibitors, and growth hormones contain derivatives of hydroxyamic acids (Arnold et al., 1998; Botos et al., 1996).Hydroxamic acid derivatives are stable chelating ligands and form coordinate bonds with metal ions due to which they have powerful biological activities (Syed et al., 2020).Hydroxamic acids are sold under the brand name Zolinca to treat cancer. Moreover, its derivatives have cytotoxic properties due to their suppression of the histone deacetylase (HDAC) enzyme (Finnin et al., 1999). They induce point mutation (Wu et al., 2021) and act as a promising scaffold for the treatment of Chagas disease (Rodrigues et al., 2014). Hydroxamic acid derivatives have wide applications in chemical industries like paints, pharmaceuticals, plastics, textiles, nuclear industries, photography, and biological activities (Chan et al., 1986). They are identified as intermediates in the nitrogen cycle, nitrogen fixation, and heterotropic nitrification (Verstraete and Alexander, 1973). Medicinally important compounds cycloserine, hedacidin, and heteroaromatic aspergillic acid are derived from hydroxamic acid (Coutts et al., 1971). Histone deacetylases and matrix metalloproteases, which are linked to a variety of illnesses like cancer, arthritis, and multiple sclerosis, are strongly inhibited by hydroxyamic acid (Cheng et al., 2000). Hydroxamic acid compounds are currently marketed as drugs for controlling various diseases. Treatments for refractory cutaneous T-cell lymphoma (CTCL), peripheral T-cell lymphoma (PTCL), and panobinostat for multiple myeloma patients have included vorinostat and balinostat (Falkenberg and Johnstone, 2014).Several reports show hydroxyamic acid to possess various biological activities like antifungal (Tsuji et al., 1976), antibacterial (Weber et al., 1983), anti-inflammatory (Miller, 1986), and anti-asthmatic properties (Miller, 1989). They also act as intermediates in synthesizing biologically active substances (Yadav et al., 2003) and are important reagents for synthesizing raw material for the polymerization inhibitor (McGill et al., 2000; Takeuchi et al., 2003). Cinnamo hydroxamic acids are hydroxamic acids having cinnamic acid moiety. They are very useful in numerous biological, environmental, analytical, medical molecular modeling, docking, and nuclear chemistry (Rajput et al., 2017). Cinnamo hydroxamic acids have the property to form stable colored

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chelate complexes with vanadium (Rajput et al., 2016). They suppress the activity of various enzymes like peroxidase (Indiani et al., 2003), urease (Asadi et al., 2023), ribonucleotide reductase (Shao et al., 2006), metalloproteinase (Sani et al., 2004), and hydrolases (Brown et al., 2004). Cinnamo hydroxamic acids though had wide applications in pharmaceuticals, they have not been extensively studied for their herbicidal activity.

Materials and methods

The Buchi B-540 digital melting point equipment was used to determine melting points. The Genesys 10 UV-Vis spectrophotometer was used to capture UV spectra and structures analysis of synthesized derivatives of hydroxamic acids, have been analyzed from FTIR and NMR spectra, ^{1}H NMR Spectra were characterized through a JNM-ECS400 MHz NMR Spectrometer. The chemical shifts were quantified in δ (ppm). Chloroform was employed as the solvent, and TMS as the internal standard. IR spectra were recorded on an FT-IR (Bruker) spectrophotometer. The radish seed (Raphanus sativus) was obtained from the crop research center (CRC) of Pantnagar University.

Preparation of substituted cinnamic acids: The modification of Doebner-Knoevenagel was used to create the substituted cinnamic acids. In a representative reaction, substituted benzaldehyde (60 mmol) and pulverized malonic acid (100 mmol) were dissolved in 20 mL of pyridine. Piperidine (0.8 mL) was added to it. The reaction mixture was stirred on a magnetic stirrer at room temperature. The reaction progress was monitored over a silica gel TLC plate. Then the formation of cinnamic acid was dissolved in triethylamine (0.1 mL) with $POCl_3$ (0.2 mL) and added dropwise with stirring and maintaining the temperature of 0°C. Hydrochloric acid was added to the reaction mixture. The resulting precipitates were filtered, cleaned with cold water, and allowed to dry (Figure 1).

