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SYNTHESIS AND EVALUATION OF NOVEL α-CYANO-N-(4-HYDROXYPHENYL) CINNAMAMIDES FOR ANTIOXIDANT, ANTI-INFLAMMATORY ACTIVITIES: *IN-SILICO* PREDICTION OF DRUG LIKENESS PROPERTIES

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Keywords:

α-Cyanocinnamamide, Knoevenagel condensation, Antioxidant properties, Anti-inflammatory activity

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ABSTRACT: A facile synthetic reaction has been used for the synthesis of novel compounds, substituted α-cyano-N-(4-hydroxyphenyl) cinnamamides from α-cyano-N-(4-hydroxyphenyl) acetamide. Their physical and spectral data characterized all the synthesized compounds. The title compounds were screened for *in-vitro* antioxidant activity in two different models which include scavenging of DPPH and nitric oxide free radicals. The compounds with hydroxy substitution on the phenyl ring of α-cyanocinnamamide moiety showed excellent antioxidant properties. Hence, the active compounds were evaluated for anti-inflammatory activity by carrageenan-induced rat paw edema assay. Among the evaluated compounds, α-cyano-N-(4-hydroxyphenyl)-4-hydroxy-3-methoxycinnamamide and α-cyano-N-(4-hydroxyphenyl)-3,4-dihydroxy-cinnamamide exhibited better activity comparable to the standard drug Diclofenac. Further, *in-silico* prediction of molecular properties of the synthesized compounds was carried out using molinspiration online software. The study revealed that all the compounds obeyed Lipinski's rule of five. The TPSA calculations revealed that the compounds possess good intestinal absorption. Finally, the present study identified these compounds as potential new drug candidates for the treatment of diseases associated with oxidative stress.

INTRODUCTION: Alkamides are a group of bioactive natural compounds with broad structural variability known to possess a wide range of biological activities such as immunomodulatory, antimicrobial, antiviral, larvicidal, insecticidal, diuretic, pungent, analgesic, cannabimimetic and antioxidant activities.

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They are also involved in the potentiation of antibiotics and the inhibition of prostaglandin biosynthesis, RNA synthesis and arachidonic acid metabolism [1]. Cinnamamides are considered as a subclass of alkamides with aromatic residue at the acid portion [2].

Some of the examples of naturally occurring cinnamamides include caffeoylputrecine, feruloyl-putrecine, feruloyltyramine, and *p*-coumaroyl-tyramine *etc*. The α-cyanocinnamamides, chemically similar to cinnamamides, contains nitrile/cyano (-C≡N) group on α-carbon of carbon-carbon double bond. These compounds can be synthesized by Knoevenagel condensation of substituted benzal-

dehydes with active methylene group of α-cyanoacetamides or α-cyanoacetanilides [3]. Many N-substituted α-cyanocinnamamides were reported to possess several pharmacological and biological activities such as anti-inflammatory activity [4] protein tyrosine kinase inhibition [5, 6, 7, 8], NMDA receptor antagonism [9], Ras farnesyl transferase inhibition [10] and antitumor activity [11].

A derivative of α-cyano caffeic acid amide, Entacapone, chemically named *E*-2-cyano-N, N-diethyl-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide developed by Orion Pharma, was a selective catechol *O*-methyl transferase (COMT) inhibitory agent and has been clinically used as an adjunct to levodopa-dopa decarboxylase inhibitors in the treatment of Parkinson's disease [12]. Further, several N-substituted α-cyanocinnamamides with anti-oxidant, anti-inflammatory and anti-bacterial activities were reported from our laboratory [13, 14, 15, 16, 17].

In the literature, several 4-aminophenol derivatives were reported to have analgesic and anti-inflammatory activities with noticeable free radical scavenging properties [18, 19, 20, 21, 22, 23]. Hence, in the present study, it was aimed to synthesis novel α-cyano- N- (4-hydroxyphenyl) cinnamamides with varied substitution on the phenyl ring of cinnamamide and to evaluate them for antioxidant and anti-inflammatory activities. Further, it was considered logical to perform an *in-silico* study of absorption, distribution, metabolism and elimination (ADME) properties using mol-inspiration online software.

MATERIALS AND METHODS: Aldehydes were procured from Sigma Aldrich and SD fine chemicals. All other chemicals are of AR grade. Melting points were determined in open capillaries on a tempo melting point apparatus and are uncorrected. IR spectra (KBr, υ_{max}, cm^{-1}) were run on Bruker FTIR spectrophotometer. ^{I}H NMR spectra were recorded on Bruker Avance-400 MHz spectrophotometer and the chemical shifts expressed as δ values (ppm) downfield from tetramethylsilane (TMS as internal standard) using DMSO as the solvent. Mass spectra were recorded on LC-MS, Agilent Technology 1200 infinity series, Apex chromatogram model.

The purity of the compounds was checked by using the glass plates coated with Silica gel-G, and the spots detected by iodine vapor.

Animals: Male Wistar albino rats (150 - 180 g) were obtained from Venkateshwara Enterprises, Bangalore, Karnataka. After ten days of acclimatization, the animals were further used as per the CPCSEA guidelines, and approval was obtained from the Institutional Animal Ethics Committee (Approval number: CPCSEA/1677/Poo /Re/S/2012/IAEC-Arpil/2017/25, dated 27/4/2017).

