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Synthesis, Characterization and Biological Activity of Novel Podophyllotoxin Bearing Pyrimidine Moieties

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ABSTRACT

Podophyllotoxin, a naturally occurring aryl tetralin-type lignan obtained from Podophyllin, an ethanolic extract of Podophyllum peltatum L.(syn.P.hexandnum Royle), exhibits marked biological activity as strong antineoplastic drugs and antiviral agents. Chemical transformations performed on podophyllotoxin resulted in analogs which also display potent cytotoxic, antiviral, and immunosuppressive activities. At present, ten novel compounds of podophyllotoxin bearing pyrimidine moieties were synthesized and characterized by 1H and 13C-NMR, elemental analysis, and Mass spectroscopy. All the synthesized compounds were tested for antimicrobial activities.

Keywords: Podophyllotoxin; 4,6-dimethoxy-2-methylsulphonyl pyrimidine; Antimicrobial activity; Mass spectroscopy; immunosuppressive activities

INTRODUCTION

Natural products of the lignan family comprises molecules with main antiviral and antineoplastic behavior belongs to a distinct group of Natural Products like podophyllotoxin and also etoposide and teniposide which are semisynthetic derivatives of podophyllotoxin that are derived as secondary metabolites via the shikimic acid route which are widely disseminated all over the plant kingdom. Owing to the biological activities, cyclolignans and lignans have become the objective of innumerable studies concentrated in preparing safer and better anticancer drugs. Podophyllotoxin (shortened as PPT), is a non-alkaloid toxin lignin also known as podofilox, procured from the roots and rhizomes of *Podophyllum* genus. PPT are incorporated in a broad range of cancer chemotherapy protocol. PPT is also used as a topical gel, which have found applications in treating the external genital warts, occurred by Human Papilloma Virus (HPV). PPT and its derivatives exhibit a broad array in medicinal use for-instance vesicant, purgative, antiviral, anti-rheumatic and antitumor agents. These derivatives comprise teniposide, etopophos, and etoposide, and the anticancer activity of these derivatives has been extensively studied and employed in numerous chemotherapies which includes genital tumors, lymphomas, and lung cancer. PPT is found to appear in the concentration range of 0.3% to 1.0% by mass in the rhizome of *Podophyllum peltatum* (American Mayapple). Another familiar source of PPT is the rhizomes of *Podophyllum hexandrum* Royle (Berberidaceae). PPT is produced biologically from the phenolic oxidative reaction of two molecules of coniferyl alcohol followed by a sequence of oxidations, reductions and methylations. PPT structure was first elucidated in the 1930's. It possess four successive chiral centers, named C-1 through C-4 (Figures 1 and 2) [1].

