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Research article

Synthesis and screening of antimicrobial and antioxidant activities of *4-(1-alkylindol-3-yl)-6-(substituted phenyl) pyrimidin-2-ol* derivatives

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ABSTRACT

In seek of effectual antimicrobial and antioxidant agents, a sequence of novel derivatives of indole clubbed with pyrimidine were synthesized. The synthesized derivatives were distinguished by different technique such as IR, ^{13}C NMR, ^{1}H NMR, and Mass spectroscopy. The antimicrobial evaluation of (1-20) was done by tube dilution method against both gram (+) and gram (-) bacteria. The Gram-positive bacteria were Bacillus subtilis and Staphylococcus aureus and Gram-negative strains were Escherichia coli and Pseudomonas aeruginosa. Candida albicans and Aspergillus Niger were used for antifungal activities. Compounds 13, 14, 15, 16 and 19 exhibited promising results of antimicrobial activity with their different MIC values. The potential of the synthesized compounds was also determined by their antioxidant activity by 2, 2-diphenylpicrylhydrazyl method. Antioxidant screening results found compounds 14 and 16 to be the most active compounds.

Keywords: Synthesis, Antibacterial Activity, Antifungal Activity, Antioxidant activity, Indoles.

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INTRODUCTION

Appearance of multi-drug obstructive bacteria such as MRSA (methicillin-resistant Staphylococcus aureus) or vancomycin-aversion enterococci is reported worldwide. Antimicrobial drug confrontation is a likely event and it is intensifying by less than an excess use of antimicrobials. Further the repeated use of therapeutic drugs increases the number of hospitals acquired infections especially in immuno-compromised patients in which incidence of Candida infections increasing more commonly. Therefore, novel antibacterial and antifungal therapies are immediately requested. This is the motive why it seems essential to inspect new antimicrobial amalgams with new working of action, to conquer antimicrobial conflict and to build up efficient cures. [1]

Antioxidant moves as a tool to defend the body in opposition to oxidative tension. Antioxidants reduce deteriorating disorder such as cancers and cardiovascular diseases by confining liberated radicals. Antioxidants shield biological prey from oxidative harm by reacting with radicals and other reactive species faster than biological substrates [2, 3]. Furthermore, the emerging antioxidant essential must own a high solidity, that is, the antioxidant radical must break off a chain reaction. Certain indole derivatives have been found to possess antioxidant activity. [4]

The indole offshoots have been appeared as the drugs of vast significance in the current epoch and famous for their momentous biological tricks such as, anti-inflammatory, antidiabetic, antimicrobial and cytotoxic behavior. Indole derivatives have gained enormous attention because of their considerable biological activities including antimicrobial [5], anti-inflammatory [6], anticancer [7], anti-HIV [8], antidiabetic [9], antiviral [10], antioxidant [11], antitubercular [12] and antimalarial activities. [13]

In viewpoint of above details, the existing learns we have intended to manufacture the novel derivatives of indole clubbed with pyrimidine and evaluate their antimicrobial and antioxidant activity.

MATERIALS AND METHODS

Procedure of the synthesis of compounds (1-20)

Step A: Universal method for the creation of 1-alkylindole-3-carbaldehyde (Int.-I)

Indole-3-carboxaldehyde (0.02mol), alkyliodide (0.02 mol), sodium hydride (catalyst) & DMF (15 ml) were refluxed for 2-3 hours Completion of the reaction was checked by TLC. Then, the fillings were poured on crushed ice. The resolute was decanted, dehydrated and re-crystallized by ethanol. [14]

Step B: General procedure for the synthesis of 3-(1-alkylindol-3-yl)-1-(substituted phenyl) prop-2-en-1-one (Int.-II)

