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Synthesis of certain cinnamic acid derivatives through heck coupling reaction and evaluation of their antioxidant activities

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ABSTRACT

The Heck reaction is one of the basic types of palladium catalyzed carbon-carbon bond forming reaction discovered by Mizoroki et al. and Heck et al in 1972. The reaction entails bond formation between sp2 carbon of an olefin and an aromatic carbon of an organo halide, proceeding with formal loss of HX under basic conditions. As part of our search for the development of viable synthetic protocols for the Heck coupling reaction, ten cinnamic acid derivatives were synthesized using Heck coupling reaction and they were characterized by NMR and LC MS spectra. The synthesized compounds were tested for antioxidant activity by DPPH assay and one compound exhibited moderate antioxidant activity. Thus it can be concluded that Heck coupling is a reliable synthetic tool for the development of newer compounds with therapeutic potential.

Key words: Heck coupling, Cimmanic acid, antioxidant activity, phenyl acrylate, DPPH assay.

INTRODUCTION

The Heck reaction is one of the basic types of palladium- catalyzed carbon-carbon bond forming reactions.[1]. The palladium catalyzed arylation of an olefin with an organic halide was discovered by Mizoroki et al [2]and Heck et al in 1972.[3] Detailed survey of the synthetic literatures reveals the application of Heck reaction in the synthesis of antiashthmatic agent Singulair, NSAID Naproxen, anticancer agent Taxol, Herbiside Prosulfiron, sunscreen component ethyl hexyl –para- methoxycinnamate, which signifies the versatility of this reaction. The reaction entails bond formation between sp2 carbon of an olefin and an aromatic carbon of an organo halide, proceeding with formal loss of HX under basic conditions[4]. This classical coupling reactions has since been known as the Heck reaction. This is eventually a substitution in which one H atom of the alkene starting material is replaced by the R' group of the vinyl or aryl halide. Palladium (II) acetate [Pd(OAc)2] in the presence of triaryl phosphine [P(O-tolyl)3] is the typical catalyst. The reaction needs the presence of a base such as triethylamine.

The first step in the mechanism of Heck reaction is the oxidative addition of aryl halide RX to the co-ordinatively unsaturated palladium (0) complex to generate a cis-1,2-Pd(II) RX species which then isomerizes to a trans configuration that is thermodynamically more stable. The electrophilicity of the complex is enhanced by the +2 oxidation state, and the olefin readily inserts into Pd-aryl bond resulting in the formation of an unstable Pd alkyl complex.[5] The coupling product is obtained by the elimination to yield the new substituted alkenes. The active palladium (0) complex is regenerated by the addition of a base to eliminate hydrogen halide allowing the catalytic cycle to continue.[6],The oxidative addition step is favored when strong when strong L-donor ligands are employed, allowing the aryl halide to readily add to the palladium complex. Palladium phosphine complexes have most

commonly been employed because they allow good control over the reactivity and selectivity in Heck coupling reactions.[7,8,9]

As part of our search for the development of viable synthetic protocols for the Heck coupling reaction we here in report the synthesis of newer cinnamic acid derivatives and it's subsequent pharmacological screening.

EXPERIMENTAL SECTION

All the reactions were carried out under an inert atmosphere with degassed distilled water. All the reagents and solvents were of analytical grade and were purified whenever necessary. The reagents were procured from Sd fine chem and Merck. The reactions were monitored by TLC using Silica gel 60 F254 using UV detection. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker Avance 300 spectrophotometer operating at 300 MHz (1 H) and 75 MHz (13 C). Spectra were recorded at 298 K in CDCl3 with TMS as internal standard. LC-MS were taking Q-TOF ultima.

Synthesis of E)- ethyl 3-(2-amino phenyl) acrylate.
2-Iodo aniline(100 mg, 0.456 mmol), ethyl acrylate 148µL,1.36 mmol), potassium carbonate (190 mg, 1.36 mmol) and Pd9OAc)$_2$ were taken in a 5 ml reaction tube. Then solvent (degassed water:acetone:3:2) was added to the mixture. The reaction mixture was ultra sonicated at 55° C for 12 hours. Progress of the reaction was reaction was monitored by TLC. After completion of reaction, crude product was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure. Purification was done by using column chromatography over silica gel. (230-400). (Ethyl acetate: hexane-10:9).