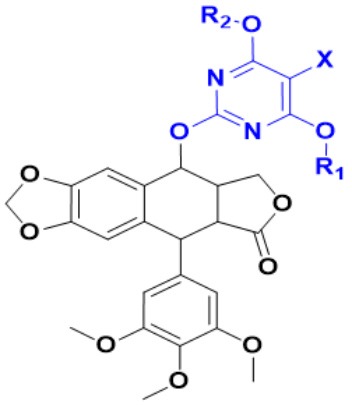

Figure 1. Pyrimidine bearing podophyllotixin derivatives

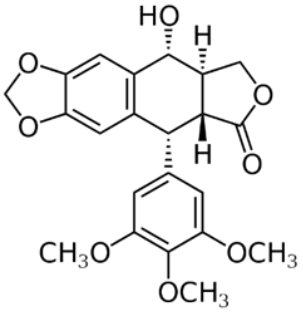

Figure 2. Podophyllotoxin

Importance of Podophyllotoxin Derivatives

PPT exhibits commanding cytotoxic activity against numerous cancer cell lines. It is potent in the treatment of non-Hodgkin's, different genital tumors, and lung cancer, Wilms tumors, lymphomas [2]. In spite of that, due its acute gastrointestinal and increased toxicity side effects of podophyllotoxin have restricted its uses as a drug in cancer chemotherapy. Substantial research has been carried out pertaining to the structural modifications resulting in several less toxic as well as more potent anticancer agents [3]. The semi synthetic podophyllotoxin derivatives such as teniposide and etoposide are presently employed in the chemotherapy for a wide array of malignancies which includes soft tissue sarcoma, small-cell lung cancer, germ-cell malignancy, leukemia, Kaposi's sarcoma, neuroblastoma, and non-Hodgkin's lymphoma (Figure 3) [4].

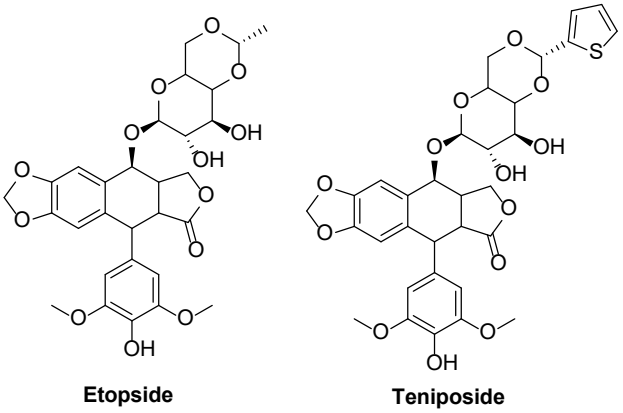

Figure 3. Structures of etopside and teniposide

Even though etoposide is extensively used in therapy [5], it poses several hindrances, like drug resistant, toxic effects metabolic inactivation, poor water insolubility, and moderate potency [6]. Henceforth, etoposide structure has been greatly modified, thereby improving the details about its structure-activity connections. The paramount structure alteration is the substitution in the 4-beta position resulting to a strong inhibitor of topoisomerase II [7]. Incorporation of heteroatom (N, O, or S) to the C-4 sugar unit of etoposide resolved the drug resistance to etoposide [8]. In recent years new methodologies are under study in finding the synthetic route of podophyllotoxin derivatives with reduced toxicity and enhanced bioactivities [9].

MATERIALS AND METHODS

Materials and Techniques

All the synthesized compounds were characterized by the following instruments. The FT-IR was recorded in the spectrophotometer -Avtar 370. Buchi melting point (m.p) device was utilized to record the melting points (m.p) of the synthesized and were uncorrected. The final compounds structures

were confirmed by ^{1}H NMR spectroscopy conducted on VARIAN (400 MHz) instrument (in DMSO solvent) and the chemical shifts were recorded in ppm relative to TMS as an internal reference. ^{13}C NMR (100 MHz) and mass spectroscopies were carried for the confirmation of molecular structure and purity [10]. Column chromatography was done with Merck silica gel of 60 mesh size. Aluminum sheets pre coated with silica gel 60 F254 (Merck) were utilized for Thin-Layer Chromatography (TLC) and it was additionally affirmed by elemental analysis utilizing a LECO Truspec CHN(S) analyzer [11]. All the chemicals except PPT were procured from commercial supplies and were utilized as such without any further filtration. Starting material PPT was borrowed from Prof. Walter J. Gensler, Boston University U.S.A and methylsulfonyl pyrimidine derivatives were procured from Merck pharmaceutical company [12].

General procedure for the coupling of podophyllotoxin and methylsulfonyl pyrimidine derivatives

Podophyllotoxin taken in THF cooled to 0°C, and then slowly 2 equivalent of sodium hydride is added to it and stirred for 15 minutes. Then 1 equivalent of methyl sulfonyl pyrimidine derivative added and stirred at same temp for 1 hour and slowly allowed it to come to RT during the span of 3 hours [13]. Then TLC checked for the disappearance of starting material, after completion of the reaction RM quenched into water and extricated with ethyl acetate and passed through the column using 10%-15% ethyl acetate in hexane to get the pure product [14].