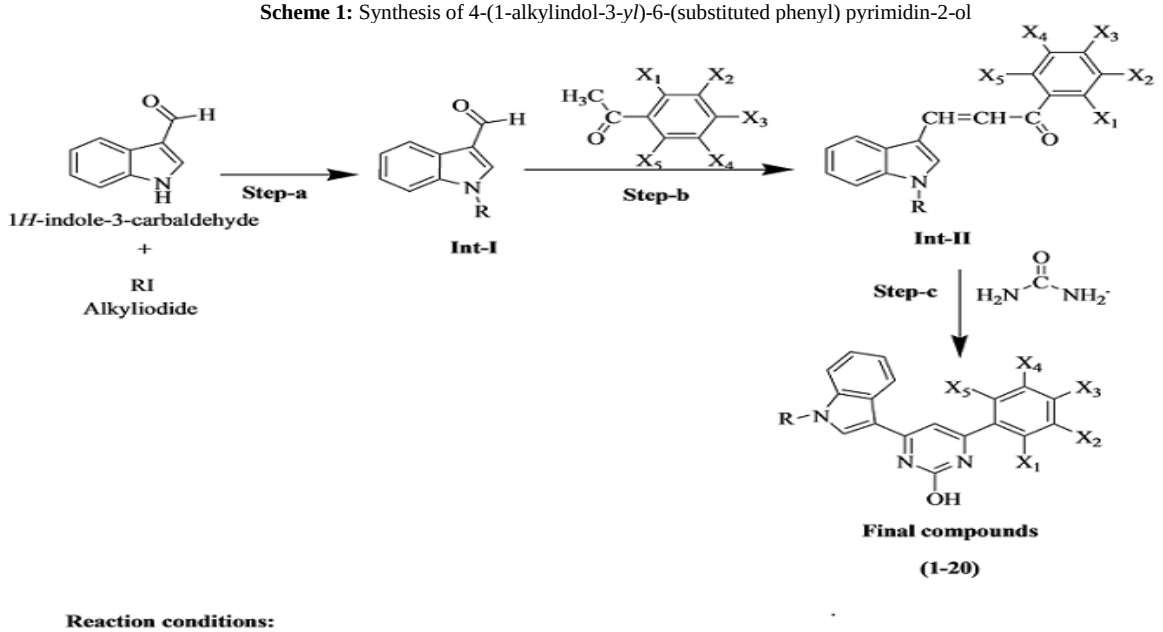
The reaction mixture of 1-alkylindole-3-carbaldehyde (0.01 mol) and substituted acetophenones (0.01 mol) were vibrated for 8-9 hours in ethanol (15–20 ml). After that sodium hydroxide solution

(10 ml of 40%) was added in drops with regular stirring at room temperature. Then reaction mixture was placed at room temperature for a night. After that it was streamed into snow icy water and acidified with hydrochloric acid. The substituted chalcone was precipitated. The solid was decanted, desiccated and re-crystallized from ethanol. [15]

Step C: General procedure for the synthesis of4-(1-alkylindol-3-yl)-6-(substituted phenyl) pyrimidin-2-ol (1-20)

A mixture of 3-(1-alkylindol-3-yl)-1-(substituted phenyl) prop-2-en-1-one (0.01 mol) liquefied in ethanol (25 mL), urea (0.01 mol) and solution of KOH (1-2 mL) was affixed and refluxed for 10-12 hours. Completions of the reaction were monitored by TLC. The reaction blend was chilled after that poured into crushed ice. The product was filtered and washed with water. The product was dried and re-crystallized from alcohol. [15]

Scheme 1: Synthesis of 4-(1-alkylindol-3-*yl*)-6-(substituted phenyl) pyrimidin-2-ol



Reaction conditions:
Step-a: NaH 60% ascatalyst, DMF as solvent, Reflux 2-3hr, **Step-b:** NaOH 40%,C_2H_5OH as solvent, Stirred 8-9hr, **Step-c:** KOH,C_2H_5OH, Reflux 10-12h

Table 1: The physicochemical properties of synthesized 4-(1-alkylindol-3-yl)-6-(substituted phenyl) pyrimidin-2-ol derivatives (1-20)

Comp.	R	X_1	X_2	X_3	X_4	X_5	M. Formula	M. Wt.	m.p. (^{0}C)	R_f *Value**	% Yield
1	CH_3	OH	H	H	H	H	$C_{19}H_{15}N_3O_2$	317.34	148-150	0.76	78.5
2	CH_3	H	OH	H	H	H	$C_{19}H_{15}N_3O_2$	317.34	143-145	0.72	61.5
3	CH_3	H	H	OH	H	H	$C_{19}H_{15}N_3O_2$	317.34	140-142	0.65	70.1
4	CH_3	H	NH_2	H	H	H	$C_{19}H_{16}N_4O$	316.36	110-112	0.64	65.7
5	CH_3	H	H	NH_2	H	H	$C_{19}H_{16}N_4O$	316.36	103-105	0.61	62.2
6	CH_3	H	NO_2	H	H	H	$C_{19}H_{14}N_4O_3$	346.34	115-117	0.75	51.9
7	CH_3	H	H	NO_2	H	H	$C_{19}H_{14}N_4O_3$	346.34	108-110	0.61	56.4
8	CH_3	Cl	H	H	H	H	$C_{19}H_{14}ClN_3O$	335.79	98-100	0.82	67.8
9	CH_3	H	H	Br	H	H	$C_{19}H_{14}BrN_3O$	380.24	95-97	0.78	69.5
10	CH_3	H	H	H	H	H	$C_{19}H_{15}N_3O$	301.34	119-121	0.81	72.3
11	C_2H_5	OH	H	H	H	H	$C_{20}H_{17}N_3O_2$	331.37	118-120	0.46	66.19
12	C_2H_5	H	OH	H	H	H	$C_{20}H_{17}N_3O_2$	331.37	108-110	0.45	81.23
13	C_2H_5	H	H	OH	H	H	$C_{20}H_{17}N_3O_2$	331.37	115-117	0.76	72.13
14	C_2H_5	H	NH_2	H	H	H	$C_{20}H_{18}N_4O$	330.38	73-75	0.54	76.88
15	C_2H_5	H	H	NH_2	H	H	$C_{20}H_{18}N_4O$	330.38	87-89	0.75	90.34
16	C_2H_5	H	NO_2	H	H	H	$C_{20}H_{16}N_4O_3$	360.37	106-108	0.45	78.56
17	C_2H_5	H	H	NO_2	H	H	$C_{20}H_{16}N_4O_3$	360.37	101-103	0.75	81.33
18	C_2H_5	Cl	H	H	H	H	$C_{20}H_{16}ClN_3O$	349.81	78-80	0.67	90.12
19	C_2H_5	H	H	Br	H	H	$C_{20}H_{16}BrN_3O$	394.26	75-77	0.78	65.01
20	C_2H_5	H	H	H	H	H	$C_{20}H_{17}N_3O$	315.37	108-110	0.50	71.12

