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Synthesis And Biological Evaluation of N-(5-Phenyl 1, 3, 4-Oxadiazole-2-yl) Cinnamamides

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ABSTARCT

Novel series of N-(5-phenyl-1,3,4-oxadiazol-2yl)cinnamamides were synthesized by condensation of substituted cinnamic acids with 2-amino-5-phenyl-1,3,4-oxadiazole using (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) & HOBt(N-hydroxy benzotriazole). Substituted cinnamic acids were prepared by reaction of aromatic aldehydes with malonic acid in presence of pyridine and piperidine. The chemical structures of synthesized compounds were confirmed by means of IR, ^{1}H NMR, mass spectral data. All the title compounds were evaluated for antibacterial and antioxidant activities. Among the series, **2j** and **2k** derivatives showed appreciable antibacterial activity against four bacterial strains *Escherichia coli, Pseudomonas aeruginosa (gram-negative)* and *Bacillus subtilis, Staphylococcus aureus* (gram-positive) which is comparable to that of standard streptomycin. Among all the title compounds, **2g** and **2i** derivatives exhibited good DPPH scavenging activity and compounds **2c** and **2b** showed good Nitric Oxide scavenging activity which is comparable to that of standard antioxidant ascorbic acid. All the title compounds were subjected to *in silico* molecular property prediction studies. Results of *in silico* studies showed that all the derivatives followed the Lipinski rule of five indicating good oral bioavailability.

Keywords: Cinnamamides, oxadiazole, antioxidant, nitric oxide, antibacterial

INTRODUCTION

The resistance among various microbial species to antimicrobial drugs has emerged as a cause of public health threat around the world at an alarming rate. Hence it is

necessary to search for new antimicrobial agents. Cinnamamide is one of the most privileged scaffold possessing diverse pharmacological properties such as antimicrobial **[1]**, antiinflammatory **[2]**, antidepressant **[3]**, anticancer **[4-7]**, antioxidant **[8-9]**, anticonvulsant **[10]**, antimelanogenic **[11]**, antitubercular activities **[12]**. Number of patented drugs and new chemical entities with different pharmacological activities were found to possess Cinnamamide pharmacophore **[13-15]**. 1,3,4-Oxadiazole is an important class of heterocyclic scaffold, serving as the main core in various therapeutic agents and reported to possess diverse pharmacological activities such as antimicrobial **[16, 17]**, anticonvulsant **[18]**, antiinflammatory **[19]**, antitubercular **[20, 21]**, antidepressant **[22]**, antioxidant activities **[23]**. Various commercially available drugs such as Furamizole (antibacterial activity), Raltegravir (antiviral drug) and Nesapidil (antiarrhythmic therapy) consists of 1,3,4-oxadiazole ring **[24]**. The *in silico* computational tools were used to establish pharmacokinetic, biological, and toxicological parameters, that helps pharmaceutical researchers to reject those molecules having low success probabilities and further to reduce the failure rate during the drug discovery process. Owing to the potentiality of cinnamamides and 1,3,4-oxadiazoles, herein we report the synthesis of new N-(5-phenyl-1,3,4-oxadiazole-2-yl)cinnamamides, *in silico* studies, antimicrobial and antioxidant activities of title compounds.

MATERIAL AND METHODS

All the chemicals and solvents utilized in this research were purchased from Merck, Hi media, S.D. fine Chemicals. Melting points were determined in Thermonik precision melting point cum boiling point apparatus in an open capillary tube. Purity of the compounds was checked by using precoated E. Merck Silica gel 60 F_{254} TLC plates (Toulene: Ethylacetate (3:1). The IR spectra were recorded using KBr Pellets on Shimadzu FT-IR spectrophotometer (cm^{-1}). ^1H NMR spectra were recorded on JEOL RESONANCE NMR spectrometer at 400 MHz in DMSO using TMS as an internal standard and chemical shift values were reported in δ ppm. Mass spectra were recorded on Agilent 6400 series equipped with an electrospray ionization source. Molinspiration and PreADMET tools were used for *in silico* studies.

Synthesis

Synthesis of substituted cinnamic acids (1a-k)

Substituted cinnamic acids **(1a-1k)** were synthesized according to the reported procedure **[25]**.

