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Synthesis And Biological Evaluation Of 5-(3,4-Methylenedioxyphenyl)-2,4-Pentadienoic Acid Derivatives *As* Potent Antimicrobial And Cytotoxicity Agents

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Abstract : *Dark pepper (Piper nigrum L.) has for quite some time been viewed as a spice added to numerous nourishments and it is additionally considered as a medicinal plant. The predominant compound got from ethanolic concentrate of P. nigrum, the piperine, was crystallized. Piperine, a noteworthy alkaloid in dark pepper is a standout amongst the most encouraging bioenhancers till date. Piperic acid was synthesized by alkaline hydrolysis of the cleaned piperine. A progression of piperine analogs were incorporated by the buildup of piperic acid with various substituted aniline (**3a-3e**). The synthesized compounds (**4a– 4e**) were assessed for their anticancer activity against human growth cell lines (HEPG 2, Liver Cancer cell line and MCF-7, Breast Cancer cell line) and antibacterial activity against human pathogens (Escherichia coli, Bacillus subtilis, Staphylococcus aureus, Vibrio cholerae and Pseudomonas aeruginosa). The efficacies of the synthesized compounds (**4a-4e**) were better than those of piperine in all tried human cancer cell lines. Among the derivatives, **4d** indicated huge anticancer action against breast cancer cell line(MCF-7) with IC50 of 3.78 µmol and 4b indicated huge action against liver cancer cell line (HEPG 2). The antibacterial activity of the derivates was additionally observed to be better for compound 4b and 4d than that of other derivatives.*
Therefore the approach is novel as the richly accessible common item piperine is used as precursor for the synthesis of new potential antimicrobial and anticancer agents.

Keywords *- Antibacterial activity, Coupling agent, Piperic acid, Piperine.*

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I. Introduction

Black pepper is known as king of spices and extensively used all over the world[1]. Piperine was isolated in good yield from ground black pepper by Oerstedt H Schweigers in 1821.Pepper's pungency was found in 1821 to be due to Piperine. Verifiably, it has been thought to cure many illnesses such as cancer, malaria and cholera [1]. Piperine ($C_{17}H_{19}NO_3$) is an alkaloid found in the fruits and roots of *Piper nigrum* and *Piper longum* species of Piperaceae family[1]. Pepper consist of Piperine alkaloid (3- 9%), pungent resin (6.0%), volatile oil (1-2.5%), piperidine and starch (about 30%) [2,3]. The volatile oil of Piperine has shown to have antimicrobial property [4]. Piperine has anti-inflammatory [5,6], analgesic [7], antiarthritic, CNS depressant, anticonvulsant [8]. The compound in pepper known as Piperine is commercially utilized in production of different insecticides to be used against houseflies and other insect pests. Piperine is 1- [5-(1, 3-Benzodioxol-5-yl)-1-oxo- 2, 4-pentadienyl]. Recent medical studies have shown Piperine to be very helpful in increasing the absorption of certain vitamins such as Selenium, Vitamin B and Beta-Carotene [9].

It is commonly used in various traditional systems of medicines[10]. Piperine has been reported to exhibit various types of pharmacological activities such as anti-inflammatory [11], anti-oxidant [12], anti-tumor [13], anti-asthmatic [14], hepato-protective [15], anti-thyroid [16], and anti-depressant [17]. Most of non-steroidal anti-inflammatory drugs (NSAIDs) used for the treatment of inflammation show adverse effects such as gastric ulcer [18], kidney damage [19] and hepatotoxicity [20]. Therefore, the development of NSAIDs with reduced side effects is still underway all over the world.