SPECTRAL DATA

1. 4-(2-hydroxyphenyl)-6-(1-methyl-1*H*-indol-3-yl) pyrimidin-2-ol

IR (KBr, cm^{-1}): 3392 (OH str.), 2928(Ar C-H str.), 1636 (N=CH), 1523 (C=C ring str.), 1393(C-N); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.33-7.40 (m, 9H, ArH), 5.51 (s, 2H, OH), 6.97 (s, 2H, CH_2), 3.91 (s, 3H, N-CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm):164.58, 155.88, 146.71, 133.12, 123.72, 121.82, 116.89, 111.82, 90.10, 66.72; ESI-MS: m/z 322 (M^+ +1).

2. 4-(3-hydroxyphenyl)-6-(1-methyl-1H-indol-3-yl) pyrimidin-2-ol

IR (KBr, cm^{-1}): 3398 (OH str.), 2910(Ar C-H str.), 1636 (N=CH), 1523 (C=C ring str.), 1391 (C-N); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.34-7.44 (m, 9H, ArH), 5.65 (s, 2H, OH), 7.11 (s, 2H, CH_2), 3.69 (s, 3H, N-CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm):166.55, 158.76, 144.22, 135.21, 121.99, 121.81, 118.11, 110.80, 90.12, 62.12; ESI-MS: m/z 321 (M^+ +1).

3. 4-(4-hydroxyphenyl)-6-(1-methyl-1H-indol-3-yl) pyrimidin-2-ol

3386 (OH str.), 2910 (Ar C-H str.), 1636 (N=CH), 1523 (C=C ring str.), 1393 (C-N); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.28-7.46 (m, 9H, ArH), 5.49 (s, 2H, OH), 7.16(s, 2H, CH_2), 3.73 (s, 3H, N-CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm):169.47, 160.75, 154.98, 144.11, 131.95, 120.09, 116.12, 113.06, 92.89, 66.32; ESI-MS: m/z 322 (M^+ +1).

4. 4-(3-aminophenyl)-6-(1-methyl-1*H*-indol-3-yl) pyrimidin-2-ol

IR (KBr, cm^{-1}): 3397 (OH str.), 3043 (NH_2 str.), 2910 (Ar C-H str.), 1617 (N=CH), 1592 (C=C ring str.), 1325 (C-N); ^{1}H NMR (400

MHz, DMSO-d_6, δ ppm):7.30-7.71 (m, 9H, ArH), 5.52 (s, 1H, OH), 7.12 (s, 2H, CH_2), 3.68 (s, 3H, N-CH_3), 4.26 (s, 2H, NH_2); ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm):165.43, 162.23, 156.81, 146.12, 134.44, 124.91, 118.21, 115.21, 90.11, 63.21; MS: m/z 320 (M^+ +1).

5. 4-(4-aminophenyl)-6-(1-methyl-1*H*-indol-3-yl) pyrimidin-2-ol

IR (KBr, cm^{-1}): 3335 (OH str.), 3218 (NH_2 str.), 2922(Ar C-H str.), 1640 (N=CH), 1594 (C=C ring str.), 1358 (C-N); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.33-8.35 (m, 9H, ArH), 4.43 (s, 1H, OH), 7.28 (s, 2H, CH_2), 3.88 (s, 3H, N-CH_3), 3.91 (s, 2H, NH_2); ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm):168.21, 163.22, 160.11, 147.76, 132.41, 122.18, 116.14, 114.99, 91.12, 65.90; MS: m/z 321 (M^+ +1).

6. 4-(1-methyl-1*H*-indol-3-yl)-6-(3-nitrophenyl) pyrimidin-2-ol

IR (KBr, cm^{-1}): 3365 (OH str.), 2862(Ar C-H str.), 1637 (N=CH), 1532 (C=C ring str.), 1382 (NO_2 str.), 1342 (C-N); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.03-7.33(m, 9H, ArH), 4.87 (s, 1H, OH), 6.85 (s, 2H, CH_2), 3.72 (s, 3H, N-CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm):165.76, 164.21, 161.56, 142.61, 137.19, 121.16, 114.45, 110.99, 88.25, 55.07; ESI-MS: m/z 341 (M^+ +1).