Spectral details for (E)- ethyl 3-(2-amino phenyl) acrylate.
^{1}H NMR (300 MHz, CDCl3) 1.32-1.38(m,3H) 3.99(s,2H), 4.24-4.31m,2H), 6.31-6.40(m,1H) 6.68-6.81(m,2H), 7.19(t, *J*=7.62,1H), 7.81-7.86(m,1H); ^{13}C NMR (75 MHz, CDCl3) 14.75, 60.87, 117.10, 118.63, 119.36, 120.34, 128.53, 131.64, 140.42, 145.91, 167.69. LC-MS MS DATA m/z calcd for $[M+H]^+$ C11 H13 NO2 192.2344 Obsd 192.1011

Synthesis of (E)- ethyl 3-p-tolyl acrylate.
4-Iodo toluene(100 mg, 0.458 mmol), ethyl acrylate 148µL,1.36 mmol), potassium carbonate (190 mg, 1.36 mmol) and Pd(OAc)$_2$ were taken in a 5 ml reaction tube. Then solvent (degassed water:acetone:3:2) was added to the mixture. The reaction mixture was ultra sonicated at 55° C for 12 hours. Progress of the reaction was reaction was monitored by TLC. After completion of reaction, crude product was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure. Purification was done by using column chromatography over silica gel. (230-400). (Ethyl acetate: hexane-5:9.5).

Spectral details for (E)- ethyl 3-p-tolyl acrylate.
^{1}H NMR (300 MHz, CDCl3) 1.30-1.37(m,3H) 2.39(s,2H), 4.24-4.31(m,2H), 6.31-6.40(m,1H) 6.68-6.81(m,2H) , 7.19(t,J=7.62,1H), 7.81-7.86(m,1H), 13C NMR (75 MHz, CDCl3) 14.75, 23.12, 60.83, 118.63, 117.55, 128.48, 128.53, 130.01, 132.11. 141.04, 145.00,167.64. LC-MS MS DATA m/z calcd for $[M+H]^+$ C12 H15O2 191.1072 Obsd 191.2438.

Synthesis of (E)- ethyl- 3(2-acetamido phenyl) acrylate.
2-Acetamido–iodo benzene (80 mg, 0.306 mmol), ethyl acrylate 98µL,0.918mmol), potassium carbonate (127 mg, 0.918mmol) and Pd(OAc)$_2$ (2.73 mg, 0.012 mmol) were taken in a 5 ml reaction tube. Then solvent (degassed water:acetone:3:2) was added to the mixture. The reaction mixture was ultra sonicated at 55° C for 12 hours. Progress of the reaction was reaction was monitored by TLC. After completion of reaction, crude product was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure. Purification was done by using column chromatography over silica gel. (230-400). (Ethyl acetate: hexane-5:9.5).

Spectral details for (E)- ethyl- 3(2-acetamido phenyl) acrylate
^{1}H NMR (300 MHz, CDCl3) 1.32-1.38(m,3H) 2.25(s,3H), 4.24-4.31(m,2H), 6.41(d,*J*=15.78,1H7.19—7.40 (m,4H) , 7.57(t,J=7.54,1H), 7.74-7.85 (m,1H). ^{13}C NMR (75 MHz, CDCl3) δ14.70, 24.62, 61.17, 121.07, 125,65, 126.30,

127.53, 127.99, 131.21, 136.24, 139.66, 167.23, 169.31 LC-MS MS DATA m/z calcd for $[M+H]^+$ C13 H15NO3 234.2711, Obsd 234.1158.

Synthesis of (E)- ethyl 3-(3-methoxy phenyl) acrylate.
3–iodo anisole (51 µL,1.281mmol), ethyl acrylate 140 µL,1.281 mmol), potassium carbonate (176 mg, 1.281 mmol) and $Pd(OAc)_2$ (2.87 mg, 0.012 mmol) were taken in a 5 ml reaction tube. Then solvent (degassed water:acetone:3:2) was added to the mixture. The reaction mixture was ultra sonicated at 55° C for 12 hours. Progress of the reaction was reaction was monitored by TLC. After completion of reaction, crude product was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure. Purification was done by using column chromatography over silica gel. (230-400). (Ethyl acetate: hexane-5:9.5).