General Procedure for the Synthesis of Substituted α-cyano- N- (4- hydroxyphenyl) cinnamamide (IIIa-IIIo, Scheme-I): To the solution of α- cyano- N- (4- hydroxyphenyl) acetamide (1.76 g 0.01 mol), in 50 ml of toluene, an equivalent amount of substituted benzaldehyde was added. To this mixture, 0.35 ml of piperidine and 1.3 ml of acetic acid were added and refluxed at a temperature of 110 - 120 ºC for 5 - 6 h. The completion of the reaction was monitored by performing TLC.

Then the reaction mixture was cooled to room temperature and the precipitate was separated by filtration. The product was washed and recrystallized with ethanol. Fifteen compounds were synthesized by following the above procedure and characterized by their physical and IR, ^{1}H NMR, Mass spectral data.

α- Cyano- N- (4- hydroxyphenyl) cinnamamide (IIIa): Yield 68%; mp 239-241 ºC; IR (KBr): 3341 m^{-1} (NH str), 3240 cm^{-1} (OH str), 2219 cm^{-1} (C≡N str), 1652 cm^{-1} (C=O str), 1604 cm^{-1} (NH def); ^{1}H NMR: δ 6.74-7.99 (m, 9H, Ar), δ 8.24 (s, 1H, -CH=), δ 9.35 (s, 1H, OH), δ 10.17 (s, 1H, NH) ppm; Mass m/z: 264 (M^{+}).

α- Cyano- N- (4- hydroxyphenyl)- 4- chloro-cinnamamide (IIIb): Yield 77%; mp 154-157 ºC; IR (KBr): 3331 cm^{-1} (NH & OH str), 2218 cm^{-1} (C≡N str), 1667cm^{-1} (C=O str), 1604 cm^{-1} (NH def).

α- Cyano- N- (4- hydroxyphenyl)- 4- methyl-cinnamamide (IIIc): Yield 78%; mp 229-232 ºC; IR (KBr): 3325 cm^{-1} (NH str), 3232 cm^{-1} (OH str), 2212 cm^{-1} (C≡N str), 1648 cm^{-1} (C=O str), 1603 cm^{-1} (NH def).

α- Cyano- N- (4- hydroxyphenyl)- 4- methoxy-cinnamamide (IIId): Yield 80%; mp 209-211 ºC; IR (KBr): 3379 cm^{-1} (NH str), 3298 cm^{-1} (OH str), 2212 cm^{-1} (C≡N str), 1675 cm^{-1} (C=O str), 1640 cm^{-1} (NH def); ^{1}H NMR: δ 3.88 (s, 3H, OCH_3), δ 6.75-8.02 (m, 8H, Ar), δ 8.17 (s, 1H, -CH=), δ 9.33 (s, 1H, OH), δ 10.03 (s, 1H, NH) ppm; Mass m/z: 295 (M+1).

α-Cyano- N-(4- hydroxyphenyl)- 3, 4-dimethoxy-cinnamamide (IIIe): Yield 81%; mp 185-187 ºC; IR (KBr): 3474 cm^{-1} (NH str), 3297 cm^{-1} (OH str), 2218 cm^{-1} (C≡N str), 1670 cm^{-1} (C=O str), 1580 cm^{-1} (NH def); ^{1}H NMR: δ 3.83-3.88 (2s, 6H, OCH_3), δ 6.75-7.71 (m, 7H, Ar), δ 8.16 (s, 1H, -CH=), δ 9.31 (s, 1H, OH), δ10.04 (s, 1H, NH) ppm; Mass m/z: 324 (M^+).

α-Cyano-N-(4-hydroxyphenyl)-3,4,5-trimethoxy-cinnamamide (IIIf): Yield 64%; mp 126-129 ºC; IR (KBr): 3432 cm^{-1} (NH str), 3335 cm^{-1} (OH str), 2215 cm^{-1} (C≡N str), 1668 cm^{-1} (C=O str), 1584 cm^{-1} (NH def); ^{1}H NMR: δ 3.93-3.96 (2s, 9H, OCH_3), δ 6.83-7.45 (m, 6H, Ar), δ 8.31 (s, 1H,CH=), δ 9.17 (s, 1H, OH), δ 9.87 (s, 1H, NH) ppm.

α- Cyano- N- (4-hydroxyphenyl)- 4- dimethyl-aminocinnamamide (IIIg): Yield 83%; mp 245-248 ºC; IR (KBr): 3307cm^{-1} (NH str), 3205 cm^{-1} (OH str), 2242 cm^{-1} (C≡N), 1665 cm^{-1} (C=O str), 1603 cm^{-1} (NH def); ^{1}H NMR: δ 3.07 (s, 6H, $N(CH_3)$), δ 6.73-7.92 (m, 8H, Ar), δ 8.03 (s, 1H, -CH=), δ 9.27 (OH), δ 9.78 (s, 1H, NH) ppm.

α- Cyano- N- (4- hydroxyphenyl)- 4- hydroxy-cinnamamide (IIIh): Yield 72%; mp 231-236 ºC; IR (KBr): 3314 cm^{-1} (NH str), 3225 cm^{-1} (OH str), 2215cm^{-1} (C≡N str), 1660 cm^{-1} (C=O str), 1610 (NH def); ^{1}H NMR: δ 6.75-7.92 (m, 8H, Ar), δ 8.10 (s, 1H, -CH=), δ 9.9 (s, 1H, NH) ppm; Mass m/z: 280 (M^+).

α- Cyano- N- (4- hydroxyphenyl)- 4- hydroxy- 3-methoxycinnamamide (IIIi): Yield 78%; mp 200-202 ºC; IR (KBr): 3522 cm^{-1} (NH str), 3285 cm^{-1} (OH str), 2242 cm^{-1} (C≡N str), 1645 cm^{-1} (C=O str), 1600 cm^{-1} (NH def); ^{1}H NMR: δ 3.84 (s, 3H, OCH_3), δ 6.73-8.10 (m, 7H, Ar), δ 8.10 (s, 1H, -CH=), δ 9.31 (s, 1H, OH), δ 9.96 (s, 1H, NH), δ 10.26 (s, 1H, OH) ppm; Mass m/z: 310 (M^+).