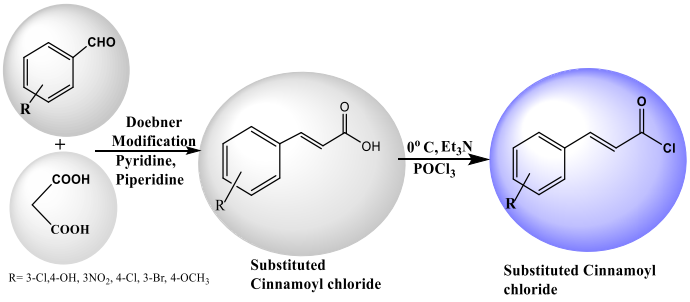


Figure 1. Synthesis of substituted cinnamoyl chloride.

Preparation of substituted aryl hydroxylamine derivatives: Hydroxylamine derivatives were prepared using the method reported in the literature (Ung et al., 2005). In a representative reaction, nitrobenzene derivative (0.024 mmol) was added to a solution of ammonium chloride (0.023 mmol) in distilled water (20 ml). The reaction mixture was stirred adding Zn dust (0.092 mmol) in installments and maintaining the temperature below 65°C. A silica gel TLC plate was used to track the reaction's development. Following the conclusion of the process, the zinc oxide precipitate was filtered, and then the filtrate was saturated with NaCl and placed in an ice bath for one hour. The shining crystals obtained were filtered and recrystallized with hexane (Figure 2).

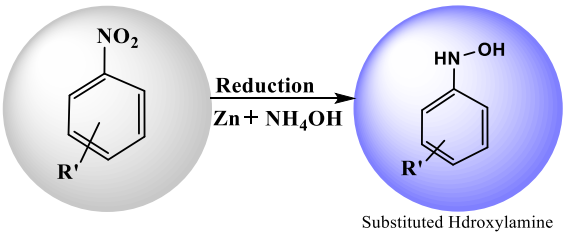


Figure 2. Synthesis of aromatic hydroxylamine derivatives using zinc catalyst.

Synthesis of Cinnamo hydroxamic acid compounds: The reaction of substituted cinnamic acids and hydroxylamine derivatives produced variants of cinnamon hydroxamic acid. (Figure 3). In a typical reaction, substituted cinnamic acyl chloride (1.0 mmol) and hydroxylamine derivative (1.0mmol) were dissolved in triethylamine (0.1 mL) was added to the solution, at 0°C. After that triethylamine (0.2 mL) was added in one portion. The reaction was stirred for an extra 30 min at a low temp. The progress of the reaction was monitored by using TLC. After completion of the reaction, the reaction mixture was poured into crushed ice. The compound was extracted with dichloromethane three times and combined extraction was washed in turn with dil. HCl, aq Na_2CO_3, water and dried over anhydrous sodium sulfate. Evaporation of solvent gave a brown residue that was recrystallized from alcohol affording 65- 75% yield. A total of ten derivatives is obtained in the above-mentioned reaction. The first set is 'A set' and its derivatives are substituted cinnamo hydroxamic acid (A-1 to A-5) and the second set are 'B set' and its derivatives are o-Tolyl-(substituted) cinnamo hydroxamic acid (B-1 to B-5). (Figure 4).

The seed germination inhibition activity of synthesized compounds was assessed using the prescribed protocol (Sahu and Devkota,2013). The compound to be tested was dissolved in a minimum amount of ethanol and then two drops of 1% Tween 20 to the solution and made up with distilled water to prepare a stock solution of concentration 200 ppm. By serial dilution solutions of concentration 100 ppm and 50 ppm were prepared. Radish seeds (Raphanus sativus) were sterilized in 1% hypochlorite solution for 30 minutes. Ten radish seeds were taken in each Petri dish containing a piece of filter paper and 7 ml of each test solution. The herbicide pendimethalin was taken as standard. Three replicates were used for each treatment. Distilled water was used as a control. The Petri dishes were closed by parafilm to prevent the loss of moisture. The Petri dishes were kept in an incubator at 25±2°C for germination. The seed germination was observed. After 120 hr of incubation, the number of seeds germinated on each plate was counted.

The synthesized compounds were input in SMILES format for prediction and simulation using the PASS online web app. This tool is designed to estimate the probable activity (Pa) and probable inactivity (Pi) of any compound, specifically focusing on 'drug-like' substances (Arya et al., 2023). Compounds with a Pa value greater than Pi are considered to exhibit a specific biological activity (Goel et al., 2011).