General procedure for synthesis of N-(5-phenyl-1,3,4-oxadiazol-2yl)cinnamamides (2a-2k)

Title compounds were synthesized by coupling substituted cinnamic acids (0.01M) with 2-amino5-phenyl-1, 3, 4-oxadiazole (0.01M) using 1-ethyl-3-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCL) and N-hydroxybenzotriazole (HOBt) as condensing agents. The mixture was refluxed in anhydrous CH_2Cl_2 for 8-10hrs and products were extracted by using ethyl acetate. The extract was washed successively with 10% HCl, saturated $NaHCO_3$ and water. The product was filtered and dried over anhydrous Sodium Sulfate to get the title compounds **2a-2k [25]**.

The physical characteristics, FT-IR, ^1H NMR, and Mass spectral data of final compounds were presented below

Physical and spectral data of title compounds

N-(5-phenyl-1,3,4-oxadiazol-2-yl)cinnamamide (2a)

M.F: $C_{17}H_{13}N_3O_2$; Yield: 73%; M.W: 291.30; MP: 156-168°C; IR (υmax, cm^{-1}): 3258 (N-H), 3065 (Ar-CH), 1689 (C=O), 1639 (C=C), 1509 (C=N), 1310 (C-N), 1039 (C-O-C); ^1H NMR (400 MHz, DMSO-d6); δ: 9.956 (s, 1H, CONH), 7.417-7.654 (m, 10H, Ar-H), 7.309 (d, 1H, CH=CH), 6.904 (d, 1H, CH=CH); Mass (m/z): 292.15 $[M+1]^+$.

(2*E*)-3-(4-methoxyphenyl)-*N*-(5-phenyl-1,3,4-oxadiazol-2-yl)prop-2-enamide (2b)

M.F: $C_{18}H_{15}N_3O_3$; Yield: 80%; M.W: 321.33; MP: 141-143°C; IR (υmax, cm^{-1}): 3239 (N-H), 3055 (Ar-CH), 2981 (CH), 1687 (C=O), 1628 (C=C), 1503 (C=N), 1236 (C-N), 1070 (C-O-C); Mass (m/z): 322.15 $[M+1]^+$.

(2*E*)-3-(4-methylphenyl)-*N*-(5-phenyl-1,3,4-oxadiazol-2-yl)prop-2-enamide (2c)

M.F: $C_{18}H_{15}N_3O_2$; Yield: 60%; M.W: 305.33; MP: 145-147°C; IR (υmax, cm^{-1}): 3210 (N-H), 3080 (Ar-CH), 2920 (CH), 1665 (C=O), 1609 (C=C), 1570 (C=N), 1307 (C-N), 1058 (C-O-C); ^1H NMR (400 MHz, DMSO-d6); δ: 10.204(s, 1H, CONH), 6.442-7.796(m, 9H, Ar-H), 7.660 (d, 1H, CH=CH), 6.402 (d, 1H, CH=CH), 2.341(s, 3H, CH3); Mass (m/z): 304.98 $[M]^+$.

(2*E*)-*N*-(5-phenyl-1,3,4-oxadiazol-2-yl)-3-[4-(propan-2-yl)phenyl]prop-2-enamide (2d)

M.F: $C_{20}H_{19}N_3O_2$; Yield: 80%; M.W: 333.38; MP: 118-120°C; IR (υmax, cm^{-1}): 3292 (N-H), 3039 (Ar-CH), 2933 (CH), 1691 (C=O), 1610 (C=C), 1517 (C=N), 1226 (C-N), 1040 (C-O-C); ^1H NMR (400 MHz, DMSO-d6); δ: 10.204(s, 1H, CONH), 6.441 - 7.805 (m, 9H, Ar-H), 7.245 (d, 1H, CH=CH), 6.401(d, 1H, CH=CH), 3.355 (m, 1H, CH), 1.157 (s, 3H,

CH_3), 1.140(s, 3H, CH_3); Mass (m/z): 334.09 $[M+1]^+$.