α-Cyano-N-(4-hydroxyphenyl)-3,5-di-*tert*-butyl-4-hydroxycinnamamide (IIIj): Yield 62%; mp 272-275 ºC; IR (KBr): 3386 cm^{-1} (NH str), 3269 cm^{-1} (OH str), 2224 cm^{-1} (C≡N str), 1654 cm^{-1} (C=O str), 1601 cm^{-1} (NH def); ^{1}H NMR: δ 1.49 (s, 18H, CH_3), δ 6.83-7.48 (m, 6H, Ar), δ 7.87(s, 1H, -CH=), δ 7.89 (s, 2H, -OH), δ 8.33 (s, 1H, NH); Mass m/z: 392 (M^+).

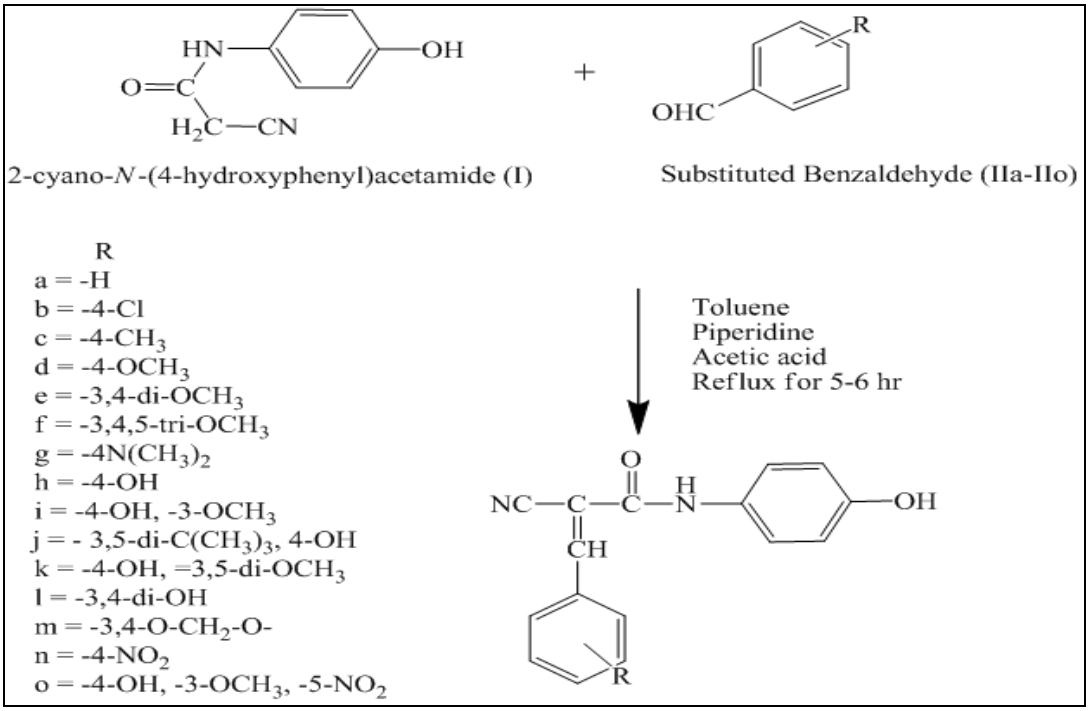
α-Cyano-N-(4-hydroxyphenyl)- 4- hydroxy- 3, 5-dimethoxycinnamamide (IIIk): Yield 79%; mp 218-220 ºC; IR (KBr): 3341 cm^{-1} (NH str), 3240 cm^{-1} (OH str), 2219 cm^{-1} (C≡N str), 1652 cm^{-1} (C=O str), 1600 cm^{-1} (NH def); ^{1}H NMR: δ 3.82-3.97 (2s, 6H, OCH_3), δ 5.86 (s, 1H, OH), δ 7.15-7.36 (m, 6H, Ar), δ 8.24 (s, 1H, -CH=), δ 9.15 (s, 1H, OH), δ 9.80 (s, 1H, NH); Mass m/z: 340 (M^+).

α-Cyano-N- (4-hydroxyphenyl)- 3, 4- dihydroxy-cinnamamide (IIIl): Yield 72%; mp 248-250 ºC; IR (KBr): 3357 cm^{-1} (NH str), 3180 cm^{-1} (OH str), 2216 cm^{-1} (C≡N str), 1654 cm^{-1} (C=O str), 1610 cm^{-1} (NH def); ^{1}H NMR: δ 6.73-7.58 (m, 7H, Ar), δ 8.00 (s, 1H, CH=), δ 9.46 (br s, 3H, OH), δ 9.92 (s,1H,NH) ppm; Mass m/z: 296 (M^+).

α-Cyano-N- (4-hydroxyphenyl)- 3, 4- methylene-dioxycinnamamide (IIIm): Yield 80%; mp 238-240 ºC; IR (KBr): 3317 cm^{-1} (NH str), 3208 cm^{-1} (OH str), 2216 cm^{-1} (C≡N str), 1649 cm^{-1} (C=O str), 1602 cm^{-1} (NH def); ^{1}H NMR: δ 6.19 (s, 2H, CH_2), 6.74-7.64 (m, 7H, Ar), δ 8.13 (s, 1H, CH=), δ 9.33 (s, 1H, OH), δ 10.03 (s, 1H, NH) ppm; Mass m/z: 308 (M^+).