Irrespective of the potentiality of piperine, not much work has been carried out to study the efficacy of piperine analogs as anticancer and antimicrobial agents. The newly synthesized analogs of piperine increased the potentiality of the natural compound piperine, and it emerged as a new approach in the discovery of new cytotoxic and antimicrobial agents. The anticancer activity of piperine lies in the amide linkage; we tried to replace the piperidine nucleus with different substituted aniline. The present study deals with the synthesis of conjugated piperine derivatives, and they are characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and MS spectral data. The biological activity of the synthesized compounds was evaluated in comparison with the parent compound piperine.

II. Experimental

All reagents for chemical synthesis were purchased from Sigma-Aldrich and used as received. Piperine were isolated from the ethanolic extract of P. nigrum plants and characterized by spectroscopic techniques. All the solvents used in reactions were distilled and dried before use. All reactions were monitored by TLC on 0.25 mm silica gel 60 F254 plates coated on aluminium sheet (MERCK). All the chemicals purchased were analytical grade.^{1}H NMR and ^{13}C NMR spectra were recorded on Brucker Avance DPX-200 instrument at 200 MHz respectively using CDCl3 as solvent. Chemical shift is expressed in δ (ppm) and coupling constant in Hertz. Mass spectra were recorded on Agilent instrument and IR spectra on Perkin – Elmer FT-IR spectrometer as KBr pellet or neat sample.

2.1 Extraction and Isolation of Piperine (1)

100 g of ground black pepper powder is taken in a 250 ml round bottomed flask, and 500 ml of 95 % ethanol is added and refluxed for 2 h. The mixture is filtered and concentrated using a rotator evaporator. The concentrated pepper extract is added to 10 ml of 10% ethanolic KOH solution. The resulting solution is heated and water is added dropwise. Yellow precipitate separates out, allowing the mixture to stand overnight. The solid precipitate is filtered and recrystallized with 10-20 ml of acetone to obtain 3g of piperine.

2.2 Synthesis of Piperic acid (2) from piperine (1) (Scheme 1)

Piperine (5g, 17.5 mmol) was refluxed with ethanolic KOH (2 N, 20 ml) for 6 h, the ethanol was evaporated under reduced pressure and the solution was cooled in ice bath. The gummy potassium salt of piperic acid was suspended in water and gradually acidified with dil. HCl, dark yellow precipitate was collected and stirred for 3-4 h in ice cold bath, filtered and washed with cold water. The compound was recrystallized from methanol yielding a yellow crystalline compound with 80% yield.

2.3 Synthesis of piperic acid amides (4a-4e)

A round bottom flask (50 ml) with piperic acid (2.50 g, 11 mmol) in dry dichloromethane (50 ml) was added to the solution of appropriate selected aromatic amines (3a-3e, 11 mmol) followed by the addition of 11mmol of Hydroxy benzotriazole (HOBt), the mixture was stirred under nitrogen atmosphere maintain the temperature -5^{o} to 5^{o}, after half an hour, slowly add 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC.HCl, 11 mmol), then followed by TLC for completion of reaction. After the reaction was completed, the reaction mixture was dissolved in ethyl acetate and transferred in a separating funnel, continuous extraction with water (2 x 50 ml) discard the aqueous layer, extracted with 2N HCl (2 x 50 ml), removes the aqueous layer, then sequential extraction with saturated sodium bicarbonate solution (2 x 50 ml) and brine solution (2 x 50 ml) the organic layer was collected and evaporated by a rotary evaporator and the residue was subjected to silica gel column chromatography with hexane : ethyl acetate (4:2) to produce the target compounds (4a-4e).

2.4 Determination of invitro anticancer activity

2.4.1 Cell lines and cell culture

The human malignancy cell lines were kept up in Dulbecco's modified essential medium (DMEM) supplemented with 4.5 g/l glucose, 2 mM L-glutamine, and 5 % fetal bovine serum (FBS) (growth medium) at 37 ^{o}C in 5 % CO_2 incubator.