(2*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*-(5-phenyl-1,3,4-oxadiazol-2-yl)prop-2-enamide (2e)

M.F: $C_{18}H_{15}N_3O_4$; Yield: 60%; M.W: 337.36; MP: 128-131°C; IR (υmax, cm^{-1}): 3498 (OH), 3309 (N-H), 3140 (Ar-CH), 2990 (CH), 1656 (C=O), 1621(C=C), 1508 (C=N), 1264(C-N), 1041 (C-O-C); Mass (m/z): 338.54 $[M+1]^+$.

(2*E*)-3-(4-hydroxy-3,5-dimethoxyphenyl)-*N*-(5-phenyl-1,3,4-oxadiazol-2-yl)prop-2-enamide (2f)

M.F: $C_{19}H_{17}N_3O_5$; Yield: 52%; M.W: 367.37; MP: 170-173°C; IR (υmax, cm^{-1}): 3415 (OH), 3257 (N-H), 3021(Ar-CH), 2978 (CH), 1671 (C=O), 1614 (C=C), 1525 (C=N), 1229(C-N), 1024 (C-O-C).

(2*E*)-3-(4-hydroxyphenyl)-*N*-(5-phenyl-1,3,4-oxadiazol-2-yl)prop-2-enamide (2g)

M.F: $C_{17}H_{13}N_3O_3$; Yield: 83%; M.W: 307.33; MP: 154-156°C; IR (υmax, cm^{-1}): 3508 (OH), 3296(N-H), 3033 (Ar-CH), 1659 (C=O), 1623 (C=C), 1509 (C=N), 1258 (C-N), 1039 (C-O-C). ^{1}H NMR (400 MHz, DMSO-d6); δ: ^{1}H NMR (400 MHz, DMSO-d6); δ: 10.195 (s, 1H, CONH), 6.993-7.839 (m, 9H, Ar-H), 7.544 (d, 1H, CH=CH), 6.687 (d, 1H, CH=CH), 5.430 (s, 1H, OH); Mass (m/z): 308.54 $[M+1]^+$.

(2*E*)-3-(3-hydroxy-4-methoxyphenyl)-*N*-(5-phenyl-1,3,4-oxadiazol-2-yl)prop-2-enamide (2h)

M.F: $C_{18}H_{15}N_3O_4$; Yield: 53%; M.W: 337.33; MP: 179-181°C; IR (υmax, cm^{-1}): 3510 (OH), 3219(NH), 3038 (Ar-CH), 2926 (CH), 1682(C=O), 1642(C=C), 1542 (C=N), 1268 (C-N), 1069 (C-O-C).

(2*E*)-3-(3,4-dimethoxyphenyl)-*N*-(5-phenyl-1,3,4-oxadiazol-2-yl)prop-2-enamide (2i)

M.F: $C_{19}H_{17}N_3O_4$; Yield: 51%; M.W: 351.30; MP: 132-134°C; IR (υmax, cm^{-1}): 3314 (N-H), 3108(Ar-CH), 2950 (CH), 1679 (C=O), 1613 (C=C), 1548 (C=N), 1223 (C-N), 1074 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d6); δ: 10.190 (s, 1H, CONH), 6.430-7.798 (m, 8H, Ar-H), 7.313 (d, 1H, CH=CH), 6.430 (d, 1H, CH=CH), 3.841 (s, 3H, OCH_3), 3.366 (s, 3H, OCH_3); Mass (m/z): 352.38$[M+1]^+$.

(2*E*)-3-(4-nitrophenyl)-*N*-(5-phenyl-1,3,4-oxadiazol-2-yl)prop-2-enamide (2j)

M.F: $C_{17}H_{12}N_4O_4$; Yield: 50%; M.W: 336.30; MP: 161-163°C; IR (υmax, cm^{-1}): 3296 (N-H), 3057(Ar-CH), 1669 (C=O), 1611 (C=C), 1558 (NO), 1523 (C=N), 1226 (C-N), 1029 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d6); δ: 9.870 (s, 1H, CONH), 7.389-7.933 (m, 9H, Ar-H), 7.346 (d, 1H, CH=CH), 6.839 (d, 1H, CH=CH); Mass (m/z): 337.08 $[M+1]^+$.