The mean percent seed germination inhibition values were calculated, and data was subjected to by analysis of variance (ANOVA) by STPR3 software. The critical differences (CDs) were calculated at $p \leq 0.0$.

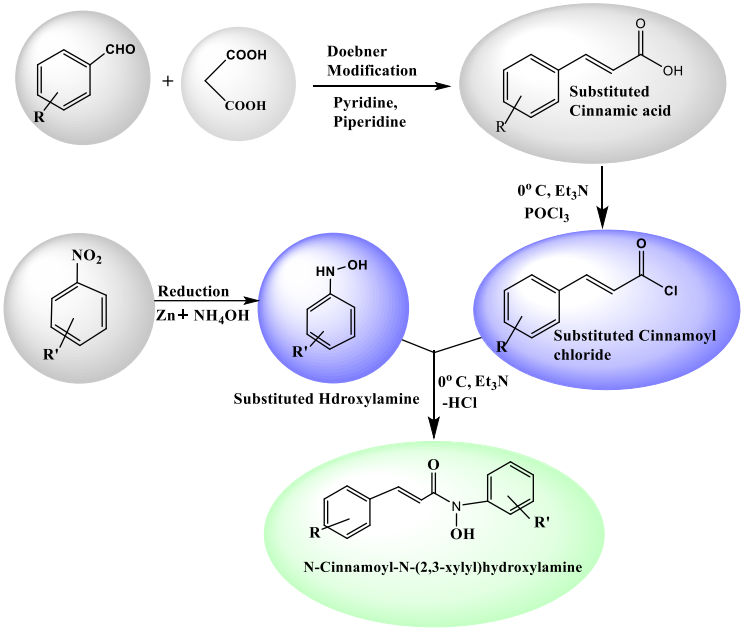


Figure 3. Synthesis of Cinnamo hydroxamic acid derivatives.

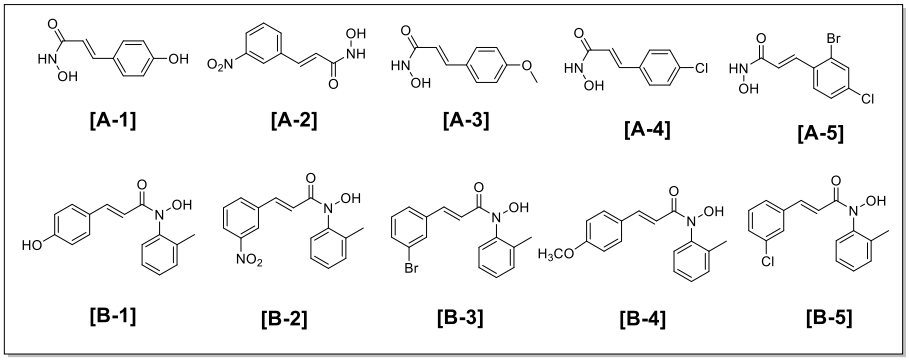


Figure 4. Derivatives of the synthesized compounds.

Results and discussion

Aryl hydroxylamine derivatives and substituted cinnamic acids were prepared by the methods reported in the literature and were obtained in good yields. To prepare cinnamo hydroxamic acid derivatives, we have developed an efficient one-pot synthesis wherein cinnamoyl chloride is formed in situ, reacting with hydroxylamine derivative to give cinnamo hydroxamic acid derivative. We successfully used the catalyst triethylamine for the first time in this reaction. The method developed is less time-consuming, easy to work up, and consequently cost-effective in comparison to the methods earlier reported in the literature (Agrawal et al., 1971; Priyadarshini et al., 1967; Vishnoi et al., 2009).

Physical and Spectral Data

(a) 4-hydroxy cinnamo hydroxamic acid [A-1]. M.P: 104˚C; **Yield**: 69 %; **Colour**: Brown; **FTIR (KBr)** 3689 cm^{-1} (OH), 1848 cm^{-1} (C=O), 1540 cm^{-1} (N-O), 1943 cm^{-1} (Ar, C=C stretch).**^{1}H NMR** (Chloroform, 400MHz): Two doublets of the protons of -CH=CH- at 6.53 and 7.46 ppm having $J \approx 16$ Hz. δ 7.24 (1H, s, N-OH), δ 9.64 (1H, s, OH), δ 7.39 (2H, d, Ar, $J \approx 16.2$ Hz), δ 7.44 (2H, d, Ar, $J \approx 16.2$ Hz), **^{13}C NMR** (Chloroform, 400MHz): 115.8, 118.6, 127.8, 130.6, 141.7, 157.7, 161.6.