7. 4-(1-methyl-1*H*-indol-3-yl)-6-(4-nitrophenyl) pyrimidin-2-ol

IR (KBr, cm^{-1}): 3376 (OH str.), 2916(Ar C-H str.), 1620 (N=CH), 1596 (C=C ring str.), 1356 (NO_2 str.), 1344 (C-N); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.23- 7.33- (m, 9H, ArH), 4.93 (s, 1H, OH), 6.77 (s, 2H, CH_2), 3.76 (s, 3H, N-CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm):167.67, 162.68, 160.00, 152.34, 144.98, 133.10, 121.51, 115.05, 90.20, 53.17; ESI-MS: m/z 342 (M^+ +1).

8. 4-(2-chlorophenyl)-6-(1-methyl-1*H*-indol-3-yl) pyrimidin-2-ol

IR (KBr, cm^{-1}): 3394 (OH str.), 3055(Ar C-H str.), 1617 (N=CH), 1458 (C=C ring str.), 1331 (C-N), 741 (Ar-Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.14-7.59 (m, 9H, ArH), 4.67 (s, 1H, OH), 7.02 (s, 2H, CH_2), 3.73 (s, 3H, N-CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm):162.77, 160.80, 157.56, 151.40, 148.80, 139.67, 128.16, 118.58, 90.90, 52.90; ESI-MS: m/z 341 (M^+ +1).

9. 4-(4-bromophenyl)-6-(1-methyl-1*H*-indol-3-yl) pyrimidin-2-ol

IR (KBr, cm^{-1}): 3371 (OH str.), 3055(Ar C-H str.), 1612 (N=CH), 1542 (C=C ring str.), 1362 (C-N), 646 (Ar-Br); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.13-7.65 (m, 9H, ArH), 4.88 (s, 1H, OH), 7.14 (s, 2H, CH_2), 3.88 (s, 3H, N-CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm):168.76, 166.08, 161.06, 159.60, 155.33, 144.77, 131.68, 128.86, 98.90, 60.12; ESI-MS: m/z 372 (M^+ +1).

10. 4-(1-methyl-1*H*-indol-3-yl)-6-phenylpyrimidin-2-ol

IR (KBr, cm^{-1}): 3168 (OH str.), 2856(Ar C-H str.), 1635 (N=CH), 1439 (C=C ring str.), 1340 (C-N); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.36-8.46 (m, 10H, ArH), 4.41 (s, 1H, OH), 7.18 (s, 2H, CH_2), 3.79 (s, 3H, N-CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm):167.66, 163.55, 160.04, 157.20, 152.54, 149.16, 138.68, 131.86, 90.60, 61.14; ESI-MS: m/z 304 (M^+ +1).

11. 4-(1-ethyl-1*H*-indol-3-yl)-6-(2-hydroxyphenyl) pyrimidin-2-ol

IR (KBr, cm-1): 3398 (OH str.), 2929(Ar C-H str.), 1636 (N=CH), 1520 (C=C ring str.), 1337 (C-N); ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.34-7.38 (m, 9H, ArH), 5.53 (s, 2H, OH), 6.89 (s, 2H, CH_2), 4.24-4.33 [m, 2H, $(CH_2)_1$], 1.57-1.61 [t, 3H, $(CH_3)_2$]; ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 165.89, 162.74, 160.80, 154.37, 133.63, 130.77, 128.82, 115.34, 111.45, 77.35; ESI-MS: m/z 326 (M^+ +1).

12. 4-(1-ethyl-1*H*-indol-3-yl)-6-(3-hydroxyphenyl) pyrimidin-2-ol

IR (KBr, cm-1): 3401 (OH str.), 2928(Ar C-H str.), 1637 (N=CH), 1520 (C=C ring str.), 1391 (C-N); ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.22-7.81 (m, 9H, ArH), 5.61 (s, 2H, OH), 7.10 (s, 2H, CH_2), 4.24-4.28 [m, 2H, $(CH_2)_1$], 1.54-1.60 [t, 3H, $(CH_3)_2$]; ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm):167.23, 164.79, 161.08, 156.61, 136.72, 134.25, 125.83, 118.32, 110.57, 78.70; ESI-MS: m/z 327 (M^+ +1).