Antibacterial activity of podophyllotoxin bearing pyrimidine compounds

The new compounds 2 (a-l) were appraised for their antimicrobial activity against gram-negative *Escherichia coli*, gram positive *Bacillus subtilis*, gram-negative *Salmonella typhi* and gram positive *Staphylococcus aureus* bacteria were used. At two concentrations of 1 mg/ml and 10 mg/ml, amoxicillin and ciprofloxacin were employed as standard drugs [15]. Using Itraconazole as a reference drug the antifungal activity profile was determined against *Candida albicans.*

The viability of new derivatives was determined by estimating the diameter of the inhibition zone produced around the well. Minimal Bacterial Concentration (MBC)/Minimal Fungicidal Concentration (MFC), and Minimum Inhibition Concentration (MIC) on agar plates were determined after incubation for 24 h. The MIC and MBC/MFC values were considered as the mean of three replicates. The method was followed in accordance to the NCCLS, 1993 by using SDA media and Petri plates containing 25 ml NA agar for antifungal and antibacterial activity respectively [16].

Procedure for antimicrobial activity

The test wells were filled with different volume of the stock solution of the test material and the control well was filled with the same amount of the solvent *i.e.,* DMSO and a positive control. The range of volume of test solution was 1µl-100 µl. These plates were then incubated at 37°C overnight. After 24 h an inhibition zone was formed in each plate around the holes and was measured as zone of inhibition in mm. The assay was repeated twice. A control test was carried consisting of inoculated broth with DMSO at the same dilutions used in the experiments and found to be inactive in culture medium, which proved that the solvent phase had no contribution on bacteria or yeast growth [17]. It was evident that MIC was found to be the lowest concentration of inhibitor at which bacterial growth was visually not noticeable. The antimicrobial results were correlated with ciprofloxacin and amoxicillin and as positive controls and are summarized in Tables 1 and 2.

RESULTS AND DISCUSSION

Our early investigations and literature findings have displayed that N-linked derivatives of podophyllotoxin are proved to be of lower bioavailability contrast to O-linked congeners. These findings have driven us to foster new derivatives of podophyllotoxin that have favorable antibacterial activity. In accordance with the details on structure action relationship studies and development of primarily changed podophyllotoxin congeners, we herein report the structure activity relationships and synthesis of a series of PPT derivatives bearing pyrimidine moieties [18].

Discussion on the Synthesis of Podophyllotoxin Bearing Pyrimidine Moieties

Literature work reveals that many derivatives prepared by modifying the alcoholic group in podophyllotoxin showed enhanced activity than podophyllotoxin itself. Rai et al., showed that 4-amino-β-apopicropodophyllin is more antimitotic activity than podophyllotoxin. For instance, etopside and teniposide were carbohydrate derivatives of podophyllotoxin clinically used as antileukaemic agent [19]. Kamal Ahmed et al., reported the synthesis of 4β-N-Polyaromatic substituted podophyllotoxins by reaction of podophyllotoxin and aromatic amine in presence of sodium iodide and BF_3 etherate. Ahmed Kamal also reported the synthesis of 4β-carbomoyl epipodophyllotoxins by reacting podophyllotoxin with amines in presence of 4-nitro phenyl chloroformate showed that all are potent reagent than podophyllotoxin. Ying-Qian Liu reported the synthesis of pyridine acid ester derivatives of PPT and 4'-demethylepipodophylloptoxin by reacting the respective pyridine acids with the hydroxyl group of PPT which showed better cytotoxic activity. This prompted us to modify the hydroxyl group in podophyllotoxin to O-substituted derivatives by treating it with 2-methyl sulphonyl pyrimidines and check for their activity [20].