(2*E*)-3-(3-chlorophenyl)-*N*-(5-phenyl-1,3,4-oxadiazol-2-yl)prop-2-enamide (2k)

M.F: $C_{17}H_{12}N_3O_2Cl$; Yield: 55%; M.W: 325.75; MP: 172-175°C; IR (υmax, cm^{-1}): 3301(N-H), 3109(C-H), 1696(C=O),

1633(C=C), 1532(C=N), 1256 (C-N), 1030(C-O-C), 797 (NO); ^{1}H NMR (400 MHz, DMSO-d6); δ: 10.102 (s, 1H, CONH), 7.448(d, 1H, CH=CH), 6.996-7.875 (m, 9H, Ar-H), 6.721 (d, 1H, CH=CH); Mass (m/z): 325.96 [M^+].

Antibacterial activity

The new derivatives obtained from the reaction sequence were screened for antibacterial activity against four test organisms such as *Escherichia coli*, *Pseudomonas aeruginosa* (gram-negative) & *Bacillus subtilis, Staphylococcus aureus* (gram-positive) at a concentration of 100µg/mL using cup plate method by measuring zone of inhibition using streptomycin as standard drug.

Nutrient agar was used as culture medium for bacterial strains using DMSO as solvent control. Bacterial inoculums were prepared by transferring the stock culture into the nutrient broth in a conical flask and incubated at 34-37^{0}C for 24 hours before experimentation. Laminar airflow bench was swapped with 70% alcohol, UV lamp was switched on for 30 minutes. Then all the glassware, reagents, inoculums and media were placed in laminar airflow cabinet following all aseptic conditions. Then 25ml of sterile hot agar medium was poured in each plate and allowed to harden. The agar plates were inoculated with bacterial strains by streaking in all the directions over the entire surface of the plate. Cups of 6 mm diameter were made with a sterile cork borer in the agar plate, once the inoculums were dried. All final derivatives were added to these cups using a micropipette and plates were incubated at a temperature of 37^0 C for 24 hrs, and zone of inhibition was measured using mm scale **[26]**.

DPPH scavenging activity

Antioxidant activity of title compounds was determined by DPPH scavenging assay. DPPH solution was prepared freshly, kept in dark place. 2ml of 100 µM final compounds and standard were added to 2ml of DPPH (100 µM) ethanolic solution. 2 ml of ethanol was added to 2ml of 100 µM DPPH ethanolic solution, treated as negative control. The tubes were covered with aluminum foil to protect from light and kept at an ambient temperature for 30 min. Then, the absorbance was read at 517 nm using ethanol as blank. Results were expressed as means of triplicate and mean ± SD (standard deviation) were calculated **[27]**.

The % inhibition of DPPH was calculated using the formula.

%inhibition = (Absorbance of control-Absorbance of test/ Absorbance of control) × 100

Nitric Oxide (NO) scavenging activity

100µM concentrations of title compounds dissolved in a suitable solvent (dioxan/methanol) and 10µM Sodium nitroprusside in phosphate buffer pH 7.4

were incubated for 120 minutes at 25ºC. Control experiment also carried out in the same manner (without test compound). After incubation, 2 mL of solution was removed and diluted with Griess reagent (2ml). The absorbance of pink colour chromophore which is formed by diazotization and coupling reaction involved in this assay was measured at 546nm. Results were expressed as means of triplicate and mean ± SD (standard deviation) were calculated **[28]**.

Nitric oxide scavenging activity was calculated by using the following formula.

%inhibition = (Absorbance of control-Absorbance of test/ Absorbance of control) × 100

In silico studies

Molinspiration software version 2011.06 was used to predict the molecular properties and bioactivity scores of the compounds towards human therapeutic targets. Bioactivity score represents the binding abilities of designed ligands for various biological tagets such as GPCR, Ion channels, Nuclear receptors etc. (https://www.molinspiration.com).

PreADMET server was used for prediction of ADME properties of the molecules (http://preadmet.bmdrc.org/). This software determines the *in vitro* Caco-2 cell permeability (<4 - low, 4-70- moderate, >70-high permeability), skin permeability, plasma protein binding (>90 - strongly bound, <90- weakly bound) and blood brain barrier penetration (BBB) (>1 - CNS active compounds (+), <1 – CNS inactive compounds) of designed derivatives.