α- Cyano- N- (4- hydroxyphenyl)- 4- nitro-cinnamamide (IIIn): Yield 60%; mp 190-193 ºC; IR (KBr): 3401 cm^{-1} (NH str), 3329 cm^{-1} (OH str), 2224 cm^{-1} (C≡N str), 1670 cm^{-1} (C=O str), 1602 cm^{-1} (N-H def); ^{1}H NMR: δ 6.76-8.43 (m, 8H, Ar), δ 8.37 (s, 1H, CH=), δ 9.39 (s, 1H, OH), δ 10.30 (s, 1H, NH) ppm; Mass m/z: 309 (M^+).

α- Cyano- N- (4-hydroxyphenyl)- 4- hydroxy-3-methoxy-5-nitrocinnamamide (IIIo): Yield 76%; mp 232-234 ºC; IR (KBr): 3437 cm^{-1} (NH str), 3256 cm^{-1} (OH str), 2209 cm^{-1} (C≡N str), 1681cm^{-1} (C=O str), 1604 cm^{-1} (N-H def); ^{1}H NMR: δ 3.93 (s, 3H, OCH_3), δ 6.75-8.16 (m, 6H, Ar), δ 8.19 (s, 1H, CH=), δ 9.35 (br s, 2H, OH), δ10.07 (s, 1H, NH) ppm; Mass m/z: 355 (M^+).



SCHEME 1: Substituted α-cyano-N-(4-hydroxyphenyl) cinnamamides (IIIa-IIIo)

***In-vitro* Antioxidant Studies:**

DPPH (1, 1-dipheny1-2-picrylhydrazy1) Free Radical Scavenging Activity: DPPH free radical scavenging activity was carried out according to the previously reported method [24]. The solutions of synthesized compounds at 100 μM concentration were added to 100 μM DPPH in 95% ethanol. These solutions were kept at ambient temperature for 20 min, and absorbance was measured at 517 nm. A positive control test was carried out with ascorbic acid. The results were expressed as the mean of triplicate measurements. The percentage of DPPH free radical scavenging was calculated using the following formula.

Percentage of DPPH free radical scavenging = (Control - Test / Control) × 100

Nitric Oxide Free Radical Scavenging Activity: Sodium nitroprusside (5 mM) in phosphate buffer pH 7.4 was incubated with 100 μM concentrations of test compound dissolved in ethanol at 25 ºC for 150 min [25]. A control experiment was kept without test compound, but an equal amount of solvent was added identically. After incubation, 2 ml of incubation solution was removed and diluted with 2 ml of Griess reagent. The absorbance of the chromophore formed during diazotization of nitrite with sulphanilamide and subsequent coupling with N-naphthylethylenediamine was read at 546 nm [26].

Pharmacological Study:

Anti-inflammatory Activity: Carrageenan-Induced Rat Paw Edema Assay: Male Wistar albino rats (150 - 180 g) were divided into groups consisting of five. One group served as vehicle control, and one more group served as positive control, while other groups of five animals received the test compounds. The rats were dosed (100mg/kg) orally with test compounds one hour before injection of 0.05 ml of 1% suspension of carrageenan into the subplantar region of hind paw [27]. The additional groups were similarly treated with Diclofenac (10 mg/kg) as positive control and 0.5% sodium carboxymethyl cellulose (10 ml/kg) as vehicle control.

The volume of the injected paw was measured by water displacement plethysmometer immediately after carrageenan injection. The paw volume was again measured after 3 h. A mark was made at the lateral malleolus of the right paw, and the foot was dipped to the same distance of the mark into the arm of plethysmometer. The average paw edema volumes of test compounds treated and positive control rats were compared statistically with those of the vehicle control animals and expressed as percentage edema inhibition.

***In-silico* Study:** The *in-silico* prediction of molecular properties of synthesized compounds

(IIIa-IIIo and I) were performed by using Molinspiration online molecular property calculation toolkit. The ADME properties of the synthesized molecules were predicted from Lipinski's rule of five, Topological polar surface area (TPSA) and percentage of absorption (%ABS). Lipinski's rule states that an orally active drug generally has no more than one violation of the following criteria [28].

i. Molecular weight ≤ 500
ii. Calculated log P ≤ 5
iii. Hydrogen bond acceptors ≤ 10 (Sum of O and N atoms)
iv. Hydrogen bond donors ≤ 5 (Sum of OH and NH groups)

The percentage of absorption was estimated using the following equation: % ABS = 109 – [0.345 × TPSA] [29].

RESULTS AND DISCUSSION: In the present research work, the title compounds substituted α-cyano-N-(4-hydroxyphenyl) cinnamamides (IIIa-IIIo) were synthesized by Knoevenagel condensation of substituted benzaldehydes with active methylene group of α-cyano-N-(4-hydroxyphenyl) acetamide, which was reported as N-cyanoacetyl-4-hydroxy aniline earlier from our laboratory [23]. The Knoevenagel reaction was carried out in the presence of toluene containing catalytic amounts of piperidine and acetic acid. The reaction was completed within 5 - 6 h to give the title compounds almost in pure form. The yields of synthesized compounds were in the range 54 - 83%. Out of fifteen compounds, four derivatives were reported earlier from our laboratory [13]. However, all the compounds were characterized by their physical data **Table 1** and spectral data.