2.4.2 MTT assay

The MTT measure developed by Mosmann (1983) was modified and used to determine the inhibitory impacts of test compounds on cell development in vitro. The trypsinized cells from T-25 flask were seeded in each well of 96-well flat-bottomed tissue culture plate at a thickness of 5 x 10^{3} cells/well in developement medium and cultured at 37 ^{o}C in 5 % CO_2 to follow. After 48 h incubation, the supernatant was disposed of and the cells were pretreated with growth medium and were subsequently mixed with different concentrations of test compounds (32, 64, 128, 256, and 500 µg/ml) in triplicates to achieve a final volume of 100 µl and then cultured for 48h. The Compound was prepared as 1.0 mg/ml concentration stock solutions in PBS. Culture medium and solvent are utilized as controls. Each well then received 5 µl of fresh MTT (0.5 mg/ml in PBS) followed by

incubation for 2 h at 37 ^{o}C. The supernatant growth medium was removed from the wells and replaced with 100 µl of DMSO to solubilize the colored formazan product. After 30 min incubation, the absorbance (OD) of the culture plate was read at a wavelength of 570 nm on an ELISA reader, Anthos 2020 spectrophotometer. The IC50 values of the test samples were calculated and tabulated in **TABLE 2**.

2.5 Determination of antibacterial activity

The antibacterial activities of the synthesized compounds were tested against Bacillus subtilis, Enterococcus faecalis, Escherichia coli, Vibrio cholera and Pseudomonas aeruginosa.

2.5.1 Disk diffusion method (DDM)

Disk diffusion method was determined by Mueller-Hinton agar (MHA) plates. A diameter of 6mm sterile disk and loaded with required concentration of drug over the agar. The test plates were incubated for 24h at 37 ^{o}C. The zone of inhibition (mm in diameter) were read and taken as the activity against the test pathogens. Ciproflaxin (20µg) was used as reference drug; the results were tabulated in **TABLE 3**.

Scheme 1 Synthesis of piperic acid and piperine derivatives from piperine

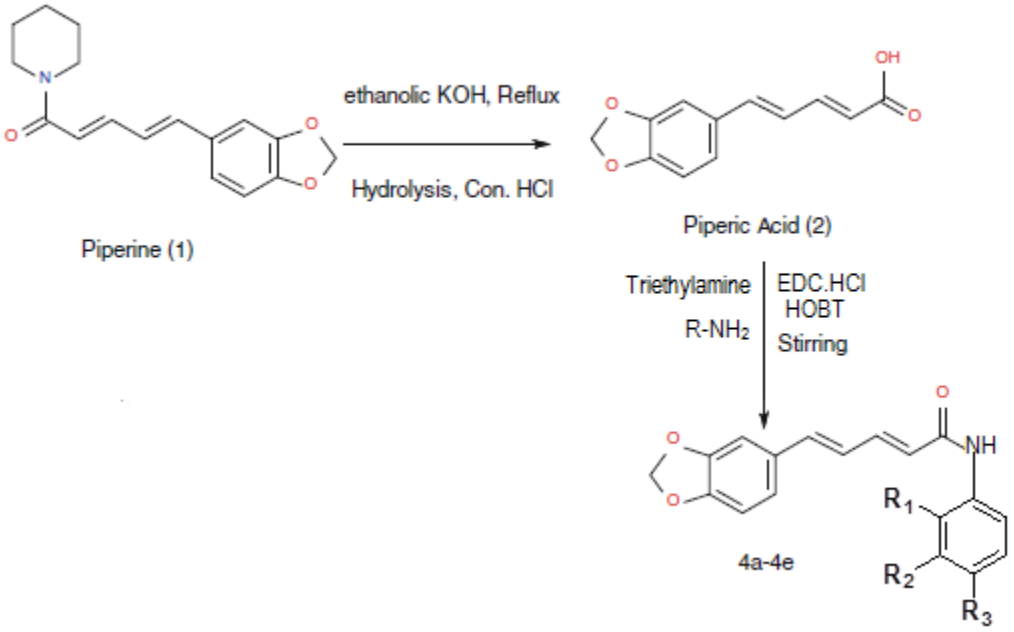
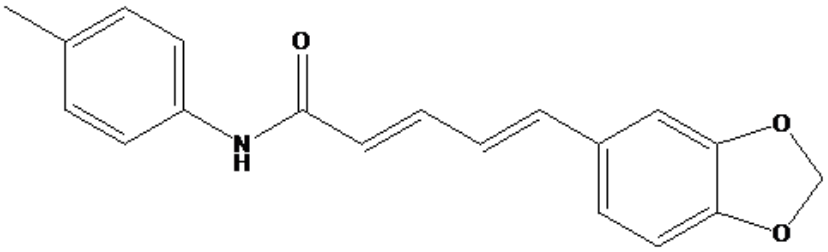