Plan of synthesis

Reaction of podophyllotoxin with 2-methylsulphonyl pyrimidines in the presence of solvent and base to form podophyllotoxin bearing pyrimidine moieties (Figure 4).

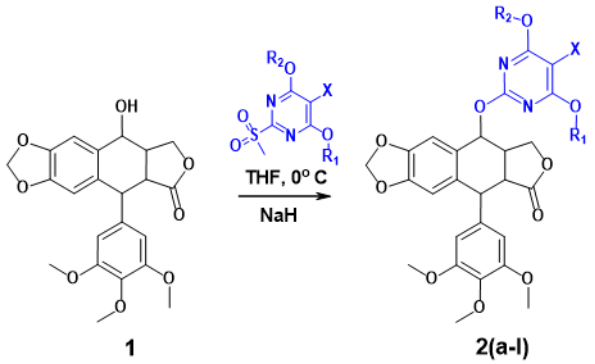

Figure 4. Synthesis of podophyllotoxin bearing pyrimidine moiety

2a	R_1	CH_3	R_2	CH_3	X	-
2b	R_1	C_2H_5	R_2	C_2H_5	X	-
2c	R_1	CH_3	R_2	CH_3	X	Cl
2d	R_1	CH_3	R_2	CH_3	X	Br
2e	R_1	C_2H_5	R_2	C_2H_5	X	Cl
2f	R_1	C_2H_5	R_2	C_2H_5	X	Br
2g	R_1	C_3H_7	R_2	C_3H_7	X	Cl
2h	R_1	C_3H_7	R_2	C_3H_7	X	Br
2i	R_1	$(CH_3)_2$-CH	R_2	$(CH_3)_2$-CH	X	Cl
2j	R_1	$(CH_3)_2$-CH	R_2	$(CH_3)_2$-CH	X	Br
2k	R_1	CH_3	R_2	C_2H_5	X	Cl
2l	R_1	CH_3	R_2	C_2H_5	X	Br

The isolated products are characterized by IR, Mass spectroscopy, ^{1}H NMR, ^{13}C-NMR, HRMS data, and elemental analysis. The IR spectrum of products showed new peaks at 700-800 cm^{-1} due to C-halogen frequency substantiate the formation of these products. IR spectra showed frequencies in the range of 1300–1000 cm^{-1} due to C-O group and 1200-1380 cm^{-1} due to C=N group. The ^{1}H NMR showed the disappearance of SO_2Me proton peaks at δ3.3 confirms the final products formation. The ^{13}C-NMR spectra of the compounds showed signals in the expected region. The HRMS spectra's of all the final synthesized compounds showed molecular ion peaks which were in accord to their molecular weight Thereby, all the characterizations carried out supported the structures of newly synthesized molecules 1a-l. The formation of product was further supported by correct elemental analysis. The antimicrobial property of newly synthesized compounds 1a-l were assessed and compiled in Tables 1 and 2.

9-((4,6-dimethoxypyrimidin-2-yl)oxy)-5-(3,4,5-trimethoxyphenyl)-5,5a,8a,9-tetrahydrofuro(3',4':6,7)naphtha(2,3-d)(1,3)dioxol-6(8H)-one; 2a (Podophyllotoxin and 4,6-dimethoxy-2-methylsulphonyl pyrimidine)
White solid. yield 1.15 g (85%), mp 192°C-193°C; IR (KBr) cm^{-1} 3019, 2240, 1587, 1497, 1298. ^{1}H NMR (DMSO-d6); 2.74 (d, 1H), 3.23 (m, 1H), 3.79 (s, 6H), 3.85 (s, 9H), 4.11 (d,1H), 4.41 (d,1H), 4.43 (d,1H), 4.51 (d, 1H), 5.92 (s, 2H), 6.10(s, 1H), 6.53 (s, 2H), 7.26 (s, 2H); ^{13}C NMR (DMSO-d6) 29.2, 55.5, 71.2, 93.3, 101.3, 101.5, 125.4, 125.7, 127.8, 139.7, 143.5, 167.5, 173.7. ESI-MS: m/z 553.17 $(M+H)^+$; analysis calculated for $C_{28}H_{28}N_2O_{10}$: C, 60.87; H, 5.11; N, 5.07; O, 28.96. Found: C, 61.37; H, 4.95; N, 5.52; O, 28.15.