13. 4-(1-ethyl-1*H*-indol-3-yl)-6-(4-hydroxyphenyl) pyrimidin-2-ol

IR (KBr, cm-1): 3417 (OH str.), 2910 (Ar C-H str.), 1636 (N=CH), 1523 (C=C ring str.), 1334 (C-N); ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.33-7.39 (m, 9H, ArH), 5.53 (s, 2H, OH), 6.74 (s, 2H, CH_2), 4.21-4.26 [m, 2H, $(CH_2)_1$], 1.56-1.61 [t, 3H, $(CH_3)_2$]; ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 163.11, 161.02, 160.80, 154.48,133.02, 131.46, 123.06, 122.67, 119.81, 76.70; ESI-MS: m/z 327 (M^+ +1).

14. 4-(3-aminophenyl)-6-(1-ethyl-1*H*-indol-3-yl) pyrimidin-2-ol

IR (KBr, cm-1): 3397 (OH str.), 3369 (NH_2 str.), 2928 (Ar C-H str.), 1617 (N=CH), 1451 (C=C ring str.), 1325 (C-N); ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.21- 7.54 (m, 9H, ArH), 5.02 (s, 1H, OH), 7.13 (s, 2H, CH_2), 3.81 (s, 2H, NH_2). 4.20-4.29 [m, 2H, $(CH_2)_1$], 1.51-1.53 [t, 3H, $(CH_3)_2$]; ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm):167.43, 164.43, 155.03, 137.62, 132.87, 123.06, 122.02, 119.78, 79.43; ESI-MS: m/z 325 (M^+ +1).

15. 4-(4-aminophenyl)-6-(1-ethyl-1*H*-indol-3-yl) pyrimidin-2-ol

IR (KBr, cm-1): 3367 (OH str.), 3218 (NH_2 str.), 2928(Ar C-H str.), 1654 (N=CH), 1454 (C=C ring str.), 1358 (C-N); ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.24-7.37 (m, 9H, ArH), 5.51 (s, 1H, OH), 6.89 (s, 2H, CH_2), 3.71 (s, 2H, NH_2). 4.24-4.28 [m, 2H, $(CH_2)_1$], 1.54-1.60 [t, 3H, $(CH_3)_2$]; ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 165.34, 161.03, 153.07, 138.85, 134.49, 125.81, 121.63, 111.48, 75.02; ESI-MS: m/z 327 (M^+ +1).

16. 4-(1-ethyl-1*H*-indol-3-yl)-6-(3-nitrophenyl) pyrimidin-2-ol

IR (KBr, cm-1): 3216 (OH str.), 2934(Ar C-H str.), 1637 (N=CH), 1527 (C=C ring str.), 1358 (NO_2 str.), 1342 (C-N); ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 8.44-8.47 (m, 9H, ArH), 4.50 (s, 1H, OH), 6.89 (s, 2H, CH_2), 4.24-4.35 [m, 2H, $(CH_2)_1$], 1.44-1.48 [t, 3H, $(CH_3)_2$]; ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 165.16, 163.78, 161.48, 150.79, 146.03, 135.27, 126.28, 120.33, 111.94, 89.03; ESI-MS: m/z 364 (M^+ +1) .

17. 4-(1-ethyl-1*H*-indol-3-yl)-6-(4-nitrophenyl) pyrimidin-2-ol

IR (KBr, cm-1): 3376 (OH str.), 2910 (Ar C-H str.), 1620 (N=CH), 1594 (C=C ring str.), 1356 (NO_2 str.); 1348 (C-N), ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.69-7.75 (m, 9H, ArH), 4.46 (s, 1H, OH), 7.02 (s, 2H, CH_2), 4.24-4.28 [m, 2H, $(CH_2)_1$], 1.54-1.60 [t, 3H, $(CH_3)_2$]; ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 169.90, 167.42, 163.26, 154.33, 150.17, 133.01, 131.53, 126.67, 115.72, 90.57; ESI-MS: m/z 365 (M^+ +1).

18. 4-(2-chlorophenyl)-6-(1-ethyl-1*H*-indol-3-yl) pyrimidin-2-ol

IR (KBr, cm-1): 3390 (OH str.), 3055 (Ar C-H str.), 1654 (N=CH), 1448 (C=C ring str.), 1335 (C-N), 742 (Ar-Cl); ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.36-7.40 (m, 9H, ArH), 5.29 (s, 1H, OH), 6.88 (s, 2H, CH_2), 4.22-4.37 [m, 2H, $(CH_2)_1$], 1.41-1.44 [t, 3H, $(CH_3)_2$]; ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 166.52, 160.38, 158.71, 148.03, 133.81, 128.89, 126.14, 76.69; MS: m/z 354 (M^+ +1).

19. 4-(4-bromophenyl)-6-(1-ethyl-1*H*-indol-3-yl) pyrimidin-2-ol

IR (KBr, cm-1): 3432 (OH str.), 3055 (Ar C-H str.), 1641 (N=CH), 1451 (C=C ring str.), 1362 (C-N), 646 (Ar-Br); ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.34-7.40 (m, 9H, ArH), 5.22 (s, 1H, OH), 6.70 (s, 2H, CH_2), 4.01-4.16 [m, 2H, $(CH_2)_1$], 1.52-1.57 [t, 3H, $(CH_3)_2$]; ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 162.82, 159.07, 156.63, 145.51, 138.69, 128.48, 127.07, 77.04; ESI-MS: m/z 399 (M^+ +1).