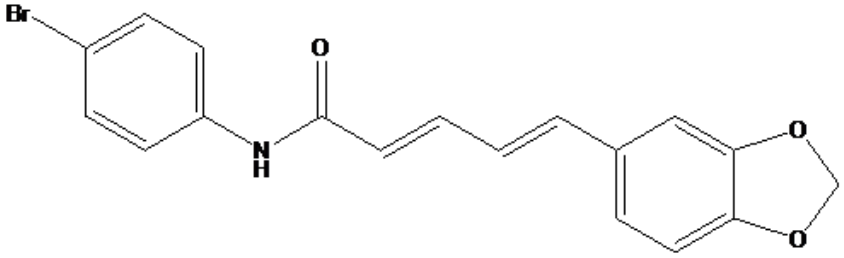
TABLE 1

Entry	R_1	R_2	R_3	Product	Yield
1	CH_3	H	H	**4a**	81
2	Br	H	H	**4b**	90
3	O-CH_3	H	H	**4c**	68
4	H	Cl	H	**4d**	73
5	H	H	Cl	**4e**	78

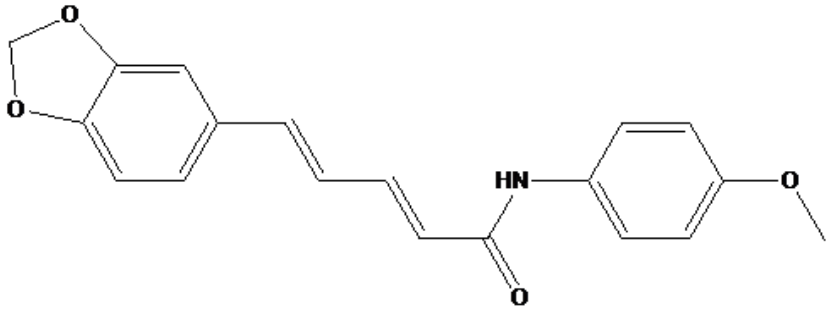
5-Benzo [1,3] dioxol-5-yl-penta-2,4-dienoic acid p-tolylamide (4a)



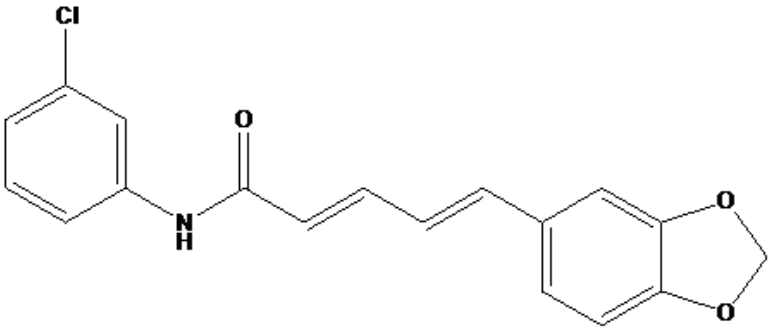
5-Benzo [1,3] dioxol-5-yl-penta-2,4-dienoic acid (4-bromo-phenyl)-amide (4b)