9-((4,6-diethoxypyrimidin-2-yl)oxy)-5-(3,4,5-trimethoxyphenyl)-5,5a,8a,9-tetrahydrofuro(3',4':6,7)naphtha(2,3-d)(1,3)dioxol-6(8H)-one; 2b (Podophyllotoxin and 4,6-diethoxy-2-methylsulphonyl pyrimidine)
White solid. yield 1.20 g (88.7%), mp 195-196°C; IR (KBr) cm^{-1} 3019, 2246, 1580, 1497, 1298. ^{1}H NMR (DMSO-d6); 1.29 (s, 6H), 3.34 (s, 9H), 4.16 (d, 2H), 4.29 (m, 4H), 4.46 (m, 4H), 5.92 (s, 2H), 6.10 (s, 1H), 6.53 (s, 2H), 7.26 (s, 2H); ^{13}C NMR (DMSO-d6) 29.2, 55.5, 71.2, 93.3, 101.3, 101.5, 125.4, 125.7, 127.8, 139.7, 143.5, 167.5, 173.7. ESI-MS: m/z 581.21 $(M+H)^+$; analysis calculated for $C_{30}H_{32}N_2O_{10}$:C, 62.06; H, 5.56; N, 4.83; O, 27.56. Found: C, 61.43; H, 5.85; N, 3.92; O, 26.02.

9-((5-chloro-4,6-dimethoxypyrimidin-2-yl)oxy)-5-(3,4,5-trimethoxyphenyl)-5,5a,8a,9-tetrahydrofuro(3',4':6,7)naphtha(2,3-d)(1,3)dioxol-6(8H)-one; 2c (Podophyllotoxin and 5-chloro-4,6-dimethoxy-2-methylsulphonyl pyrimidine)
White solid. yield 1.15 g (85%), mp 190°C-191°C; IR (KBr) cm^{-1} 3019, 2246, 1580, 1497, 1298. ^{1}H NMR (DMSO-d6); 2.74 (d, 1H), 3.23 (m, 1H), 3.79 (s, 6H), 3.85 (s, 9H), 4.11 (d,1H), 4.41 (d,1H), 4.43 (d,1H), 4.51 (d, 1H), 5.92 (s, 2H), 6.10(s, 1H), 6.53 (s, 2H), 7.26 (s, 2H); ^{13}C NMR (DMSO-d6) 38.70, 45.12, 53.62, 56.09, 56.12, 69.0, 77.36, 82.62, 101.21, 106.4, 109.6, 130.9, 136.7, 146.1, 153.4, 153.47, 159.4, 173.5, 175.66. ESI-MS: m/z 587.97 $(M+H)^+$; analysis calculated for $C_{28}H_{27}ClN_2O_{10}$: C, 57.29; H, 4.64; Cl, 6.04; N, 4.77; O, 27.26. Found: C, 58.43; H, 4.85; Cl, 6.50; N, 4.92; O, 27.50.