Spectral details for (E)- ethyl 3-(3-methoxy phenyl) acrylate.
^{1}H NMR (300 MHz, CDCl3) δ 1.36(t, J=7.13, 3H) 3.85(s, 2H), 4.24-4.31m, 2H), 4.25—4.32(m, 2H) 6.44(d, J=15.99, 1H), 6.93-6.69(m, 1H), 7.06(t, J=7.62, 1H), 7.81-7.86(m, 1H) ^{13}C NMR (75 MHz, CDCl3) δ 14.73, 55.69, 60.95, 113.26, 118.95, 121.17, 128.53, 130.28, 136.21, 144.92, 160.27, 167.37. LC-MS MS DATA m/z calcd for $[M+H]^+$ C12 H15O3 207.1021 Obsd 207.2436.

Synthesis of (E)- ethyl 3-(4-hydroxy phenyl) acrylate.
4-Hydroxy iodobenzene (100µgm, 0.454mmol), ethyl acrylate 145 µL,1.363 mmol), potassium carbonate (249mg, 1.81 mmol) and $Pd(OAc)_2$ (4mg, 0.0181 mmol) were taken in a 5 ml reaction tube. Then solvent (degassed water:acetone:3:2) was added to the mixture. The reaction mixture was ultra sonicated at 55° C for 12 hours. Progress of the reaction was reaction was monitored by TLC. After completion of reaction, crude product was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure. Purification was done by using column chromatography over silica gel. (230-400). (Ethyl acetate: hexane-5:9.5).

Spectral details for (E)- ethyl 3-(4-hydroxy phenyl) acrylate.
^{1}H NMR (300 MHz, CDCl3) δ 1.27-1.37(m,3H) 4.24-4.31m,2H), 6.31-6.40(m,1H) 6.68-6.81(m,2H), 7.19(t,J=7.62,1H), 7.81-7.86(m,1H) ^{13}C NMR (75 MHz, CDCl3) δ 14.74, 60.95, 115.89, 118.63, 116.28, 127.50, 130.38, 144.95, 158.27, 162.72, 168.16. LC-MS MS DATA m/z calcd for $[M+H]^+$ C11 H13O3 193.2191, Obsd 193.2171.

Synthesis of E) - ethyl 3-(2-nitro phenyl) acrylate
2-Nitro iodobenzene (100mgm, 0.401mmol), ethyl acrylate 108 µL,1.203mmol), potassium carbonate (166mg, 1.203 mmol) and $Pd(OAc)_2$ (3.59 mg, 0.016mmol) were taken in a 5 ml reaction tube. Then solvent (degassed water:acetone:3:2) was added to the mixture. The reaction mixture was ultra sonicated at 55° C for 12 hours. Progress of the reaction was reaction was monitored by TLC. After completion of reaction, crude product was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure. Purification was done by using column chromatography over silica gel. (230-400). (Ethyl acetate: hexane-5:9.5).

Spectral details for (E) - ethyl 3-(2-nitro phenyl) acrylate
^{1}H NMR (300 MHz, CDCl3) δ 1.29-1.36(m,3H) 3.99(s,2H), 4.21-4.28m,2H), 6.34(D,j=15.79,1H) 7.50-7.55-6.81(m,1H) , 7.60-7.67(M,2H), 7.99—8.09(m,1H) ^{13}C NMR (75 MHz, CDCl3) δ 14.63, 61.30, 117.10, 125.27, 129.52, 130.72, 130.90, 133.99, 140.23, 148.64, 166.19. LC-MS MS DATA m/z calcd for $[M+H]^+$ C12 H15O2 221.211 Obsd 221.2267..

Synthesis of (E)- ethyl 3-(2-methoxy phenyl) acrylate.
2- iodoanisole (111.11 µL,0.854mmol), ethyl acrylate (272 µL,2.56 mmol), potassium carbonate (353mg, 2.56 mmol) and $Pd(OAc)_2$ (7.6mg, 0.034 mmol) were taken in a 5 ml reaction tube. Then solvent (degassed water:acetone:3:2) was added to the mixture. The reaction mixture was ultra sonicated at 55° C for 12 hours. Progress of the reaction was reaction was monitored by TLC. After completion of reaction, crude product was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure. Purification was done by using column chromatography over silica gel. (230-400). (Ethyl acetate: hexane-5:9.5).