5-Benzo [1,3] dioxol-5-yl-penta-2,4-dienoic acid (4-methoxy-phenyl)-amide (4c)



5-Benzo [1,3] dioxol-5-yl-penta-2,4-dienoic acid (3-chloro-phenyl)-amide (4d)



5-Benzo [1,3] dioxol-5-yl-penta-2,4-dienoic acid (4-chloro-phenyl)-amide (4e)

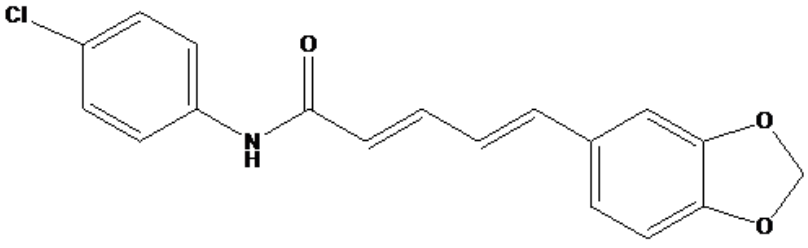


TABLE 2 Determination of anticancer activity of piperine and its derivatives given as IC_{50} in µmol

Cell line	1	4a	4b	4c	4d	4e
Liver cancer cell line	1.35	1.75	3.50	1.08	0.89	2.80
Breast cancer cell line	1.29	1.59	1.96	1.25	3.78	3.50

TABLE 3 Determination of antimicrobial activity of piperine and its derivatives given at 500 µmol in mm

Bacteria	1	4a	4b	4c	4d	4e	Ciproflaxin (20 µmol)
Bacillus subtilis	14	16	35	16	36	27	23
E. faecalis	15	7	7	17	34	34	26
E. Coli	13	7	31	7	34	7	25
V. Cholerae	15	16	36	12	32	28	24
P. aeruginosa	13	27	36	19	34	33	24

2.7 Spectral data of synthesized compounds (4a-4e)

IR spectra were recorded on Perkin Elmer spectrometer with KBr pellets. The 1H and 13C NMR were recorded on a Bruker FT-400 MHz spectrometer at 400 MHz for 1H and 100 MHz for 13C, respectively, using TMS as internal standard. Mass spectra were measured on Agilent 5975C GC-MSD instrument.

5-Benzo [1,3] dioxol-5-yl-penta-2,4-dienoic acid p-tolylamide (4a)

It is a pale yellow crystalline solid, molecular formula: $C_{19}H_{17}NO_3$, mp 194–195 ^oC. IR (KBr) λmax: 3360, 2934, 2854, 2362, 1743, 1656, 1406, 1258, 1096, 1044, 762 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 2.24 (s, 3H), 5.98 (d, 1H, J = 14.78 Hz), 6.02 (s, 2H), 6.60–6.67 (m, 2H), 6.98–7.18 (m, 7H), 7.36 (d, 1H, J = 14.78, 9.23 Hz). $_{13}C$ NMR (100 MHz, $CDCl_3$): 22.4, 101.6, 107.6, 108.4, 120.8, 121.6, 124.9, 124.7, 125.6, 126.5, 128.6, 129.9, 129.8, 130.7, 139.9, 143.5, 147.2, 147.7, 165.2; m/z 307.

5-Benzo [1,3] dioxol-5-yl-penta-2,4-dienoic acid (4-bromo-phenyl)-amide (4b)

It is a pale white color solid, molecular formula: $C_{18}H_{14}BrNO_3$; m.p. 145–148 ^oC; IR (KBr) λmax: 3567,1615, 1498, 1294, 1167, 1086, 1007, 824, 632, 506, 1654,1629, 1672, 1604, 1517, 1502 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 9.52 (s, 1H), 7.54–7.46 (m, 2H), 7.42–7.34 (m, 2H), 7.15–7.02 (m, 2H), 6.94 (d, 1H, J = 7.5 Hz), 6.85–6.70 (m, 3H), 6.06 (s, 2H), 5.40 (d, 1H, J = 14.9 Hz);^{13}C NMR (100 MHz, $CDCl_3$): 106.6, 131.2, 122.6, 108.7, 148.4, 147.8, 164.6, 142.5, 138.7, 136.8, 132.6, 126.2,122.8, 122.1, 119.6, 101.6; m/z 371.02.