20. 4-(1-ethyl-1*H*-indol-3-yl)-6-phenylpyrimidin-2-ol

IR (KBr, cm-1): 3386 (OH str.) 2940 (Ar C-H str.), 1636 (N=CH), 1438 (C=C ring str.), 1388 (C-N); ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.33-7.36 (m, 10H, ArH), 5.53 (s, 1H, OH), 6.82 (s, 2H, CH_2), 4.12-4.45 [m, 2H, $(CH_2)_1$], 1.53-1.57 [t, 3H, $(CH_3)_2$]; ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 155.12, 147.03, 135.21, 132.26, 128.54, 124.34, 121.99, 118.06, 111.42, 76.69; ESI-MS: m/z 319 (M^+ +1).

Antimicrobial activity

The antimicrobial prospective of the synthesized compounds was resolved by the turbidimetric approach (tube dilution method). The germ destroying activity was determined

against both Gram-negative and Gram-positive bacteria such as Gram (-) Escherichia coli (MTCC1652), Pseudomonas aeruginosa (MTCC424) and Gram (+) Staphylococcus aureus (MTCC7443), Bacillus subtilis (MTCC441). Norfloxacin as a standard drug used. The fungicide learning was conceded out against fungal strains: Candida albicans (MTCC227) and Aspergillus Niger (MTCC8189). Fluconazole was included as the positive control. Antimicrobial screening results demonstrated that compound 19 (MICsa = 1.58 μM/ml and MICec = 0.79 μM/ml) to exhibit talented action against S. aureus and E. coli. Alternatively, compound 13 was set up most active against B. subtilis (MICbs = 0.94 μM/ml). Compounds 14 and 15 were found to be active against P. aeruginosa (MICpa = 0.94 μM/ml). Antifungal activity fallout verified that compound 16 (MICca = 0.86 μM/ml) and compound 19 (MICan = 0.79 μM/ml) were highly effective against C. albicans and A. Niger, respectively. The consequences of antibacterial and antifungal estimation were spoken as minimal interdictory concentration (MIC) (Table 2).

Antioxidant evaluation

(2, 2-Diphenyl-1-picrylhydrazyl radical scavenging assay) All the synthesized 4-(1-alkylindol-3-yl)-6-(substituted phenyl) pyrimidin-2-ol derivatives were subjected for their in vitro antioxidant activity by 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging method using 0.16 mmol solution of DPPH in methanol [18]. Sample solution was prepared to have different concentrations of 100, 50 and 25 μg/mL. DPPH solution (1ml) was added to the sample solution (1ml) of derivatives of different concentrations. DPPH gives purple color. Then, shake the mixture vigorously. After that, the fusion was incubating in shady for 30 min at room hotness and absorbance was measured by spectrophotometer at a wavelength 517 nm (UV-1800EN240V SOFT, SHIMADZU, FR. Germany). Melatonin was used as reference drug. For blank, mixture of 1ml DMSO and 1ml DPPH used for readings and 2 mL DMSO was used as control. The radical scavenging activity was expressed as IC_{50} values and IC_{50} values is inversely proportional to antioxidant activity and the % inhibition of free radical DPPH was obtained by calculation according to the equation as follows:

Radical scavenging activity% = [(Absorbance of control– Absorbance of sample)/ Absorbance of control] × 100

RESULT AND DISCUSSION

Chemistry

We describe here a convenient approach for the preparation of 4-(1-alkylindol-3-yl)-6-(substituted phenyl) pyrimidin-2-ol (1-20). All composite was made as per to Scheme 1. At the first stage, Indole-3-carboxaldehyde was reacted with alkyliodide to form the 1-alkylindole-3-carbaldehyde (step-a, Int-I). Further reaction of 1-alkylindole-3-carbaldehyde with substituted acetophenones yielded the 3-(1-alkylindol-3-yl)-1-(substituted phenyl) prop-2-en-1-one (step-b, Int-II), which on further with urea and solution of KOH yield the 4-(1-alkylindol-3-yl)-6-(substituted phenyl) pyrimidin-2-ol (1-20). The molecular make-up of the synthesized compounds was established by elemental properties (Table 1) and shadowy uniqueness (IR, Mass spectrum and NMR). The IR spectrum of synthesized compounds was determined by KBr pellet method. IR spectra of all compounds (1-20) showed absorption band at around 3369–3043, 3432-3168, 3055-2910, 1654-1612, 1393-1325, 1382-1356 cm^{-1} regions, conforming the presence of various groups i.e. NH, OH, Ar C-H, N=CH, C–N, NO_2 respectively. In ^{1}HNMR characteristic signal were observed at δ 7.28-6.70 (CH_2 of indole), 4.26-3.71(C-NH_2), 5.65-4.41 (C-OH of pyrimidine) confirming the structure of titled compounds.