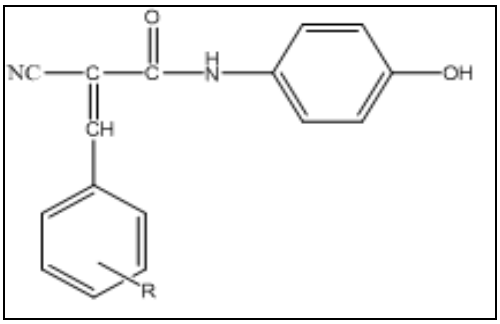


TABLE 1: PHYSICAL DATA OF SUBSTITUTED α-CYANO-N-(4-HYDROXYPHENYL) CINNAMAMIDES (IIIa-IIIo)

S. no.	R	M.F	M.W	M.P (°C)	Yield (%)
IIIa	H	$C_{16}H_{12}O_2N_2$	264	239-241	68
IIIb	4-Cl	$C_{16}H_{11}O_2N_2Cl$	298	154-157	77
IIIc	4-CH_3	$C_{17}H_{14}O_2N_2$	278	229-232	78
IIId	4-OCH_3	$C_{17}H_{14}O_3N_2$	294	209-211	80
IIIe	3,4-di-OCH_3	$C_{18}H_{16}O_4N_2$	324	185-187	81
IIIf	3,4,5-tri-OCH_3	$C_{19}H_{18}O_5N_2$	354	126-129	54
IIIg	4-$N(CH_3)_2$	$C_{18}H_{17}O_2N_3$	307	245-248	83
IIIh	4-OH	$C_{16}H_{12}O_3N_2$	280	231-236	72
IIIi	4-OH,3-OCH_3	$C_{17}H_{14}O_4N_2$	310	200-202	78
IIIj	4-OH,3,5-di-$C(CH_3)_3$	$C_{24}H_{28}O_3N_2$	392	272-275	62
IIIk	4-OH,3,5-di-OCH_3	$C_{18}H_{16}O_5N_2$	340	218-220	79
IIIl	3,4-di-OH	$C_{16}H_{12}O_4N_2$	296	248-250	72
IIIm	3,4-O-CH_2-O-	$C_{17}H_{12}O_4N_2$	308	238-240	80
IIIn	4-NO_2	$C_{16}H_{11}O_4N_2$	309	190-193	60
IIIo	4-OH,3-OCH_3,5-NO_2	$C_{17}H_{13}O_6N_3$	355	232-234	76

The IR spectra of synthesized compounds (IIIa-IIIo) showed absorption bands at 3474 - 3308 cm^{-1} indicative of N-H stretching. The absorption bands in the region of 3335 - 3180 cm^{-1} indicate O-H stretching vibration. The absorption bands corresponding to C≡N stretching appeared in the region of 2224-2209 cm^{-1}. Peaks due to a carbonyl group (C=O) of amide appeared in the region of 1681-1645 cm^{-1} and the absorption bands corresponding to N-H deformation were appeared in the region of 1610-1580 cm^{-1}.

The ^1H NMR spectra of compounds IIIa-IIIo showed singlets in the region of δ 7.87-8.37 due to benzylidene protons. This indicates that the carbonyl group of substituted benzaldehydes was condensed with active methylene group of α-cyano-N-(4-hydroxyphenyl) acetamide, which was supported by the absence of singlet peak at δ 3.8 due to methylene protons of α-cyano-N-(4-hydroxyphenyl) acetamide. The spectra of compounds IIIa-IIIo showed multiplets in the region of δ 6.73-8.43 due to aromatic protons.

The spectra of the compounds also revealed the presence of broad singlets in the region of δ 5.86-9.46 indicative of OH protons. The appearance of peaks representing the OH protons at higher delta value indicates that these protons involved in hydrogen bonding. Attenuation of OH peaks was observed in the spectra of compounds IIIh, IIIl and IIIo. This may be due to rapid proton exchange or due to the intramolecular hydrogen bonding. The spectra of all synthesized compounds showed singlets in the region of δ 8.33 to 10.30 indicative of NH proton of the amide. The compounds containing methoxy group (compounds IIId-IIIf, IIIi, IIIk, and IIIo) exhibited characteristic signals at δ 3.82-3.93 as singlets representing methoxy protons. The spectrum of compound IIIg showed a singlet at δ 3.07 indicates the protons of N-dimethylamino group. The spectrum of compound IIIj exhibited a singlet at δ 1.49 representing eighteen protons of 3, 5-di-*tert*butyl group. The spectrum of compound IIIm exhibited singlet at δ 6.19 due to the two proton of methylene group of 3, 4-methylenedioxy ring system.

Mass spectra of the compounds (IIIa-IIIo) revealed the presence of characteristic molecular ion peaks which indicated the molecular weight of respective compounds. Thus, the structures of the compounds were confirmed by IR, NMR and Mass spectral data.

***In-vitro* Antioxidant Studies:**

DPPH (1, 1-dipheny1-2-picrylhydrazy1) Free Radical Scavenging Activity: The DPPH free radical scavenging activity was a preferred method to determine the antioxidant potential of the test compounds. The molecule DPPH was a stable free radical under delocalization of its odd electron over the molecule as a whole, and this gives rise to a deep violet color, which can be characterized in ethanol by measuring the absorbance at 517 nm. A radical scavenging antioxidant reacts with DPPH stable free radical and converts it to 1, 1-diphenyl-2-picrylhydrazine. The ability of test compound to scavenge the DPPH was measured by a decrease in the absorbance at 517 nm.