RESULTS AND DISCUSSION

Chemistry

Novel series of N-(5-phenyl-1, 3, 4-Oxadiazol-2yl) Cinnamamides were synthesized as per the proposed protocol represented in **Figure 1**. The compounds were obtained in moderate to good yield ranging from 50-80%. Chemical structures of synthesized derivatives were confirmed by IR, ^{1}H NMR and Mass spectra. IR data suggests that appearance of bands in the region of 3210-3314 cm^{-1} indicates the presence of NH linkage of amide bond with in the title compounds. The appearance of bands in the region of 1024-1070 cm^{-1}, 1226-1310 cm^{-1}, 1503-1570 cm^{-1}, 1610-1642 cm^{-1} and 1656-1696 cm^{-1} indicates presence of C-O-C, C-N, C=N, C=C and C=O respectively with in the title compounds. The appearance of bands between 2920-3140 cm^{-1} indicates the presence of aliphatic and aromatic C-H of title compounds. The appearance of broad bands in the range of 3415-3510 indicates OH stretch of compounds 2e, 2f, 2g and 2h. The ^{1}H-NMR spectra of title compounds 2a-2k showed aromatic protons in the range of δ 6.430-7.933. The appearance of singlet around δ9.870-10.204 confirmed the presence of CONH in title compounds. Mass spectra of compounds 2a, 2b, 2c, 2d,

2e, 2g, 2i, 2j and 2k exhibited molecular ions at m/z 292.15, 322.15, 304.98, 334.09, 338.54, 308.54, 352.38, 337.08 and 325.96 with different intensities confirming the structures of title compounds.

Antibacterial activity

Antibacterial activity of title compounds was evaluated by cup plate method and diameter of the zone of inhibition was measured in millimeters **(Table 1)**. Among all the title compounds, 4-nitro **2j (28mm)** and 3-chloro **2k (25mm)** derivatives exhibited appreciable antibacterial activity against *E.coli* which were comparable with that of standard drug streptomycin **(29mm)**. 4-nitro **2j (26mm),** 4-isopropyl **2d (24mm)** and 3-chloro **2k (23mm)** derivatives showed comparable antibacterial activity with that of standard drug streptomycin **(26mm)** against *P. aeruginosa*. 3-chloro **2k (19mm)**, 4-nitro **2j (18mm)** and unsubstituted **2a (18mm)** derivatives exhibited good activity among all the derivatives screened against *B. subtilis*. 4-nitro **2j (27mm)** derivative displayed good activity compared with that of standard streptomycin **(28mm)** against *S. aureus* followed by 3-chloro **2k (20mm)** derivative. Among the series, highest activity was observed with 4-nitro and 3-chloro substitutions against four bacterial strains.

Antioxidant activity

a) DPPH assay

All the synthesized compounds **(2a-2k)** were evaluated for stable free radical DPPH scavenging activity. The experimental results revealed that majority of the title compounds exhibited moderate to good DPPH scavenging activity when compared with that of the standard drug ascorbic acid **(Table 2)**. Among the series, 3,4-dimethoxy **2i (72%)** and 4-hydroxy **2g (72%)** derivatives exhibited highest activity which is comparable with that of the standard antioxidant ascorbic acid **(74%)**.

b) Nitric Oxide (NO) Scavenging activity

All the compounds **(2a-2k)** were evaluated for Nitric oxide scavenging activity. Most of the synthesized derivatives displayed notable antioxidant activity **(Table 2)**. Among all the title compounds, 4-methyl **2c (75%)** and 4-methoxy **2b (74%)** derivatives exhibited potent activity which is closer to that of standard antioxidant ascorbic acid **(78%)**.

***In Silico* studies**

Molecular descriptors

Molecular properties such as Partition coefficient, Molecular weight, H-bond acceptors and donors of a molecule were evaluated by Molinspiration **(Table 3)**. All the derivatives followed the Lipinski rule, exhibited good percentage of oral absorption **69%-100%**. Bioactivity scores of title compounds revealed that all of them were moderately active as kinase inhibitors,

nuclear receptor ligands, protease inhibitors, GPCR ligands, enzyme inhibitors **(Table 4)**.

