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Synthesis and Antibacterial Activity of Pinanyl-2-amino Pyrimidines

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A new series of pinene-2-alkyl amino pyrimidines were synthesized from (-)-β-pinene. (+)-No-pinone was obtained from (-)-β-pinene by selective oxidation with potassium permanganate and it was reacted with aromatic aldehydes including benzaldehyde, *p*-methylbenzaldehyde, *p*-methoxylbenzaldehyde, *p*-hydroxybenzaldehyde, *p*-chlorobenzaldehyde, *p*-nitrobenzaldehyde, *p*-fluorobenzaldehyde, *o*-chlorobenzaldehyde, *m*-nitrobenzaldehyde, *o*-vanillin and furfural catalyzed with alkali catalysts to get optically active 3-arylidenenopinones **2a-2l**. Then in the alkali catalytic conditions, they were used to synthesize pinanyl-2-amino pyrimidines (**3a-3l**) with guanidine hydrochloride. The structures of the synthesized compounds were identified by ^{1}H NMR, ^{13}C NMR, FT-IR, GC-MS and elemental analysis. The antimicrobial activity of the newly synthesized pinanyl-2-amino pyrimidines (**3a-3l**) was done against *C. albicans*, *A. niger*, *G. tropicalis*, *E. coli*, *S. aureus*, *B. Subtilis* and *P. fluorescens*. It has been observed that compounds **3a** and **3g** have strong inhibition effect against *Candida albicans*, **3g** has strong inhibition effect against *Aspergillus niger*, while **3g** also has strong inhibition effect against *Candida tropicalis*.

Keywords: (-)-β-Pinene, (+)-Nopinone, 3-Arylidenenopinones, Pinanyl-2-amino pyrimidines, Antibacterial activity.

INTRODUCTION

In the recent years, antimicrobial agents have been received a great deal of attention due to their potential biological application in different fields. Pyrimidines continue to attract considerable attention of researchers in different countries because of their great practical usefulness, primarily, due to a wide spectrum of their biological activities. Pyrimidines and their derivatives are considered to be important for drugs and agricultural chemicals. A number of synthetic pharmacophores based upon the pyrimidyl structure exhibit antimicrobial[1-7], anticancer[8-15], antiinflammatory[16-18], antitumor[19] and antiviral[20] activities, *etc*. Besides, emerging and re-emerging of bacterial infectious diseases which still cause death and disability worldwide[21]. Moreover, antibiotics have revolutionized the medical care in the 20th century and with their discovery, people were convinced that infectious diseases might some day be wiped out[22]. Thus scientists are working to find new ways to defeat bacteria that are increasingly resistant to the antibiotics already available.

On the other hand, antioxidants have gained a lot of importance because of their potential prophylactic and therapeutic activities against many diseases. Free radicals are constantly formed as a result of normal organ functions or excessive oxidative stress[23]. High levels of free radicals can cause damage to biomolecules such as lipids, proteins, enzymes and DNA in cells and tissues, resulting in mutations that can lead to malignancy. The development of synthetic compounds, capable of scavenging free radicals has been of great success. In recent years, many publications have covered the antimicrobial, antioxidant and cytotoxic roles of several heterocyclic compounds[24,25].

It is well known that the α,β-unsaturated ketones are considered to be precursors of flavonoids and isoflavonoids when found as naturally-occurring compounds, but it could be considered that their true importance is extended in two branches. The biological activity associated with them, as well as they are widely used as versatile precursors for synthesis of several types of heterocyclic compounds, such as pyrazoles, isoxazoles, pyrimidines, chromenes and fused heterocyclic derivatives which are of great biological interest, especially as antimicrobials[26-32] and antioxidants[33-35]. The research about the turpentine focused on synthetic spices, other chemicals are relatively less[36-39].

Encouraged by these observations, the present study aimed to synthesize a new series of pinanyl-2-amino pyrimidines by using a low-cost and abundant renewable resource β-pinene as the raw material, in order to examine their antimicrobial

activities against different bacteria and fungi in comparison with several control drugs and also to evaluate the minimum inhibitory concentrations (MICs) of the newly synthesized compounds. Structure activity relationships were also studied. The synthetic route were shown in **Scheme-I**.

EXPERIMENTAL

All the reagents and solvents used were of analytical grade. Starting material (-)-β- pinene (98.09 %, $[\alpha]_D^{20}$ = -18°, neat) was purchased from Guangdong Deqing Chemical Factory. All kinds of aromatic aldehydes used were purchased from Sinopharm Chemical Reagent Co., Ltd, neat.