All the compounds were found good scavengers of DPPH free radical. The activity data were given in **Table 2**. The activity data revealed that all the compounds except compound IIIb and IIIo were more active than the precursor α-cyano-N-(4-hydroxyphenyl) acetamide, as evident from the previous report [23]. This indicates that the conversion of α- cyano- N- (4- hydroxyphenyl) acetamide to α- cyano- N- (4- hydroxyphenyl) cinnamamide with suitable substituent found beneficial. Among all the evaluated compounds, α-cyano- N- (4- hydroxyphenyl)- 3, 4- dihydroxy-cinnamamide (Compound IIIl) showed the highest activity. The percentage inhibition of DPPH free radical by this compound was 89.47 comparable to that of standard compound, ascorbic acid (92.12%). The highest activity of compound IIIl may be due to the presence of catechol group, a 3, 4-dihydroxy functionality on the phenyl ring of cinnamamide, together with the additional phenolic group on N-phenyl ring. As the compound IIIl was found more active, it was further evaluated at different concentrations 100, 75, 50 and 25 μM **Table 3** and found to possess excellent DPPH scavenging activity even at 25 μM.

The other active compounds of the series include compounds containing hydroxy substitution at 4th position of the phenyl ring of α-cyanocinnamamide as in compounds IIIh, IIIi, IIIj and IIIk. The percentage inhibitions of DPPH free radical by these compounds were 66.80, 79.67, 78.39 and 80.31 respectively. The effective DPPH free radical scavenging activity of this phenolic α-cyano-N- (4-hydroxyphenyl) cinnamamides may be due to the high resonance stabilization of resultant phenoxyl radicals [30]. Modification of 3, 4-dihydroxy substituents of compound IIIl to 3, 4-methylenedioxy ring system, as in compound IIIm, resulted in a slight reduction in DPPH scavenging activity. The percentage inhibition of DPPH free radical exhibited by compound IIIm was 64.93, which was greater than the value obtained with 3, 4-dimethoxy derivative, compound IIIe. This signifies the importance of 3, 4-methylenedioxy ring system for free radical scavenging activity similar to piperine and sesamol. Furthermore, another non-phenolic α-cyano-N-(4-hydroxy-phenyl) cinnamamides IIIa-IIIg were less active than the phenolic derivatives.

The DPPH scavenging activity data revealed that the introduction of nitro group *ortho* to phenolic hydroxyl group as in compound IIIo (α-cyano-N-(4-hydroxyphenyl)-4-hydroxy-3-methoxy-5-nitro-

cinnamamide) resulted in the drastic decrease in DPPH free radical scavenging activity (29.03%). However, the percentage inhibition of DPPH free radical exhibited by *p*-nitro derivative, α-cyano-N-(4- hydroxyphenyl)- 4- nitrocinnamamide (compound IIIn) was found to be 74.90. The better activity of this compound may be due to the presence of nitro group at *para* position on α-cyanocinnamamide moiety which enhances the acidic properties of the molecule, causing increased proton donor ability to DPPH free radical.

Nitric Oxide Free Radical Scavenging Activity: Sodium nitroprusside in aqueous solution at physiological pH spontaneously generates nitric oxide. Scavengers of nitric oxide, as well as other nitrogen oxide intermediates in the reaction that produces nitrate and nitrite from nitric oxide and oxygen, will affect the accumulation of nitrite detectable by Griess reagent [26].

The compounds with better DPPH scavenging activity (IIIh-IIIn) were tested for their ability to scavenge nitric oxide at 100 μM concentration. The activity data were presented in **Table 2**. Among the evaluated derivatives, compounds IIIh to IIIl were more active than the precursor α-cyano-N-(4-hydroxyphenyl) acetamide as evident from the previous report from our laboratory [23], which indicates the importance of α-cyanocinnamamide with phenolic substitution. The activity data revealed that the α-cyano-N-(4-hydroxyphenyl)-3, 4-dihydroxycinnamamide (Compound IIIl) showed the highest activity.

The percentage of nitric oxide scavenging of this compound was 74.03. The other active compounds of series include IIIh, IIIi, IIIj, and IIIk with percentage nitric oxide scavenging activity 54.74, 67.24, 62.68 and 68.97 respectively. The better activity of all these compounds may be due to the presence of one or two phenolic hydroxyl groups on cinnamamide moiety and an additional phenolic hydroxyl group on the aromatic amine part. The activity data revealed that the conversion of diphenolic functionality of compound IIIl to 3, 4-methylenedioxy group, as in compound IIIm, causes a decrease in activity (51.01%). This signifies the importance of the catechol group, which is essential for better antioxidant activity. Further, the compound IIIn with the nitro group at the 4th position of α-cyanocinnamamide was found to be moderately active (52.74%) in this nitric oxide scavenging model.

It was observed that the activity data of nitric oxide scavenging was well correlated with the antioxidant activity data of DPPH free radical scavenging. The antioxidant activity data of both the models demonstrate that the α-cyano-3, 4-dihydroxy-cinnamamide moiety was essential for better antioxidant activity. This observation was supported by previous literature that the 3,4-hydroxycinnamoyl group along with cyano group on an alpha position of carbon-carbon double bond was essential for inhibition of 12-lipoxygenase when compared with caffeic acid, 3,4-dihydroxycinnamic acid [31]. Further, it was established that the presence of hydroxyl groups on both cinnamamide moiety and arylamino part led to the compounds with excellent antioxidant activity [32].