(b) 3-nitro cinnamo hydroxamic acid [A-2]. M.P: 65˚C; **Yield**: 68 %; **Colour**: Brown; **FTIR (KBr)**: 3689 cm^{-1} (OH), 1792 cm^{-1} (C=O), 1471 cm^{-1} (N-O), 1956 cm^{-1} (Ar C=C stretch).**^{1}H NMR** (Chloroform, 400MHz): Two doublets of the protons of -CH=CH- at 6.54 and 7.54 ppm having $J \approx 16$ Hz, δ 7.24 (1H, s, N-OH), δ 7.48 (1H, s, Ar,J=16.2 Hz), δ 7.53 (1H, d, Ar, $J \approx 16.2$ Hz), 7.58 (1H, d, Ar, $J \approx 16.2$ Hz), 7.25 (1H, t, Ar, $J \approx 16.2$ Hz), **^{13}C NMR** (Chloroform, 400MHz): 118.8, 122.7, 123.1, 129.5, 134.6, 137.7, 141.7, 147.8, 161.6.

(c) 4-methoxy cinnamo hydroxamic acid [A-3]. M.P: 70˚C; **Yield**: 70 %; **Colour**: Brown; **FTIR (KBr)**: 3689 cm^{-1} (OH), 2870 cm^{-1} (OCH_3), 1542 cm^{-1} (N-O), 1793 cm^{-1} (C=O), 1966 cm^{-1} (Ar, C=C stretch), **^{1}H NMR** (Chloroform, 400MHz): Two doublets of the protons of -CH=CH- at 6.31 and 7.46 ppm having $J \approx 16$ Hz, δ 7.24 (1H, s, N-OH), δ 3.83 (3H, s, OCH_3), δ 7.42 (2H, d, Ar, $J \approx 16.2$ Hz), δ 7.46 (2H, d, Ar, $J \approx 16.2$ Hz), **^{13}C NMR** (Chloroform, 400MHz): 55.8, 114.2, 118.8, 127.5, 130.2, 141.7, 159.8, 162.6.

(d) 4-chloro cinnamo hydroxamic acid [A-4]. M.P: 60˚C; **Yield**: 66 %; Colour: Brown; **FTIR (KBr)**: 3674 cm^{-1} (OH), 1540 cm^{-1} (N-O), 1868 cm^{-1} (C=O), 1943 cm^{-1} (Ar, C=C stretch), 1792 cm^{-1} (Cl), **^{1}H NMR** (Chloroform, 400MHz): Two doublets of the protons of -CH=CH- at 6.31 and 7.46 ppm having $J \approx 16$ Hz, δ 7.89 (1H, s, N-OH), δ 7.36 (2H, d, Ar, $J \approx 16.2$ Hz), δ 7.48 (2H, d, Ar, $J \approx 16.2$ Hz), **^{13}C NMR** (Chloroform, 400MHz): 118.8, 128.7, 129.0, 133.3, 133.5, 141.7, 161.8.

(e) 2-bromo-(4-chloro) cinnamon hydroxamic acid [A-5].M.P: 88˚C; **Yield**: 70 %; Colour: Brown; **FTIR (KBr)**: 3674 cm^{-1} (OH), 1540 cm^{-1} (NO),740 cm^{-1} (Cl),1868 cm^{-1} (C=O), 1921 cm^{-1} (Ar, C=C stretch), 1791 cm^{-1} (Br), **^{1}H NMR** (Chloroform, 400MHz): Two doublets of the protons of -CH=CH- at 6.6 and 7.35 ppm having $J \approx 16$ Hz, δ 7.30 (1H, s, N-OH), δ 7.37 (1H, s, Ar,$J \approx 16.2$ Hz), δ 7.39 (1H, d, Ar, $J \approx 16.2$ Hz), 7.42 (1H, d, Ar, $J \approx 16.2$ Hz), **^{13}C NMR** (Chloroform, 400MHz): 118.8, 120.2, 127.7, 130.0, 130.2, 133.9, 134.2, 143.9, 162.6.