5-Benzo [1,3] dioxol-5-yl-penta-2,4-dienoic acid (4-methoxy-phenyl)-amide (4c)

It is a brown crystalline solid, molecular formula: $C_{19}H_{17}NO_4$; m.p 167–168 ^oC. IR (KBr) λmax: 3237, 2919, 2848, 1606, 1507, 1246, 1032, 759 cm^{-1}. ^1H NMR: 3.89 (s, 3H), 5.99 (s, 2H), 6.09 (d, 1H, J = 15.0 Hz), 6.72 (d, 2H, J = 8.2 Hz), 6.82–7.35(m, 6H), 7.53 (d, 2H, J = 8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 58.1, 99.6, 107.6, 108.6, 115.3, 120.4, 123.6, 124.8,126.9, 128.7, 129.2, 131.6, 143.8, 148.6, 148.4, 158.2, 165.9; m/z 323.

5-Benzo [1,3] dioxol-5-yl-penta-2,4-dienoic acid (3-chloro-phenyl)-amide (4d)

It is a dark brown solid, molecular formula: $C_{18}H_{14}ClNO_3$; m.p. 139–141 ^oC; IR (KBr) λmax: 3602, 1616, 1494, 1284,1176, 1086, 1008, 823, 632, 502, 1672, 1629, 1687, 1603,1517, 1502 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 9.52 (s, 1H), 7.89–7.81 (m, 2H), 7.44–7.36 (m, 2H), 7.15–7.02 (m, 3H), 6.97–6.82 (m, 2H), 6.68 (d, 1H, J = 15.0 Hz), 6.06 (s, 2H), 5.27 (d, 1H, J = 15.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 106.1, 131.2, 122.7, 108.2, 148.9, 147.5, 101.1, 138.5, 126.7,142.7, 122.8, 164.3, 137.2, 128.8, 127.4, 122.6; m/z 327.07.

5-Benzo [1,3] dioxol-5-yl-penta-2,4-dienoic acid (2-chloro-phenyl)-amide (4e)

It is a brown solid, molecular formula: $C_{18}H_{14}ClNO_3$; m.p. 143–147 ^oC; IR (KBr) λmax: 3602, 1614, 1496, 1286, 1177, 1088, 1002, 826, 634, 507, 1676, 1627, 1683, 1606, 1514, 1506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 9.62 (s, 1H), 7.84–7.86 (m, 2H), 7.42–7.34 (m, 2H), 7.14–7.04 (m, 3H), 6.98–6.84 (m, 2H), 6.66 (d, 1H, J = 15.0 Hz), 6.04 (s, 2H), 5.29 (d, 1H, J = 15.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 106.1, 131.4, 122.4, 108.7, 148.8, 147.4, 101.6, 138.7, 126.6,142.8, 122.1, 164.4, 137.6, 128.6, 127.3, 122.5; m/z 327.07.