TABLE 2: *IN-VITRO* ANTIOXIDANT ACTIVITY OF SUBSTITUTED α-CYANO-N-(4-HYDROXYPHENYL) CINNAMAMIDES (IIIa-IIIo)

Compound	R	% DPPH free radical scavenging	% Nitric oxide free radical scavenging
IIIa	H	50.90	NT
IIIb	4-Cl	32.76	NT
IIIc	4-CH_3	58.30	NT
IIId	4-OCH_3	36.32	NT
IIIe	3,4-di-OCH_3	42.01	NT
IIIf	3,4,5-tri-OCH_3	56.76	NT
IIIg	4-$N(CH_3)_2$	55.70	NT
IIIh	4-OH	66.80	54.74
IIIi	4-OH,3-OCH_3	79.67	67.24
IIIj	4-OH,3,5-di-$C(CH_3)_3$	78.39	62.68
IIIk	4-OH,3,5-di-OCH_3	80.31	68.97
IIIl	3,4-di-OH	89.47	74.03
IIIm	3,4-O-CH_2-O-	64.93	51.01
IIIn	4-NO_2	74.90	52.74
IIIo	4-OH,3-OCH_3,5-NO_2	29.03	NT
Standard	Ascorbic acid	92.12	NT

NT = Not Tested

TABLE 3: DPPH FREE RADICAL SCAVENGING ACTIVITY OF α-CYANO-N-(4-HYDROXY PHENYL)-3, 4-DIHYROXYCINNAMAMIDES (IIIl)

Concentration	% DPPH free radical scavenging
100 μM	88.48
75 μM	88.38
50 μM	88.28
25 μM	87.27

Pharmacological Study:

Anti-inflammatory Activity:

Carrageenan-Induced Rat Paw Edema Assay: The anti-inflammatory activity of selected compounds (IIIi, IIIk, IIIl, and IIIm) was screened by the carrageenan-induced rat paw edema assay at a dose of 100 mg/kg, given by oral route. Diclofenac at a dose of 10 mg/kg, was used as a reference standard for comparing the results. The activity data has been presented in **Table 4**.

Among the tested derivatives, compound IIIi, α-cyano- N- (4- hydroxyphenyl)- 4- hydroxy- 3-methoxycinnamamide was found more potent (83.33% edema inhibition) and the percentage edema inhibition was very much close to the value obtained with standard drug Diclofenac (85.71% edema inhibition). The greater activity of compound IIIi may be due to the feruloyl acid amide with a cyano group on an alpha position of carbon-carbon double bond. This observation can be further supported by the literature report that the feruloyl derivatives are displaying a major role in improved digestibility and absorption [33].

It was evident from the activity data that the compound IIIl, α-cyano-N-(4-hydroxyphenyl)-3,4-dihydroxy-cinnamamide exhibited better activity (80.95%), which may be due to the presence of 3,4-diphenolic hydroxyl groups. However, conversion of 3, 4-diphenolic functionality of compound IIIl to 3, 4-methylenedioxy group, as in compound IIIm, decreased the anti-inflammatory activity. The percentage inhibition of edema exhibited by this compound was 66.67. From this observation, it can be concluded that the 3, 4-methylenedioxy substitution may be partially responsible for anti-inflammatory activity similar to piperine [34].

The activity data also indicated that the compound IIIk, α-cyano-N-(4-hydroxyphenyl)-4-hydroxy-3, 5-dimethoxycinnamamide exhibited 73.80% edema inhibition. The slight reduction in the activity of compound IIIk may be due to the additional methoxy group *ortho* to the phenolic hydroxyl group, which may cause variation in intestinal absorption. Finally, it can be concluded that the better anti-inflammatory activity of the evaluated compounds may be due to the presence of phenolic hydroxyl groups on both cinnamamide moiety and an aromatic amine.

TABLE 4: ANTI-INFLAMMATORY ACTIVITY OF SUBSTITUTED α- CYANO- N- (4-HYDROXYPHENYL) CINNAMAMIDES

Compound	R	Edema Volume (ml) (±SD)	(%) Edema inhibition
Control		0.42 (0.04)	0
Diclofenac		0.06 (0.06)	85.71*
IIIi	4-OH,3-OCH_3	0.07 (0.02)	83.33*
IIIk	4-OH,3,5-di-OCH_3	0.11 (0.04)	73.80*
IIIl	3,4-di-OH	0.08 (0.05)	80.95*
IIIm	3,4-O-CH_2-O-	0.14 (0.03)	66.67*

* Statistically significant ($p<0.05$ Mann Whitney test)

Drug-Likeness Score of Substituted α-cyano-N-(4-hydroxyphenyl) cinnamamides (IIIa - IIIo): Prediction of *in-silico* ADME properties are currently used widely to determine whether it is possible for a drug candidate to reach its site of action. Drug-likeness is a promising paradigm to identify a balance that influences the pharmacodynamic and pharmacokinetic properties of a compound that ultimately optimizes its ADME in the human body [29].

The *in-silico* study of ADME properties of substituted α- cyano- N- (4- hydroxyphenyl) cinnamamides (IIIa-IIIo) and α- cyano- N- (4-hydroxyphenyl) acetamides (I) were performed using molinspiration software and the data presented in **Table 5**. The Lipinski's rule of five is widely used as a filter for drug-likeness, which is estimated from the molecular properties such as partition coefficient (log P), molecular weight (MW), hydrogen bond acceptors and donors of a molecule. The results indicated that all the derivatives except IIIj presented lipophilicity (log P) less than 5, with values ranging from 0.09 to 3.39. All the compounds (IIIa-IIIo and I) have 4 to 9 number of hydrogen bond acceptors and 2 to 4 number of hydrogen bond donors. The molecular weights of the compounds were less than 500. Hence, all the compounds obeyed the Lipinski's rule, as it states that an orally active drug generally has no more than one violation [28].