(f) o-tolyl-(4-hydroxyl) cinnamo hydroxamic acid [B-1].M.P: 98˚C; **Yield**: 75%; **Colour**: Yellow**; FTIR (KBr)**:3679 cm^{-1} (OH), 1786 cm^{-1} (C=O), 1506 cm^{-1} (N-O), 1697 cm^{-1} (Ar, C=C stretch), **^{1}H NMR** (Chloroform, 400MHz): Two doublets of the protons of -CH=CH- at 6.53 and 7.35 ppm having $J \approx 16$ Hz, δ 7.39 (2H, d, Ar, $J \approx 16.2$ Hz), δ 7.44 (2H, d, Ar, $J \approx 16.2$ Hz), δ 7.24 (1H, s, N-OH), δ 7.39-7.42 (4H, m, Ar), δ 3.12 (3H, s, CH_3),**^{13}C NMR** (Chloroform, 400MHz): 17.6, 102.3,115.8, 118.8, 123.5, 127.8, 128.3, 128.4, 129.3, 130.6, 141.7, 150.8, 157.1, 158.2.

(g) o-tolyl -(3-nitro) cinnamo hydroxamic acid [B-2].M.P: 80˚C; **Yield**: 68 %; Colour: Brown; **FTIR (KBr)**: 3669 cm^{-1} (OH), 1786 cm^{-1} (C=O),1479 cm^{-1} (N-O), 1636 cm^{-1} and 1455 cm^{-1} (Ar, C=C stretch),**^{1}H NMR** (Chloroform, 400MHz): Two doublets of the protons of -CH=CH- at 6.45 and 7.27 ppm having $J \approx 16$ Hz, δ 3.10 (3H, s, CH_3), δ 7.48 (1H, s, Ar, $J \approx 16.2$ Hz), δ 7.53 (1H, d, Ar, $J \approx 16.2$ Hz), 7.58 (1H, d, Ar, J≈16.2 Hz), 7.25 (1H, t, Ar, $J \approx 16.2$ Hz), δ 7.24 (1H, s, N-OH), δ 7.63-7.68 (4H, m, Ar), **^{13}C NMR** (Chloroform, 400MHz): 17.5, 102.3, 118.8, 122.7, 123.5, 128.3, 128.6, 129.5, 134.6, 137.7, 141.7, 147.8, 150.7, 157.1.

(h) o-tolyl-(3-bromo) cinnamo hydroxamic acid [B-3]. M.P: 71˚C; **Yield**: 70 %; Colour: Brown; **FTIR (KBr)**: 3689 cm^{-1} (OH),1540 cm^{-1} (N-O), 1844 cm^{-1} (C=O), 1942 cm^{-1} (Ar, C=C stretch), 1828 cm^{-1} (Br), **^{1}H NMR** (Chloroform, 400MHz), Two doublets of the protons of -CH=CH- at 6.45 and 7.54 ppm having $J \approx 16$ Hz, δ 2.35 (3H, s, CH_3), δ 7.47 (1H, s, Ar, J≈16.2 Hz), δ 7.58 (1H, d, Ar, $J \approx 16.2$ Hz), 7.66 (1H, d, Ar, $J \approx 16.2$ Hz), 7.25 (1H, t, Ar, J≈16.2 Hz, δ 7.24 (1H, s, N-OH), δ 7.66-7.79 (4H, m, Ar), **^{13}C NMR** (Chloroform, 400MHz): 17.8, 103.8, 117.6, 123.0, 123.7, 127.8, 128.3, 128.7, 129.3, 129.8, 130.8, 133.1, 137.7, 142.4, 150.7, 157.3.

(i) o-tolyl-(4-methoxy) cinnamo hydroxamic acid [B-4]. **M.P**: 80˚C; **Yield**: 68 %; **Colour**: Brown; **FTIR (KBr)**: 3689 cm^{-1} (OH), 1868 cm^{-1} (C=O), 1637 cm^{-1} (Ar, C=C stretch), 3064 cm^{-1} (OCH_3), **^{1}H NMR** (Chloroform, 400 MHz: Two doublets of the protons of -CH=CH- at 6.45 and 7.54 ppm having $J \approx 16$ Hz, δ 2.12 (3H, s, CH_3), δ 3.81 (3H, s, OCH_3), δ 8.24 (1H, s, N-OH), δ 7.06 (2H, d, Ar, J=16.2 Hz), δ 7.68 (2H, d, Ar, J=16.2 Hz), δ 7.29-7.62 (4H, m, Ar) **^{13}C NMR** (Chloroform, 400MHz): 17.6, 55.8, 114.4, 118.2, 123.5, 127.8, 128.3, 128.4, 129.4, 130.2, 141.8, 150.7, 157.1, 159.8.