Prediction of ADME Properties

Compounds **(2a-2k)** showed % absorption ranging from 65%-90%, moderate Caco2 cell permeability. % plasma protein binding data reveals that 4-hydroxy-3-methoxy **(2e),** 4-hydroxy-3,5-dimethoxy **(2f)** derivatives were more active. Most of the derivatives found to be inhibitors of CYP1A2, CYP2C19 and CYP2C9 **(Table 5 and 6)**.

Table 1: Antibacterial activity of N-(5-Phenyl 1, 3, 4-Oxadiazole-2-yl)Cinnamamides at concentration of 100µg/mL

S. No.	R	Diameter of zone of inhibition(mm)			
		Gram negative		Gram positive	
		E. coli	*P. aeruginosa*	*B. subtilis*	*S. aureus*
2a	H	16	12	18	NA
2b	4-OCH_3	NA	15	NA	NA
2c	4-CH_3	10	12	17	15
2d	4-$CH(CH_3)2$	NA	24	NA	13
2e	4-OH,3-(OCH_3)	14	NA	NA	15
2f	4-OH,3,5-(OCH_3)$_2$	15	17	16	NA
2g	4-OH	20	15	14	17
2h	3-OH,4-(OCH_3)	12	13	14	14
2i	3,4-(OCH_3)$_2$	07	NA	14	NA
2j	4-NO_2	28	26	18	27
2K	3-Cl	25	23	19	20
standard	Streptomycin	29	26	26	28
*NA- Not Active					

Table 2: Antioxidant activity of N-(5-Phenyl 1, 3, 4-Oxadiazole-2-yl) Cinnamamides

S. No.	R	% inhibition at 100µM(Mean ±SD)	
		Interaction With Stable Free Radical DPPH	Nitric Oxide scavenging activity
2a	H	54±1.01	52±0.66
2b	4-OCH_3	47±0.5	74±0.62
2c	4-CH_3	58±1	75±0.75
2d	4-$CH(CH_3)_2$	56±1.04	55±0.85
2e	4-OH,3-(OCH_3)	71±1.47	59±1.08
2f	4OH,3,5-(OCH_3)$_2$	62±0.5	46±0.70
2g	4-OH	72±0.8	48±0.57
2h	3-OH,4-(OCH_3)	69±0.36	51±0.9
2i	3,4-(OCH_3)$_2$	72±0.9	49±0.60
2j	4-NO_2	41±0.5	70±0.41
2k	3-Cl	38±0.7	59±0.04
Standard	Ascorbic acid	74±0.5	78±0.26

*All values are expressed as mean ± SD of triplicate determination

Table 3: Molecular properties of N-(5-Phenyl 1, 3, 4-Oxadiazole-2-yl)Cinnamamides

Comp. No	R	MW (Da)	RoB	HBA	HBD	TPSA	Mi LogP	N. Viol	Vol	% ABS
2a	H	291.31	4	5	1	68.02	3.46	0	258.92	85.53
2b	4-OCH_3	321.34	5	6	1	77.26	3.52	0	284.46	82.34
2c	4-CH_3	305.34	4	5	1	68.02	3.91	0	275.48	85.53
2d	4-$CH(CH_3)_2$	333.39	5	5	1	68.02	4.97	0	308.87	85.53
2e	4-OH,3-(OCH_3)	337.33	5	7	2	97.48	2.80	0	292.48	75.36
2f	4OH,3,5-(OCH_3)$_2$	367.36	6	8	2	106.7	2.82	0	318.03	72.18
2g	4-OH	207.31	4	6	2	88.25	2.98	0	266.94	8.55
2h	3-OH,4-(OCH_3)	337.33	5	7	2	97.48	2.80	0	292.48	79.16
2i	3,4-(OCH_3)$_2$	351.36	6	7	1	86.49	3.11	0	310.01	69.27
2j	4-NO_2	336.35	5	8	1	113.8	3.42	0	282.25	85.53
2k	3-Cl	325.75	4	5	1	68.02	4.14	0	272.45	85.53

*MILOGP- Lipophilicity; TPSA- Topological Surface Area; MW - Molecular Weight; HBA – Hydrogen bond acceptors; HBD – Hydrogen bond donors; N Viol. - Number of Violations; ROTB- Number of Rotatable Bonds; Vol: VOLUME; % ABS – Percentage absorption.