III. Results and Discussion

In this work, several biological active Piperic acid amides were synthesized by simple, economical and effective one step procedure by coupling of Piperic acid (2) derived from Piperine (1) and with selected aromatic amines (**3a-3e**) using EDC.HCl and HOBT as coupling agents. Satisfactory yields were obtained in all

cases (**4a-4e**). The transformation of Piperine into Piperic acid was also confirmed by FT-IR analysis, we can observe the appearance of a band emerging at 1678.76 which corresponds to carbonyl group of Piperic acid, also shows the disappearance of the band at 1633.95, corresponding to the amide group of isolated Piperine. Bands between 2500 and 3000 correspond to the -C-H aromatic ring. The piperidine amide of natural Piperine was replaced by substituted aniline derivatives to obtain compound **4a-4e**. All the synthesized compound was characterized by FT-IR, Mass and ^{1}H and ^{13}C NMR spectral analysis. The FT-IR peaks at 1630-1690 for all the synthesized compounds arise due to the C=O and those at 3500-3700 are due to the N-H group. The amide coupling in **4a-4e** derivatives was confirmed by the presence of N-H proton in aromatic region at 7.52-7.62 ppm.

The compounds (**4a-4e**) exhibited inhibition zones ranging from 7mm to 34mm diameter, with the most noteworthy results shown by compound 4b, 4d and 4e. Ciproflaxin 20 µg disk (36mm – 40mm) showed a resistant result. The diameters included the 6-mm filter paper disk. The compound 4b, demonstrated inhibition zones greater than 34 mm in diameter for pathogens B. Subtilis, V. Cholerae, and P. Aeruginosa, as shown in

TABLE 3. The greatest zones (17mm – 36mm) produced against all the pathogens by compound 4d. Additionally, the compound 4a shows better inhibition on gram negative bacterial strain of p. Aeruginosa (7mm-27mm). The compound 4a and 4c shows little bit activity compared to 4b, 4d and 4e for all the pathogens tested. Among all the tested compounds, compound 4b containing p-bromoaniline nucleus was found to be the best against the selected human pathogens. Compound 4d and 4e containing meta and para-chloroaniline was also proves to be good inhibition.

As shown in **TABLE 2**, some of the synthesized compounds showed moderate to potent anticancer activities against all the tested cells. Among them, compound 4b and 4d were the most promising compounds. The most outstanding compound out of these was 4d which displayed stronger cytotoxicity against MCF-7 cell lines with IC_{50}values 3.78 µg/ml. The next most promising compound, 4b depicted stronger cytotoxicity against the cell

line HEPG2 with IC_{50} values 3.50µg/ml. Furthermore, 4e exhibited significant cytotoxicity with the IC_{50} values ranging between 2.80and 3.50 µg/ml against both the cell lines. Compounds 4a showed moderate activity with the IC_{50} values of 1.75 and 1.59 µg/mL against HEPG2 and MCF-7 cell lines. Compounds 4c showed moderate activity against HEPG2 cell line and showed least cytotoxicity with IC_{50} values of 1.25 µg/mL against MCF-7 cell line.

In general, it was observed that Bromo and Chloro substitution compounds 4b, 4d and 4e showed excellent anticancer activity. This might be because of the stronger electron withdrawing tendency of the chloro and Bromo groups, which played an important role in cytotoxicity effect. Next, we examined the impact of substituent on the p-OCH_3 group, which shows good anticancer activity against both the cell lines. Comparatively, the compounds 4b-4e shows better activity compared to methyl substituted derivatives 4a**.** From the above results Piperine derivatives along with the electron withdrawing groups increase the potent of the cytotoxicity when compared to electron donating methyl group.

IV. Conclusion

The 5-(3,4-methylenedioxyphenyl)-2,4-pentadienoic acid derivatives (Piperic acid derivatives) have been synthesized by reaction of Piperic acid with appropriated selected amines in the presence of EDC.HCl/HOBT as coupling agent and these were structurally characterized by spectroscopic method. All the newly synthesized compounds were evaluated for antibacterial and cytotoxicity studies. The outcomes supported that the compounds could exhibit excellent antibacterial and cytotoxicity activities. We conclude that the synthesized derivatives were superior to piperine with respect to both cytotoxicity and antibacterial activity. Further investigation on these studies will route a way for the synthesis of cost effective drug with less side effects. Through research work was needed to be done on this potential synthesis way which may yield many bio-active compounds.

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