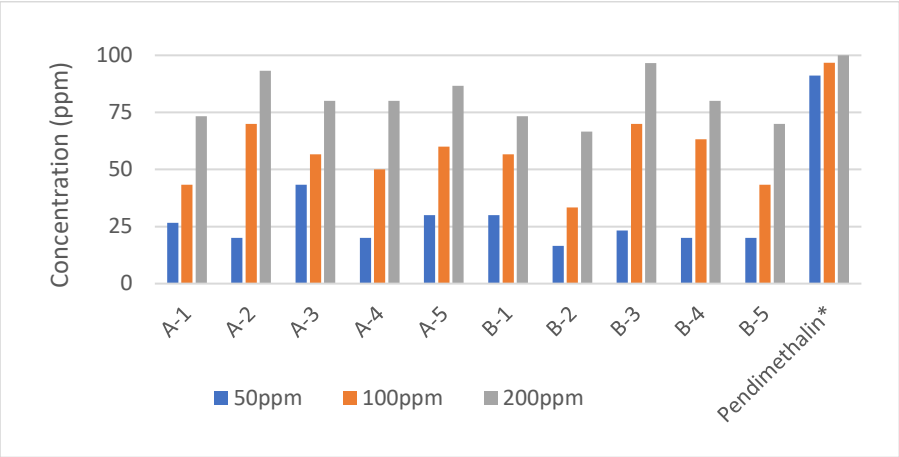
(j) o-tolyl-(3-chloro) cinnamo hydroxamic acid [B-5]M.P: 80˚C; **Yield**: 76 %; **Colour**: Yellow; **FTIR (KBr)**: 3689 cm^{-1} (OH), 1540 cm^{-1} (NO), 1868 cm^{-1} (C=O), 1942 cm^{-1} (Ar, C=C stretch), 1792 cm^{-1} (Cl).**^{1}H NMR** (Chloroform, 400MHz: Two doublets of the protons of -CH=CH- at 6.45 and 7.54 ppm having $J \approx 16$ Hz, δ 2.12 (3H, s, CH_3), δ 8.14 (1H, s, N-OH), δ 7.29 (1H, s, Ar, J=16.2 Hz), δ 7.53 (1H, d, Ar, $J \approx 16.2$ Hz), 7.69 (1H, d, Ar, $J \approx 16.2$ Hz), 7.32(1H, t, Ar, $J \approx 16.2$ Hz), δ 7.29-7.60 (4H, m, Ar) **^{13}C NMR** (Chloroform, 400MHz): 17.7, 102.6, 118.6, 123.5, 126.4, 126.6, 127.8, 128.0, 128.3, 129.3, 130.0, 134.2, 136.5, 141.4, 150.7, 157.2.

Herbicidal Activity

Mean percent germination inhibition values were calculated and subjected to analysis of variance (ANOVA). (Table 1) reveals that for all the compounds there is a significant increase in activity with an increase in concentration from 50 ppm to 200 ppm. At a concentration of 50 ppm, all the compounds have significantly lower activity than the standard pendimethalin. At a concentration of 100 ppm, all the compounds exhibited substantially lower activity than standard pendimethalin. At a concentration of 200 ppm, the compounds A_2, B_3, and C_1 exhibited activity at par with standard pendimethalin. The compound A_2 has a nitro group substituted at the benzene ring of cinnamic acid moiety and the hydroxylamine benzene ring has no substituent. The good activity of compound A_2 may be due to an electron-withdrawing group on the benzene ring of the cinnamic acid moiety. The good activity of compound B_3 may be due to the bromo group on the benzene ring of the cinnamic acid moiety. Significant activity of compound C_1 may be due to the combined effect of chloro and bromo substituents at benzene rings of cinnamic acid moiety and hydroxylamine moiety respectively. A perusal of the structures of all the compounds indicates that electron-withdrawing substituents like chloro, bromo, or nitro contribute to increasing the activity of the compounds. While electron donating groups eg. -CH_3 decrease the activity (Figures 5 and 6).