9-((5-bromo-4,6-dimethoxypyrimidin-2-yl)oxy)-5-(3,4,5-trimethoxyphenyl)-5,5a,8a,9-tetrahydrofuro(3',4':6,7)naphtha(2,3-d)(1,3)dioxol-6(8H)-one; 2d (Podophyllotoxin and 5-bromo-4,6-dimethoxy-2-methylsulphonyl pyrimidine)
White solid. yield 1.25 g (95%), mp 184°C–185°C; IR (KBr) cm^{-1} 3019, 2246, 1580, 1497, 1298. ^{1}H NMR (DMSO-d6); 2.74 (d, 1H), 3.23 (m, 1H), 3.79 (s, 6H), 3.85 (s, 9H), 4.11 (d, 1H), 4.41 (d, 1H), 4.43 (d, 1H), 4.51 (d, 1H), 5.92 (s, 2H), 6.10(s, 1H), 6.53 (s, 2H), 7.26 (s, 2H); ^{13}C NMR (DMSO-d6) 38.70, 45.12, 53.62, 56.09, 56.12, 69.0, 77.36, 82.62, 101.21, 106.4, 109.6, 130.9, 136.7, 146.1, 153.4, 153.47, 159.4, 173.5, 175.66. ESI-MS: m/z 631.08 $(M+H)^+$; analysis calculated for $C_{28}H_{27}BrN_2O_{10}$: C, 53.26; H, 4.31; Br, 12.65; N, 4.44; O, 25.34. Found: C, 54.43; H, 4.85; Br 12.50; N, 4.92; O, 24.50.

Figure 4 shows the synthesis of the target molecule. All the examined molecules exhibited modest to exceptional behavior against both gram-positive bacteria (*Bacillus Subtilis* and *Staphylococcus aureus*) and gram-negative bacteria (*Escherichia coli* and *Salmonella Typhi*). The antibiotics *Itraconazole* and *Ciprofloxacin* were used as standard antifungal and antibacterial agents respectively. Amidst the tested compounds, 1e, 1f, 1g, 1h, 1i and 1j displayed exceptional antimicrobial activity in different concentrations owing to the presence of alkoxy groups and electron-withdrawing -Cl, -Br groups. Compound 1i showed enhanced antibacterial and antifungal agent among all the examined molecules.

Table 1. Antibacterial activity of synthesized compounds 1a-f based on the zone of inhibition (mm/mg sample)

Compounds			**Antibacterial activity**		**Antifungal activity**
	Gram-positive		**Gram-negative**		
	S. aureaus	***B. subtilis***	***E. coli***	***S. typhi***	***C. albicans***

	1 mg/mL ± SD	10 mg/mL ± SD	1 mg/mL ± SD	10 mg/mL ± SD	1 mg/mL ± SD	10 mg/mL ± SD	1 mg/mL ± SD	10 mg/mL ± SD	1 mg/mL ± SD	10 mg/mL ± SD
1a	15 ± 0.27	17 ± 0.12	19 ± 0.21	10 ± 0.19	11 ± 0.21	21 ± 0.19	19 ± 0.20	12 ± 0.10	18 ± 0.10	21 ± 0.13
1b	19 ± 0.17	18 ± 0.9	20 ± 0.25	18 ± 0.09	19 ± 0.11	20 ± 0.17	18 ± 0.12	20 ± 0.14	11 ± 0.13	14 ± 0.23
1c	19 ± 0.15	14 ± 0.20	16 ± 0.29	15 ± 0.21	21 ± 0.25	14 ± 0.15	12 ± 0.14	16 ± 0.15	19 ± 0.13	15 ± 0.25
1d	11 ± 0.27	15 ± 0.27	15 ± 0.29	17 ± 0.13	13 ± 0.16	19 ± 0.27	18 ± 0.22	15 ± 0.12	19 ± 0.15	18 ± 0.12
1e	13 ± 0.13	10 ± 0.29	13 ± 0.27	12 ± 0.13	10 ± 0.07	09 ± 0.15	10 ± 0.09	12 ± 0.07	12 ± 0.17	13 ± 0.11
1f	10 ± 0.12	12 ± 0.88	12 ± 0.29	10 ± 0.07	12 ± 0.03	12 ± 0.27	13 ± 0.23	10 ± 0.20	09 ± 0.10	12 ± 0.13
1g	11 ± 0.12	10 ± 0.88	11 ± 0.21	15 ± 0.11	13 ± 0.13	13 ± 0.20	14 ± 0.25	13 ± 0.05	10 ± 0.10	11 ± 0.10
1h	13 ± 0.13	11 ± 0.21	11 ± 0.29	12 ± 0.09	11 ± 0.19	09 ± 0.12	12 ± 0.24	13 ± 0.23	12 ± 0.11	08 ± 0.30
1i	12 ± 0.16	10 ± 0.17	12 ± 0.30	10 ± 0.16	08 ± 0.02	13 ± 0.15	12 ± 0.10	13 ± 0.24	08 ± 0.12	12 ± 0.19
1j	13 ± 0.17	08 ± 0.29	10 ± 0.11	12 ± 0.20	10 ± 0.21	12 ± 0.10	11 ± 0.11	12 ± 0.04	13 ± 0.15	08 ± 0.13
1k	14 ± 0.17	21 ± 0.12	18 ± 0.19	19 ± 0.13	30 ± 0.21	18 ± 0.11	19 ± 0.09	21 ± 0.10	25 ± 0.18	15 ± 0.28
1l	19 ± 0.17	23 ± 0.16	25 ± 0.11	16 ± 0.17	20 ± 0.18	19 ± 0.13	18 ± 0.17	21 ± 0.30	25 ± 0.13	14 ± 0.09
Ciprofloxacin	25 ± 0.17	11 ± 0.29	15 ± 0.09	10 ± 0.18	19 ± 0.20	15 ± 0.09	10 ± 0.06	17 ± 0.20	17 ± 0.21	19 ± 0.24
Itraconazole	--	--	--	--	--	--	--	--	19 ± 0.17	14 ± 0.17