Topological polar surface area (TPSA) is widely used molecular descriptor and a very good predictor of drug transport properties such as intestinal absorption and blood-brain barrier penetration. It is, therefore, linked to the bioavailability of drug molecule [35]. The percent absorption (% ABS) of the derivatives can be calculated by using TPSA values.

For all the substituted α- cyano- N- (4-hydroxyphenyl) cinnamamides (IIIa-IIIo) and α-cyano-N-(4-hydroxyphenyl) acetamides (I), TPSA values were predicted and found in the range between 73.12 and 148.40. Hence, all the predicted molecules showed good intestinal absorption except compound IIIo as its TPSA value was 148.40 and the % ABS was 57.80. Furthermore, the predicted compounds did not have adequate blood-brain barrier Penetration; therefore the compounds were CNS inactive. It was observed from the predicted data that the α-cyano-N-(4-hydroxyphenyl) acetamide (Compound I) had lower TPSA and log P values than the title compounds indicating the conversion of α-cyano-N-(4-hydroxyphenyl) acetamide to α-cyano-N-(4-hydroxyphenyl) cinnamamides improved the drug-likeness properties.

On comparison of the anti-inflammatory activity data with the *in-silico* ADME prediction of compounds IIIi, IIIk, and IIIl, it can be concluded that the molecules must have an optimum log P value between 1.74 and 2.07 and TPSA value ranging from 102.58 to 113.57, hence better % ABS. The prediction data revealed that the compound IIIm possess a log P value 2.60 and TPSA value 91.59, hence the % ABS higher than the active compounds. However, compound IIIm possesses less anti-inflammatory activity than the compounds IIIi, IIIk, and IIIl. This indicates that the importance phenolic hydroxyl group substitution on α-cyano-N-(4-hydroxyphenyl) cinnamamides.

Further, the *in-silico* ADME prediction indicated low log P value and high TPSA value for compound IIIl, hence lower % ABS of compound IIIl compared to compound IIIi and IIIk. But the compound IIIl exhibited good anti-inflammatory activity because of the presence of 3, 4-diphenolic hydroxyl group responsible for free radical scavenging properties at low concentration **Table 3**. Further, it was evident from the literature that the caffeic acid (3, 4-dihyroxycinnamic acid) derivatives inhibited cyclooxygenase enzymes especially COX-2 [36]. Therefore, it can be assumed that the compound IIIl may exert its anti-inflammatory activity by specific inhibition of COX-2 enzyme.

TABLE 5: DRUG LIKENESS SCORE OF SUBSTITUTED α-CYANO-N-(4-HYDROXYPHENYL) CINNAMAMIDES (IIIa-IIIo)

Compound	milogP	M. Wt	HBA	HBD	Volume	n-Violations	n- rotb	TPSA	% ABS
IIIa	2.71	264.28	4	2	239.13	0	3	73.12	83.77
IIIb	3.39	298.73	4	2	252.67	0	3	73.12	83.77
IIIc	3.16	278.31	4	2	255.69	0	3	73.12	83.77
IIId	2.77	294.31	5	2	264.68	0	4	82.35	80.59
IIIe	2.36	324.34	6	2	290.22	0	5	91.59	77.40
IIIf	2.34	354.36	7	2	315.77	0	6	100.82	74.21
IIIg	2.81	307.35	5	2	285.04	0	4	76.36	82.66
IIIh	2.23	280.28	5	3	247.15	0	3	93.35	76.79
IIIi	2.05	310.31	6	3	272.70	0	4	102.58	73.61
IIIj	5.76	392.50	5	3	379.52	1	5	93.35	76.79
IIIk	2.07	340.33	7	3	298.24	0	5	111.81	70.42
IIIl	1.74	296.28	6	4	255.17	0	3	113.57	69.82
IIIm	2.60	308.29	6	2	263.06	0	3	91.59	77.40
IIIn	2.67	309.28	7	2	262.47	0	4	118.94	67.96
IIIo	2.17	355.31	9	3	296.03	0	5	148.40	57.80
I	0.09	176.18	4	2	157.11	0	2	73.12	83.77

Logarithm of partition coefficient between n-octanol and water (miLogP); Molecular weight (MW); Number of hydrogen bond acceptors (n-ON) - HBA; Number of hydrogen bond donors (n-OHNH) - HBD; Number of Violations (n-Violations); Number of rotatable bonds (n-rotb); Topological polar surface area (TPSA); Percentage of absorption (%ABS).

CONCLUSION: The present study concludes that the conversion of α-cyano-N-(4-hydroxyphenyl) acetamide to α-cyano-N-(4-hydroxyphenyl) cinnamamide with phenolic hydroxyl substitution resulted in novel bioactive compounds. Especially, α-cyano- N- (4- hydroxyphenyl)- 4- hydroxy- 3-methoxycinnamamide (compound IIIi), α-cyano-N-(4- hydroxyphenyl) 3, 4- dihydroxycinnamamide (compound IIIl) and α- cyano- N- (4- hydroxy-phenyl)- 4- hydroxy- 3, 5- dimethoxycinnamamide (compound IIIk) were found active as anti-inflammatory agents with excellent antioxidant properties. Further, the *in-silico* ADME prediction identified these compounds as potential drug

candidates. The compounds IIIi, IIIl and IIIk are amide derivatives of natural molecules ferulic acid, caffeic acid, sinapic acid and 4-aminophenol with a nitrile/cyano group on α-position of carbon-carbon double bond. Hence, use of these compounds may be beneficial for the treatment of diseases associated with oxidative stress such as inflammation, cancer, Parkinsonism and also Alzheimer's disease. However, more studies are required to know the specific inhibition of enzymes by various *in-vitro* enzymatic assays.

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