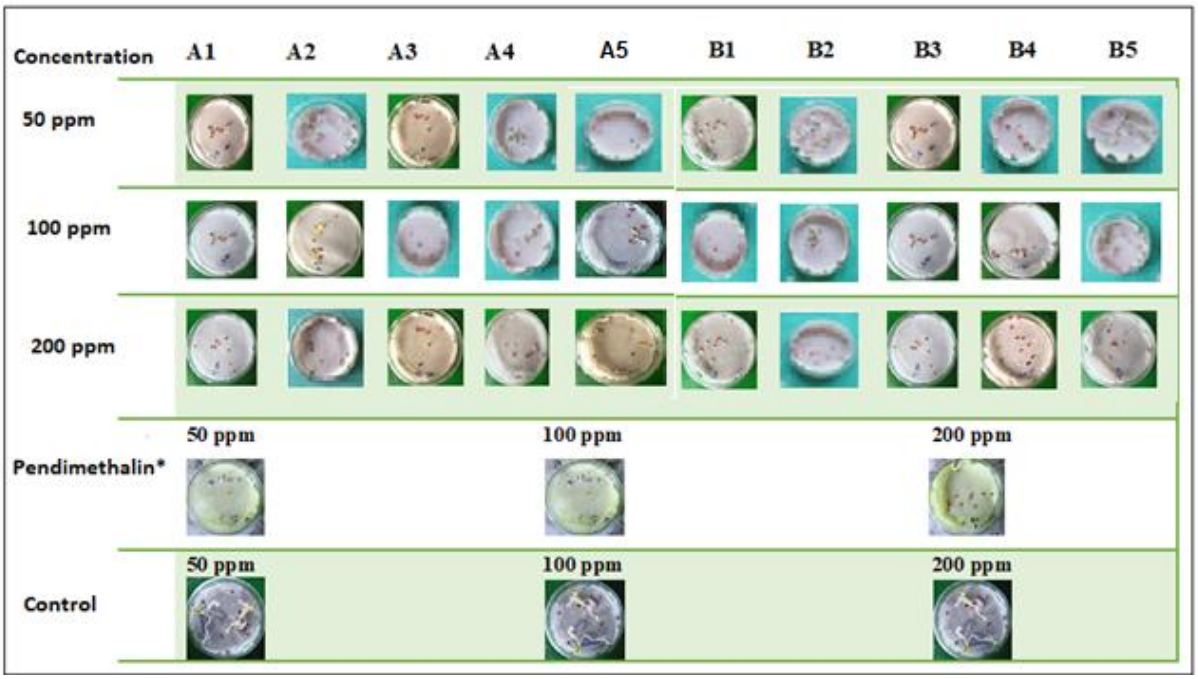
Table 1. Seed germination inhibition activity of cinnamo hydroxamic acid derivatives against *raphanus sativus.*

Compound codes	Mean percent germination inhibition			
	50ppm	**100ppm**	**200ppm**	**CD at 5%**
A-1	26.6 ± 0.57	43.3± 0.33	73.3 ± 0.66	44.83
A-2	20± 0.66	70±0.66	93.3± 0.33	26.46
A-3	43.3± 0.33	56.6± 0.66	80± 0.57	17.59
A-4	20± 0.33	50± 0.57	80± 0.88	23.03
A-5	30± 0.57	60± 1.20	86.6± 0.57	28.98
B-1	30± 0.33	56.6± 0.33	73.3±0.57	14.87
B-2	16.6± 0.57	33.3±0.57	66.6± 0.66	21.03
B-3	23.3±0.33	70± 0.88	96.6±0.33	21.03
B-4	20± 0.33	63.3±0.88	80± 0.33	22.05
B-5	20± 0.33	43.3± 0.33	70±0.66	16.29
Pendimethalin*	91.1± 0.57	96.7± 0.57	100± 0.57	19.95
CD at 5%	**12.84**	**21.05**	**17.68**	



*Standard-Standard herbicide (Pendimethalin); Cinnamo hydroxamic acid derivatives: Substituted cinnamo hydroxamic acid [A-1 to A-5] and o-Tolyl-(Substituted) cinnamo hydroxamic acid [B-1 to B-5]

Figure 5. Comparison of mean percent seed germination inhibition value of cinnamo hydroxamic acid derivatives against *Raphanus sativus.*



*Standard herbicide; Cinnamo hydroxamic acid derivatives: Substituted cinnamo hydroxamic acid [A-1 to A-5] and o-Tolyl-(Substituted) cinnamo hydroxamic acid [B-1 to B-5]

Figure 6. Diagrammatic representation of mean percent seed germination inhibition value of cinnamo hydroxamic acid derivatives against *Raphanus sativus*.