Table 4: Bioactivity scores of N-(5-Phenyl 1, 3, 4-Oxadiazole-2-yl)Cinnamamides

Comp	R	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
2a	H	-0.24	-0.65	-0.09	-0.30	0.48	-0.21
2b	4-OCH_3	-0.25	-0.68	-0.11	-0.27	-0.46	-0.25
2c	4-CH_3	0.26	-0.71	-0.12	-0.30	0.50	-0.27
2d	4-$CH(CH_3)_2$	0.19	-0.59	-0.11	-0.19	-0.39	-0.19
2e	4-OH,3-(OCH_3)	0.21	-0.63	-0.07	-0.21	0.46	-0.19
2f	4OH,3,5-(OCH_3)$_2$	-0.22	-0.58	-0.06	-0.22	-0.42	-0.16
2g	4-OH	-0.17	-0.58	-0.03	-0.12	-0.42	-0.15
2h	3-OH,4-(OCH_3)	-0.21	-0.63	-0.07	-0.21	-0.42	-0.19
2i	3,4-(OCH_3)$_2$	-0.24	-0.65	-0.10	-0.28	-0.46	-0.24
2j	4-NO_2	-0.35	-0.64	-0.21	-0.35	-0.53	-0.31
2k	3-Cl	-0.21	-0.63	-0.10	-0.29	-0.48	-0.24

***GPCR ligand : G-Protein Coupled Receptor ligand**

Table 5: ADME properties of N-(5-Phenyl 1, 3, 4-Oxadiazole-2-yl)Cinnamamides

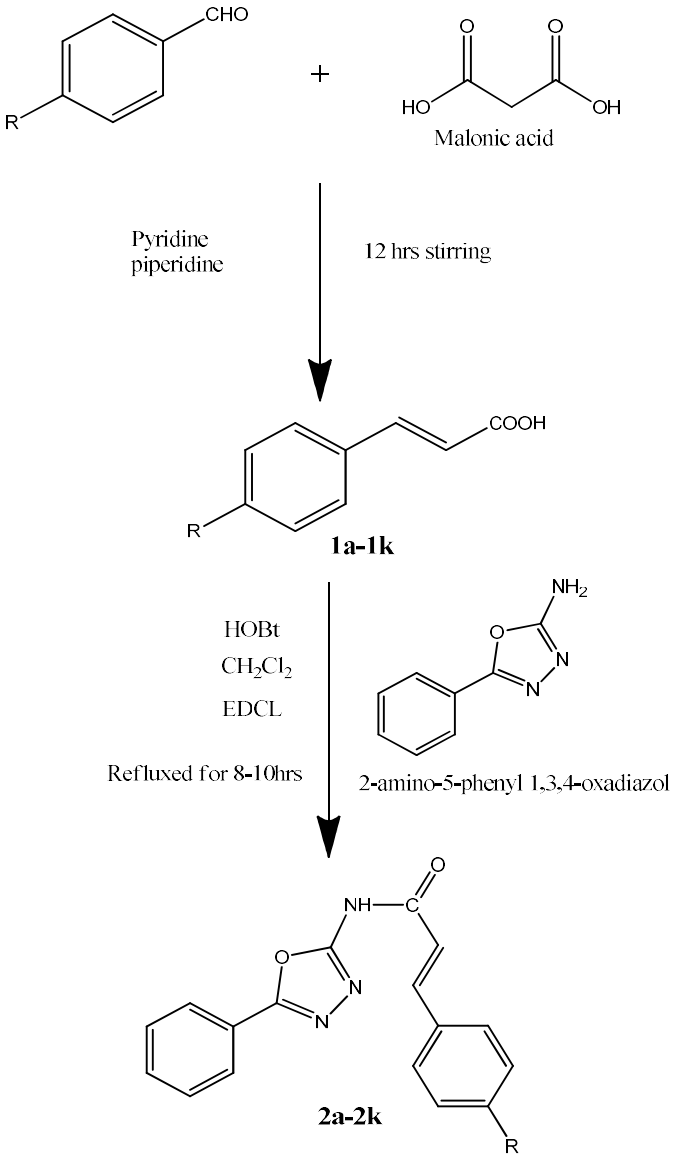
Comp	R	Caco2 perm	MDCK	GI abs	% ABS	SKIN (cm/s)	BBB perm	% PPB	P-gp sub
2a	H	20.32	19.9	H	85.5	-5.94	Y	96.8	N
2b	4-OCH_3	22.37	8.77	H	82.3	-6.14	Y	96.4	N
2c	4-CH_3	20.06	4.39	H	85.5	-5.77	Y	97.9	N
2d	4-$CH(CH_3)_2$	21.56	0.61	H	85.5	-5.40	Y	95.5	N
2e	4-OH,3-(OCH_3)	20.33	5.85	H	75.3	-6.50	N	89.4	N
2f	4-OH,3,5-(OCH_3)$_2$	18.56	3.20	H	72.1	-6.70	N	84.9	N
2g	4-OH	20.99	12.3	H	78.5	-6.29	N	93.3	N
2h	3-OH,4-(OCH_3)	20.82	5.85	H	79.1	-6.50	N	90.0	N
2i	3,4-(OCH_3)$_2$	25.24	6.30	H	69.2	-6.35	N	90.5	N
2j	4-NO_2	17.38	4.04	H	85.5	-6.34	N	93.6	N
2k	3-Cl	24.2	2.93	H	85.5	-5.71	Y	93.5	N