The antimicrobial movement of the blend combination was achieved by the tube dilution method and outcomes specified that none of the title compounds was originate as superior antimicrobial agent than the typical drugs fluconazole and norfloxacin. Among the synthesized derivatives, compound 13 was establish to be the most effective antimicrobial agent against B. subtilis (MICbs=0.94 μM/ml). Compound 14 and 15 was found to be active against P. aeruginosa (MICpa =0.94 μM/ml). Compound 19 (MICsa = 1.58 μM/ml, MICec = 0.79 μM/ml & MICan = 0.79 μM/ml) to exhibit promising activity against S. aureus, E. coli and A. Niger. Antifungal activity results demonstrated that compound 16 (MICca = 0.86 μM/ml) was reported the most active in opposition to C. albicans the titled compounds were also evaluated for their antioxidant activity by the DPPH radical scavenging method. The results of antioxidant activity are shown in Table 2. Compound 14 (IC_{50}=3.49 μM/ml) and 16(IC_{50}=3.78 μM/ml) were the most active derivatives as antioxidant agents as compared to standard drug Melatonin.

S.A.: Staphylococcus aureus (MTCC7443); B.S.: Bacillus subtilis (MTCC441); E.C.: Escherichia coli (MTCC1652); P.A.: Pseudomonas aeruginosa (MTCC424); C.A.: Candida albicans (MTCC227) and A.N.: Aspergillus Niger (MTCC8189).

Antimicrobial evaluation (in vitro)

The synthesized 4-(1-alkyl-indol-3-yl)-6-(substituted phenyl) pyrimidin-2-ol derivatives were screened for their in vitro antimicrobial potential using norfloxacin (antibacterial) and fluconazole (antifungal) as reference drugs. The antimicrobial activity against Gram-positive bacteria: S. aureus (MTCC 7443), B. subtilis (MTCC 441), Gram-negative bacterium: E. coli (MTCC 1652), P. aeruginosa (MTCC 424) and fungal strains: C. albicans (MTCC 227), A. Niger (MTCC 8189) was determined using tube dilution method.[16] Firstly, a stock solution (1mg/ml) was diluted to final concentrations of 100, 50, 25, 12.5, 6.25 & 3.125 μg/ml. Dilutions of standard and test compounds were prepared in double strength nutrient broth I.P. (bacteria) or Sabouraud dextrose broth I.P.

(fungi) [17]. Then, 0.9% NaCl solution was prepared autoclave and after cooling 0.1ml bacteria were added in twofold power nutrient broth solution and 0.1ml fungus was added in Sabouraud dextrose broth solution. Then after this dilution 0.1µl solution of bacteria or fungus were in mixed all test tubes. The bacterial samples were incubated at 37 ± 1°C for 24 h, A. Niger at 25 ± 1°C for 7d and C.

Table 2: Antimicrobial and antioxidant activities of synthesized 4-(1-alkylindol-3-yl)-6-(substituted phenyl) pyrimidin-2-ol derivatives (1-20)

	Antimicrobial Screening (MIC = µM/ml)						Antioxidant screening
	Microbial species						
	Bacterial				Fungal		*IC_{50} = µM/ml
Comp.	*S.A.*	*B.S.*	*E.C.*	*P.A.*	*C.A.*	*A.N.*	
1	3.93	1.96	1.96	1.96	1.96	3.93	8.71
2	1.96	1.96	3.93	1.96	1.96	1.96	16.13
3	3.93	1.96	1.96	1.96	1.96	1.96	12.83
4	1.97	1.97	1.97	1.97	0.98	0.98	5.15
5	1.97	3.95	3.95	1.97	0.98	3.95	5.74
6	1.80	3.60	3.60	1.80	1.80	1.80	9.98
7	1.80	3.60	1.80	1.80	1.80	1.80	6.17
8	1.86	1.86	0.90	1.86	1.86	1.86	3.95
9	3.28	1.64	1.64	3.28	1.64	1.64	8.54
10	2.07	2.07	2.07	4.14	2.07	2.07	5.33
11	1.88	1.88	1.88	1.88	1.88	3.77	4.33
12	3.77	3.77	1.88	1.88	1.88	3.77	4.84
13	1.88	0.94	1.88	1.88	1.88	0.94	4.03
14	1.89	1.89	1.89	0.94	1.89	1.89	3.49
15	1.89	1.89	3.78	0.94	1.89	1.89	3.92
16	1.73	1.73	3.46	1.73	0.86	1.73	3.78
17	3.46	3.46	3.46	1.73	3.46	1.73	4.49
18	3.57	1.78	3.57	1.78	1.78	0.89	4.54
19	1.58	1.58	0.79	3.17	3.17	0.79	7.83
20	1.98	1.98	0.99	0.99	3.96	0.99	4.83
Norfloxacin	0.47	0.47	0.47	0.47	-	-	-
Fluconazole	-	-	-	-	0.50	0.50	-
Melatonin	-	-	-	-	-	-	2.98

* IC_{50} is the concentration required to kill 50% of cell population albicans at 37 ± 1°C for 48 h respectively and the results were noted as to MIC.