Spectral details for (E)- ethyl 3(2-methoxy phenyl) acrylate.
^{1}H NMR (300 MHz, CDCl3) 1.32-1.38(m,3H) 3.99(s,2H), 4.24-4.31m,2H), 6.31-6.40(m,1H) 6.68-6.81(m,2H) , 7.19(t,J=7.62,1H), 7.81-7.86(m,1H) ^{13}C NMR (75 MHz, CDCl3) 14.75, 60.87, 117.10, 118.63, 119.36, 120.34, 128.53, 131.64, 140.42, 145.91, 167.69. LC-MS MS DATA m/z calcd for $[M+H]^+$ C12 H15O2 207.2457, Obsd. 207.2423.

Synthesis of (E)- ethyl 3-(4-nitro phenyl) acrylate.
4-Nitro iodobenzene (51µL, 0.427mmol), ethyl acrylate (140 µL,1.281 mmol), potassium carbonate (176mg, 1.281 mmol) and $Pd(OAc)_2$ (2.87mg, 0.0128 mmol) were taken in a 5 ml reaction tube. Then solvent (degassed water: acetone: 3:2) was added to the mixture. The reaction mixture was ultra sonicated at 55° C for 12 hours. Progress of the reaction was reaction was monitored by TLC. After completion of reaction, crude product was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure. Purification was done by using column chromatography over silica gel. (230-400). (Ethyl acetate: hexane-5:9.5).

Spectral details for (E)- ethyl 3-(4-nitro phenyl) acrylate.
^{1}H NMR (300 MHz, CDCl3) 1.32-1.38(m,3H) 3.99(s,2H), 4.24-4.31m,2H), 6.31-6.40(m,1H) 6.68-6.81(m,2H) , 7.19(t,J=7.62,1H), 7.81-7.86(m,1H). ^{13}C NMR (75 MHz, CDCl3) 14.75, 60.87, 117.10, 118.63, 119.36, 120.34, 128.53, 131.64, 140.42, 145.91, 167.69. LC-MS MS DATA m/z calcd for $[M+H]^+$ C12 H15O2 222.2173 Obsd 222.1016.

Synthesis of (E)- ethyl 3-(4-acetoxy phenyl) acrylate.
4-acetoxy phenyl iodo benzene (51µL, 0.427mmol), ethyl acrylate (140 µL,1.281 mmol), potassium carbonate (176mg, 1.281 mmol) and $Pd(OAc)_2$ (2.87mg, 0.0128 mmol) were taken in a 5 ml reaction tube. Then solvent (degassed water:acetone:3:2) was added to the mixture. The reaction mixture was ultra sonicated at 55° C for 12 hours. Progress of the reaction was reaction was monitored by TLC. After completion of reaction, crude product was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure. Purification was done by using column chromatography over silica gel. (230-400). (Ethyl acetate: hexane-5:9.5).

Spectral details for (E)- ethyl 3-(4-acetoxy phenyl) acrylate.
^{1}H NMR (300 MHz, CDCl3) 1.32-1.38(m,3H) 3.99(s,2H), 4.24-4.31m,2H), 6.31-6.40(m,1H) 6.68-6.81(m,2H) , 7.19(t,J=7.62,1H), 7.81-7.86(m,1H) ^{13}C NMR (75 MHz, CDCl3) 14.75, 60.87, 117.10, 118.63, 119.36, 120.34, 128.53, 131.64, 140.42, 145.91, 167.69. LC-MS MS DATA m/z calcd for $[M+H]^+$ C12 H15O2 235.2558 Obsd 235.2656.

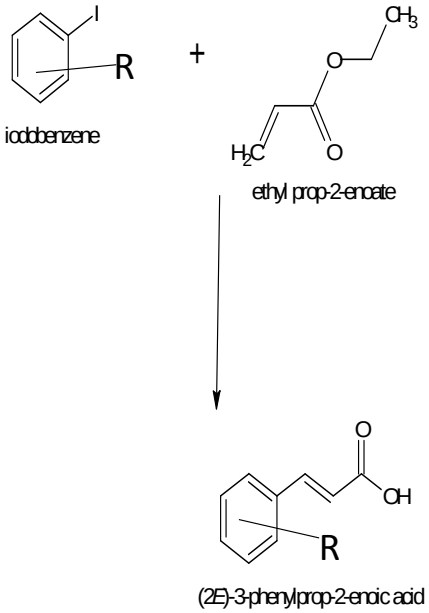
Synthesis of (E)- 2-(ethoxy carbonyl) benzoic acid
4- Iodo benzoic acid (100mg, 0.403mmol), ethyl acrylate (128 µL,1.209mmol), potassium carbonate (223 mg, 1.621mmol) and $Pd(OAc)_2$ (4 mg, 0.0181mmol) were taken in a 5 ml reaction tube. Then solvent (degassed water:acetone:3:2) was added to the mixture. The reaction mixture was ultra sonicated at 55° C for 12 hours. Progress of the reaction was reaction was monitored by TLC. After completion of reaction, crude product was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure. Purification was done by using column chromatography over silica gel. (230-400). (Ethyl acetate: hexane-5:9.5).