***CaCo2 Perm. - CaCo2 Cell Permeability; MDCK- Maden Darby Canine Kidney cell permeability; SKIN - Skin Permeability; GI abs - Gastrointestinal absorption; % ABS- % of absorption; BBB- Blood brain barrier; PPB - Plasma protein binding; P-gp sub - P-glycoprotein Substrate, BBB Perm.– BBB Permeability; PPB – Plasma Protein Binding; H- High; Y-yes; N- No.**

Table 6: Enzyme Inhibition properties of N-(5-Phenyl 1, 3, 4-Oxadiazole-2-yl)Cinnamamides

Comp. No	R'	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
2a	H	Yes	Yes	Yes	No	No
2b	4-OCH_3	Yes	Yes	Yes	No	No
2c	4-CH_3	Yes	Yes	Yes	No	No
2d	4-$CH(CH_3)_2$	Yes	Yes	Yes	No	No
2e	4-OH,3-(OCH_3)	Yes	No	Yes	No	No
2f	4OH,3,5-(OCH_3)$_2$	Yes	No	Yes	No	Yes
2g	4-OH	Yes	No	Yes	No	No
2h	3-OH,4-(OCH_3)	Yes	No	No	No	No
2i	3,4-(OCH_3)$_2$	Yes	Yes	Yes	No	Yes
2j	4-NO_2	Yes	Yes	Yes	No	No
2k	3-Cl	Yes	Yes	Yes	No	No

SCHEME



Comp.	R
2a	H
2b	4-OCH_3
2c	4-CH_3
2d	4-$CH(CH_3)_2$
2e	4-OH,3-(OCH_3)
2f	4-OH,3,5-(OCH_3)$_2$
2g	4-OH
2h	3-OH,4-(OCH_3)
2i	3,4-(OCH_3)$_2$
2j	4-NO_2
2K	3-Cl

Figure 1: Synthesis of N-(5-Phenyl 1,3,4-oxadiazole-2-yl) cinnamamides

CONCLUSION

In present study, new series of N-(5-phenyl-1,3,4-oxadiazol-2yl)cinnamamides derivatives were synthesized and screened for antibacterial and antioxidant activities. Among the series, 4-nitro **(2j)** and 3-chloro **(2k)** derivatives showed appreciable antibacterial activity against four bacterial strains in comparison to streptomycin as the reference drug. Among all the title compounds, 4-hydroxy **(2g)** and 3,4-dimethoxy **(2i)** derivatives exhibited good DPPH scavenging activity and 4-methyl **(2c)** and 4-methoxy **(2b)** derivatives exhibited good Nitric oxide scavenging activity which is closer to that of standard antioxidant ascorbic acid. All the compounds obeyed Lipinski rule of five indicating compounds oral bioavailability. Hence, the present investigation suggests that N-(5-Phenyl-1, 3, 4-Oxadiazole-2-yl)Cinnamamide scaffold can be used as a lead in future for the development of novel antibacterial and antioxidant agents.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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