Antioxidant activity

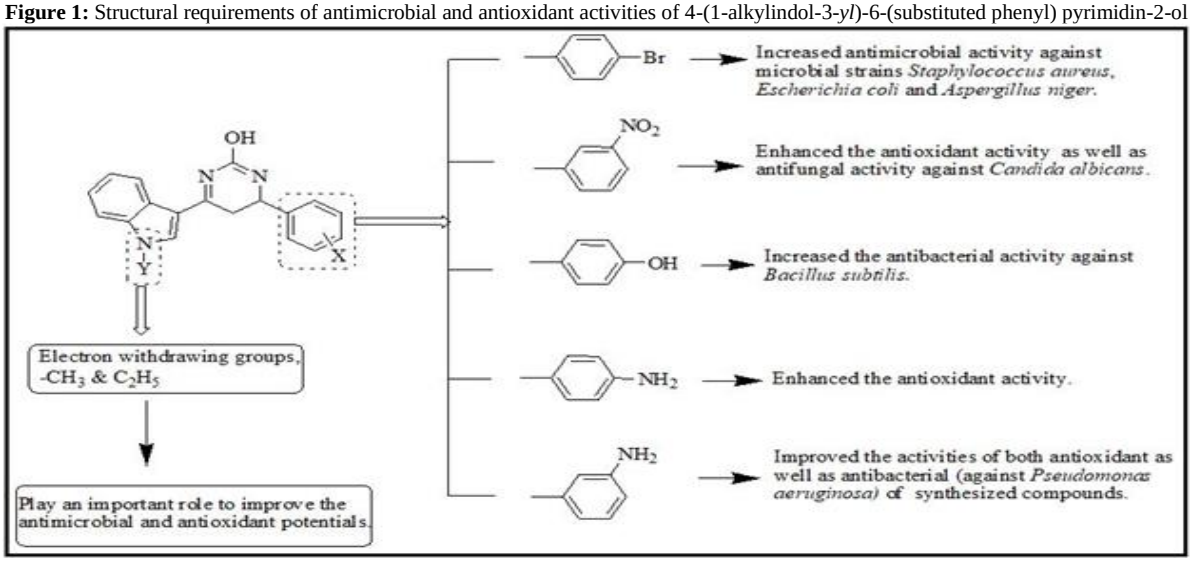
Antioxidant action of the title compounds was tested against 2, 2-diphenylpicrylhydrazyl (DPPH) method. The antioxidant activity results were comparable to the standard drug (Melatonin). Compounds 14 (IC_{50} =3.49 µM/ml) and 16 (IC_{50} =3.78 µM/ml) were the two most active compounds against DPPH method. The results of antioxidant activity were as given in the Table 2.

Structure activity relationship study

The in vitro antimicrobial and antioxidant outcomes established the subsequent SAR (structure activity relationship) for 4-(1-alkylindol-3-yl)-6-(substituted phenyl) pyrimidin-2-ol derivatives as shown in Figure 1.

- Electron withdrawing group (-Br, compound 19) at para-position enhanced the antimicrobial properties of synthesized compounds against microbial strains S. aureus, E. coli and A. Niger, respectively.
- Electron withdrawing groups (-NO_2, compound 16) at meta -location improved antifungal activity against C. albicans and also exhibited good antioxidant activity of synthesized compounds.
- Occurrence of electron releasing group (-OH, compound 13) at para-place enhanced the antibacterial activity of synthesized compounds against B. subtilis.
- The presence of electron releasing group (-NH_2, compound 14) at meta-position improved both antibacterial (against P. aeruginosa strain) as well as antioxidant properties of synthesized compounds and -NH_2 present at para-position in compound 15 also improved the antioxidant activity.

Figure 1: Structural requirements of antimicrobial and antioxidant activities of 4-(1-alkylindol-3-*yl*)-6-(substituted phenyl) pyrimidin-2-ol



CONCLUSION

A novel series of indole clubbed with pyrimidine was synthesized and evaluated for its *in-vitro* antimicrobial and antioxidant activities. Among the synthesized compounds, compounds 13, 14, 15, 16 and 19 showed promising antimicrobial activity that comparable to standard drug norfloxacin and fluconazole. Also, for the antioxidant activity, compounds 14 and 16 found to be most active compounds. The active compounds may be utilized as lead for further optimization and rational drug designing.

DECLARATION

Conflict of interest: No conflict of interest.
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Ethical clearance: Not Required.

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