Spectral details for (E)- 2-(ethoxy carbonyl) benzoic acid
^{1}H NMR (300 MHz, CDCl3) 1.32-1.38(m,3H) 3.99(s,2H), 4.24-4.31m,2H), 6.31-6.40(m,1H) 6.68-6.81(m,2H) , 7.19(t,J=7.62,1H), 7.81-7.86(m,1H) ^{13}C NMR (75 MHz, CDCl3) 14.75, 60.87, 117.10, 118.63, 119.36, 120.34, 128.53, 131.64, 140.42, 145.91, 167.69. LC-MS MS DATA m/z calcd for $[M+H]^+$ C12 H15O2 235.2558 Obsd.235.2656.

DPPH ASSSAY
The DPPH assay is a qualitative indicator of free radical scavenging activity. It is the simplest and fast method as compared to other methods to determine the free radical scavenging activity. DPPH is reduced from a stable free radical that is purple in colour to diphenylpicryl hydrazine that is yellow in presence of antioxidant. DPPH radical has strong absorption at 517 nm when it accepts electron or hydrogen radical, it is converted to a stable molecule

and the absorption decreases with respect to the number of electrons taken up. The antioxidant activity using DPPH assay was determined by modified method of Blois.[10].100 µL of different concentrations of the synthesized compounds were added to 2.0 mL of the 100µM DPPH solution prepared in methanol. The mixture was shaken vigorously and allowed to stand at 230 C in the dark for 30 minutes. The blank was prepared by adding 100 µL of methanol instead of samples and following the same protocol and decrease in absorbance of the resulting sample solutions were monitored at 517 nm against blank. All measure were done in triplicate.

SCHEME OF SYNTHESIS



RESULTS AND DISCUSSION

By using Heck coupling reaction, a total of 10 cinnamic acid derivatives were synthesized. The structure of the synthesized compounds were confirmed using ^{1}HNMR AND ^{13}C NMR spectra. All the synthesized compounds were screened for free radical scavenging activity by DPPH method. Out of ten compounds screened, only one compound, (E)-ethyl-3-(4-hydroxy phenyl) acrylate exhibited moderate DPPH free radical scavenging activity with 54.68% inhibition (E)-ethyl-3-(4-hydroxy phenyl) acrylate following the logarithmic shaped at different concentrations'. The IC50 values associated with was recorded to be 962.48 which was calculated from the regression equation. The regression coefficient and IC_{50} of the compound (E)-ethyl-3-(4-hydroxy phenyl) acrylate is presented in table no. 2. All the other synthesized compounds were found to be ineffective towards DPPH radical. The free radical scavenging activity of the synthesized compounds along with standard ascorbic acid is presented in table no.3. The percentage inhibition of the synthesized compounds at concentrations 500 µg/ml, 1000µg/ml and 2000µg/ml are presented graphically in figures 1,2 and 3.

Cinnamic acid derivatives which occupies a prime position in the pharmaceutical sector as a therapeutic agent and as an intermediate in many drug synthesis. Heck coupling reaction is a versatile tool in many synthetic reactions where new c-c bond formation is involved. As the J value is around 15, the synthesized compounds c=c are trans in configuration, where as the aromatic c=c are cis because their coupling constant is around 8.