***In silico* PASS prediction of the cinnamo hydroxamic acid derivatives**

Results of *In silico* PASS prediction results indicated that all the cinnamo hydroxamic acid derivatives- 4-hydroxy cinnamo hydroxamic acid, 3-Nitro cinnamo hydroxamic acid, 4-Methoxy cinnamo hydroxamic acid, 4-chloro cinnamo hydroxamic acid, o-tolyl-(4-hydroxyl) cinnamo hydroxamic acid, o-tolyl -(3-nitro) cinnamo hydroxamic acid, o-tolyl-(3-bromo) cinnamo hydroxamic acid, o-tolyl-(4-methoxy)cinnamo hydroxamic acid, o-tolyl-(3-chloro) cinnamo hydroxamic acid, 2-bromo-(4-chloro) cinnamon hydroxamic acidcompounds were found to possess significant Pa/Pi values for anti-inflammatory, antiviral and herbicidal activity. However, as predicted by PASS, several compounds were found to have very low Anticarcinogenic activity (Table 2). These data align with the herbicidal activity of the tested compounds having significant Pa/Pi values. Furthermore, specific cinnamo hydroxamic acid derivatives, namely 4-Methoxy cinnamo hydroxamic acid, o-Tolyl-(4-hydroxyl) cinnamo hydroxamic acid, and o-Tolyl-(4-methoxy) cinnamo hydroxamic acid compounds exhibited a significant Pa/Pi range for the antioxidant activity. Overall, the PASS prediction confirmed the correlation of compounds with herbicidal activity.Consequently, further exploration of these compounds is warranted to elucidate the underlying mechanisms contributing to their diverse biological activities, especially anti-inflammatory and antiviral activity.

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Table 2. *In silico* pass prediction for anti-inflammatory, antiviral, anticarcinogenic, antioxidant, and herbicidal (GABA aminotransferase inhibitor) activity of cinnamo hydroxamic acid derivatives.

S. nº.	Compound name	Pass (Pa>Pi)				
		Anti-inflammatory	Anti-Viral	Anti-Carcinogenic	Antioxidant	Herbicidal (GABA aminotransferase inhibitor)
1	4-Hydroxy cinnamo hydroxamic acid	0.248> 0.215	0.417> 0.035	-	-	0.627> 0.007
2	3-Nitro cinnamo hydroxamic acid	0.199> 0.101	0.238> 0.153	-	-	0.306> 0.110
3	4-Methoxy cinnamo hydroxamic acid	0.535> 0.005	0.360> 0.060	0.195> 0.125	0.139> 0.116	0.469> 0.027
4	4-Chloro cinnamo hydroxamic acid	0.352> 0.040	0.281> 0.057	-		0.399> 0.049
5	o-Tolyl-(4-hydroxyl) cinnamo hydroxamic acid	0.537> 0.005	0.263> 0.119	-	0.189> 0.062	0.416> 0.042
6	o-Tolyl -(3-nitro) cinnamo hydroxamic acid	0.402> 0.022	0.385> 0.122	-	-	0.226> 0.126
7	o-Tolyl-(3-bromo) cinnamo hydroxamic acid	0.369> 0.057	0.305> 0.086	-	-	0.226> 0.126
8	o-Tolyl-(4-methoxy)cinnamo hydroxamic acid	0.579> 0.004	0.229> 0.157	-	0.148> 0.106	0.309> 0.107
9	o-Tolyl-(3-chloro) cinnamo hydroxamic acid	0.362> 0.035		-	-	0.240> 0.197
10	2-Bromo-(4-chloro) cinnamon hydroxamic acid	0.222> 0.155	0.207> 0.148	-	-	0.255> 0.174

PASS= Prediction of activity spectra for substance; Pa= Probable activity; Pi= Probable inactivity

Conclusions

Cinnamo hydroxamic acid derivatives have been found to exhibit significant seed germination inhibition activity which at 200 ppm is at par with pendimethalin. Structure-activity relationship reveals that structural modifications may largely alter the activity. Therefore, cinnamo hydroxamic acids have the potential to be developed as classes with promising herbicidal activity. We have also developed a one-pot efficient method for the synthesis of cinnamo hydroxamic acids from cinnamic acids and hydroxylamine derivatives using triethylamine as a catalyst.

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