Table 2. The Minimal Inhibitory Concentration (MIC), Minimal Bactericidal Concentration (MBC), and Minimal Fungicidal Concentration (MFC) in mg/mL of compounds 1a-l

Compounds					**Antibacterial activity**				**Antifungal Activity**	
	Gram-positive				**Gram-negative**					
	S. aureaus		***B. subtilis***		***E. coli***		***S. typhi***		***C. albicans***	
	1 mg/mL ± SD	10 mg/mL ± SD	1 mg/mL ± SD	10 mg/mL ± SD	1 mg/mL ± SD	10 mg/mL ± SD	1 mg/mL ± SD	10 mg/mL ± SD	1 mg/mL ± SD	10 mg/mL ± SD
1a	50	255	50	220	50	245	45	230	50	250
1b	50	255	35	140	45	210	50	220	50	255
1c	50	220	50	250	200	220	50	240	25	120
1d	25	125	50	255	50	230	100	220	30	50
1e	20	125	30	150	20	125	30	120	25	120
1f	25	130	25	125	30	135	30	125	30	120
1g	35	145	25	155	30	150	25	100	20	120
1h	20	125	20	120	20	120	30	120	25	120
1i	30	120	20	125	25	135	30	125	25	130
1j	10	110	30	120	20	120	20	125	25	120
1k	200	350	200	285	200	320	200	250	25	130
1l	400	550	400	290	800	450	800	290	30	70
Ciprofloxacin	10	105	15	110	15	130	9	110	--	--
Itraconazole	--	--	--	--	--	--	--	--	20	110

CONCLUSION

In summary, a simple and convenient procedures were employed to synthesize all the 12 podophyllotoxin bearing pyrimidine moieties in moderate to good yields. The final prepared molecules were characterized by different spectroscopic techniques. The antimicrobial activity of the synthesized compounds convinced that the podophyllotoxin bearing pyrimidine moieties proved to be potent against both fungal and bacterial strains with MIC values ranging from 15 mg/mL to 20 mg/mL and compound 1i exhibited pronounced effect. Therefore, synthesized compounds can be used as a potential lead for the design of new antibacterial agents and there is a future scope of characterizing its anti-leukemic, anti-inflammatory properties too.

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