TABLE:1 Physico-chemical characterization of synthesized compounds

Sl.no.	Compound code	Colour	Physical state	Molecular formula	Molecular weight	M.P/B.P (c)	%yield	Rf value
1	P1	Dark yellowish	Oily	C11H13NO2	191.23	160	35	0.16
2	P2	Light yellowish	Gummy liquid	C12H14O2	190.24	130	59	0.33
3	P3	White	Fine powder	C13H15NO3	233.26	132-134	46	0.27
4	P4	Dark yellowish	Gummy liquid	C12H14O3	206.24	145	40	0.46
5	P5	White	Coarse Powder	C1H12O3	192.21	68-72	41	0.23
6	P6	Yellowish	Liquid	C11H11NO4	221.21	135	22	0.21
7	P7	Light yellowish	Liquid	C12H14O3	206.24	148	56	0.48
8	P8	Light yellowish	Crystalline pellets	C11H11NO4	221.21	138-140	23	0.29
9	P9	Light Brown	Powder	C13H14O4	234.25	60-63	56	0.30
10	P10	White	Fine powder	C12H12O4	220.22	225-230	41	0.40

Ethyl Acetate: n-Hexane

Table 2 Regression Coefficient and IC_{50} value for (E)-ethyl-3-(4-hydroxy phenyl) acrylate

E)-ETHYL-3-(4-HYDROXY PHENYL) ACRYLATE	
Curve shape	logarithmic
Regression equation	y=8.15321Ln(x)-6.0085
Regression coefficient	r2=0.9868
IC_{50}	962.48

TABLE:3 Percentage scavenging of synthesized compounds for antioxidant activity

Compound Code	Percentage Scavenging (µg/ml)				
	2000	1000	500	250	125
P1	9.54	5.32	5.69	5.32	4.22
P2	8.44	6.24	4.59	7.16	4.22
P3	10.64	9.91	8.07	7.34	6.79
P4	54.68	51.56	45.50	38.72	32.84
P5	9.91	9.17	8.99	8.07	8.07
P6	9.72	9.36	9.36	7.34	6.79
P7	11.01	9.91	8.26	7.16	5.87
P8	5.69	4.40	5.69	5.50	1.65
P9	9.36	5.50	2.57	3.12	4.95
P10	5.45	5.32	3.02	4.08	4.76
AA(standard)	89.72	88.99	60.73	39.45	25.14

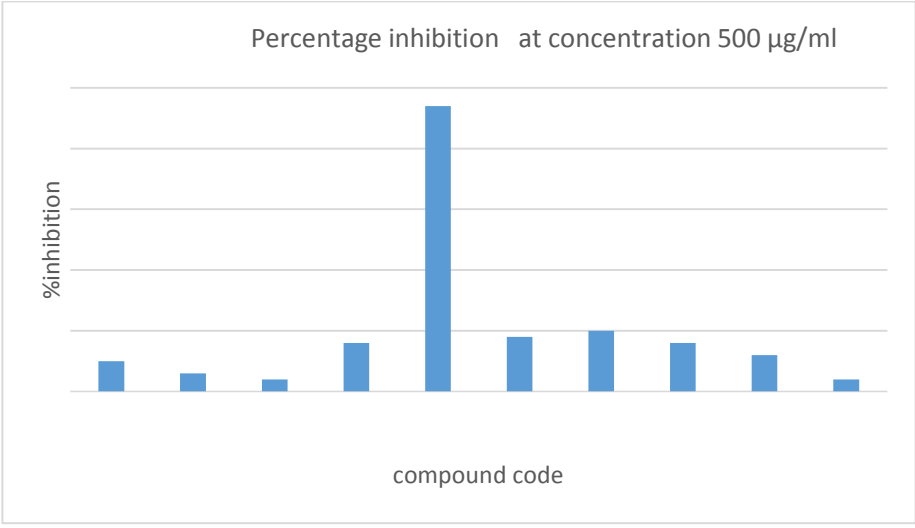


Fig.1 Percentage inhibition at concentration 500 µg/ml

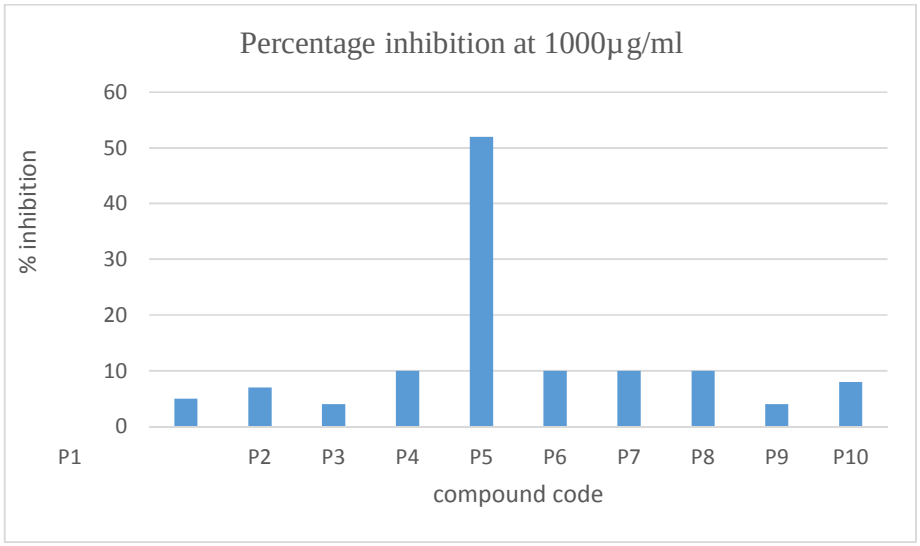


Fig.2 Percentage inhibition at concentration 1000 µg/ml

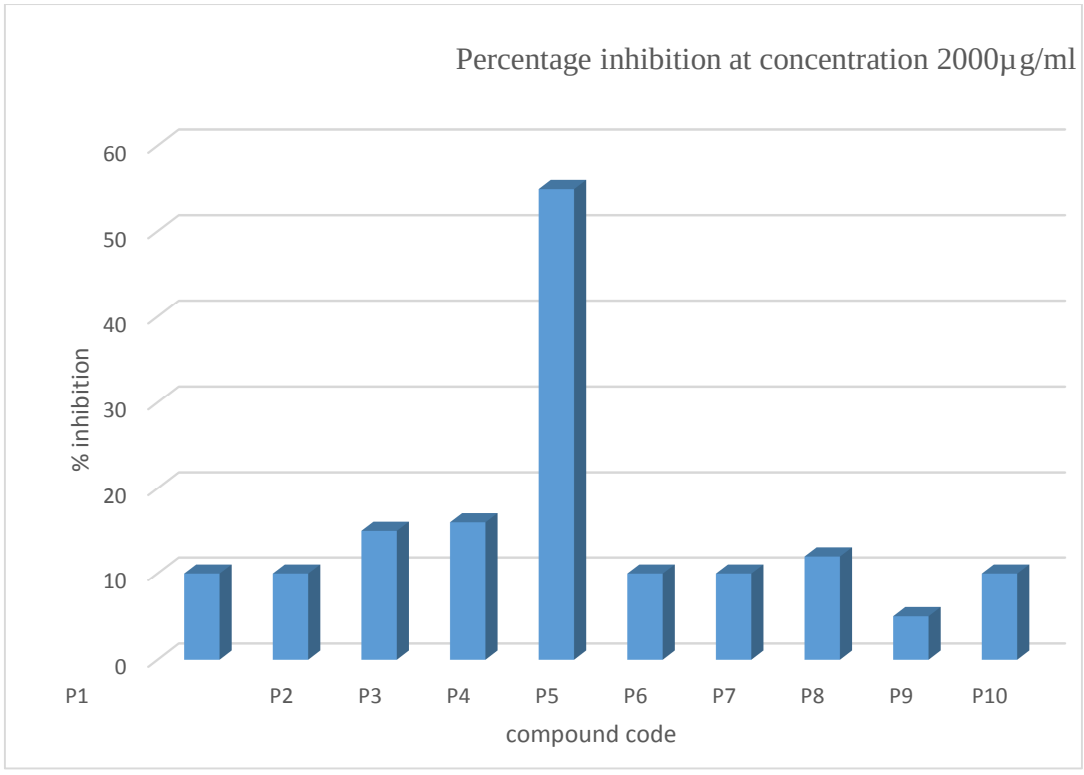


Fig 3 Percentage inhibition at concentration 2000 µg/ml

CONCLUSION

Heck coupling reaction, an efficient tool in the synthesis of many drugs and pharmaceuticals was utilized in the synthesis of cinnamic acid derivatives, which are important agents and intermediates in the pharmaceutical sector. Cinnamic acid derivatives were found to possess various pharmacological activities, like antioxidant, antidiabetic, anticancer, antihyperlipidemic activities. Thus it can be concluded that Heck coupling reaction is an effective

strategy in the synthetic development of newer moieties with therapeutic potential. The utility of such reaction strategies in the development of newer therapeutic agents should be exploited to the core so that the pharmaceutical sector may get many viable alternatives in their search for safe and effective therapeutic agents.

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