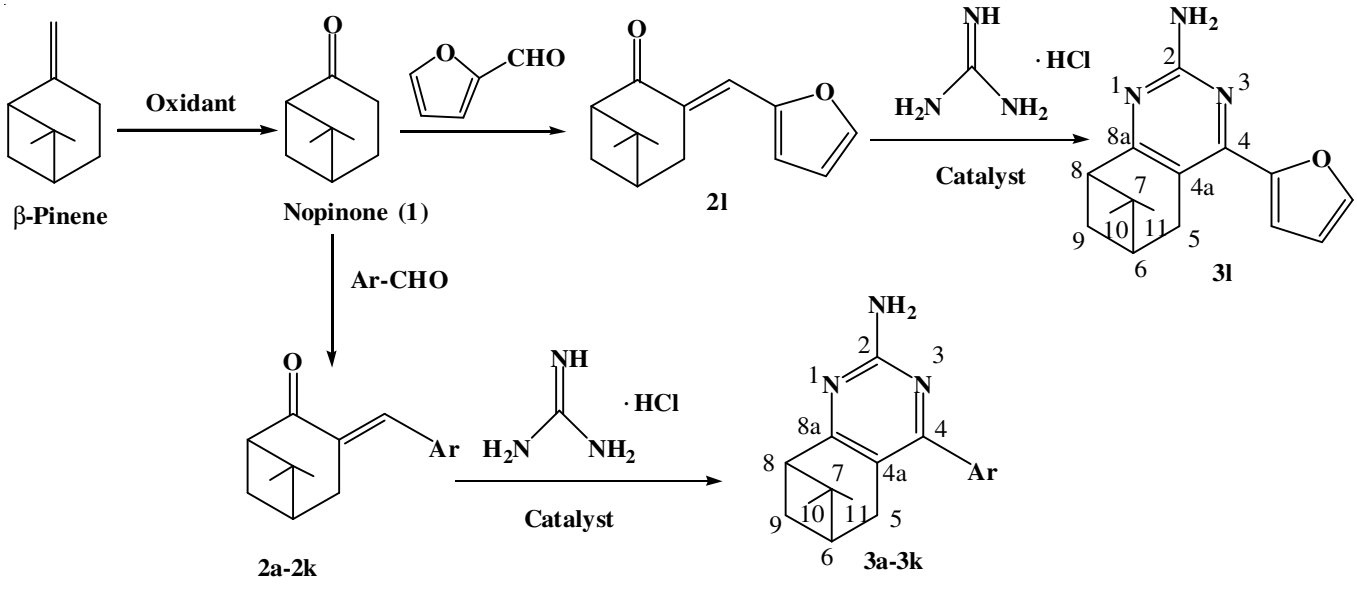
All reactions were monitored by GC. Melting points are in degree centigrade and were determined on Beijing Tektronix X-6 micro melting point determination apparatus and are uncorrected. Optical rotations were recorded at 20 °C on Shanghai precision scientific WZZ-2S digital automatic polarimeter. The IR spectra ν/cm^{-1} (KBr) were recorded on Nicolet 380 FT-IR infrared spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were obtained on Bruker 500 MHz FT-NMR spectrometer in $CDCl_3$ or DMSO with TMS as internal standard. Mass spectra were obtained on the America Agilent 5975c mass spectrometer. Purity were recorded on the America Agilent 7890A gas chromatograph.

Synthesis of nopinone: A 100 mL dried three-necked flask equipped with a thermometer condenser and stirrer was charged with acetone 25 mL, 2 mol/L H_2SO_4 3 mL and β-pinene 5 g and cooled with ice bath to about 15 °C. 17.4 g of $KMnO_4$ fully crashed was added in portions within 1-1.5 h. The ice bath was removed after finishing addition of $KMnO_4$ and the reaction was kept at room temperature for another 5-6 h. The reaction was monitored by GC until the peak of β-pinene was disappeared. The resulting mixture was filted with a sand-core funnel to remove the solid MnO_2 and was rewashed for two times with acetone (2 × 10 mL). The filtrate was concentrated by a rotor evaporator to recover acetone and the bottom residue was diluted with 100 mL of hexane. The diluted residue was washed with saturated brine to neutral and the organic layer was dried over Na_2SO_4 and then was distilled to collect the fraction at 100-102 °C/266 kPa, a colourless oily liquid with a yield over 83.9 %, purity 95.04 % (GC), specific rotation $[\alpha]_D^{25}$ = + 27.3° (c = 1.0, $CHCl_3$).

Synthesis of (-)-3-arylidenenopinones

Synthesis of 2a: A 100 mL dried flash equipped with a agitator, thermometer and condenser was charged with (+)-nopinone (**1**) (1.38 g, 10 mmol), *p*-methylbenzaldehyde (1.44 g, 12 mmol) and 3 g of sodium methoxide in 30 mL of *tert*-butyl alcohol under a nitrogen atmosphere and the resulting mixture was refluxed for 2-3 h until the conversion ratio of nopinone reached over 95 % (monitored with GC) and then water was added. The mixture was extracted with ethyl acetate for three times and the combined organic layers were washed with water and saturated brine to neutrality, dried over Na_2SO_4 and concentrated to afford the yellow crude product, which was purified by recrystallization in acetone and ethanol to provide 2.06 g of compound **2a** as a colourless transparent crystal; yield = 85.7 %; purity of 98.3 %; m.p. 95.2-95.8 °C; $[\alpha]_D^{20}$ = -43.0° (c = 1.0, $CHCl_3$).

Synthesis of compound 2b: A mixture of **1** (1.38 g, 10 mmol), benzaldehyde (1.27 g, 12 mmol), NaOH (6 g, 150 mmol) and distilled water (30 mL) was refluxed for 8 h, other conditions were same as in **2a**. Colourless transparent crystal;



a: Ar = p-CH_3-C_6H_4
b: Ar = C_6H_5
c: Ar = p-OH-C_6H_4
d: Ar = p-OCH_3-C_6H_4
e: Ar = m-OCH_3-p-OH-C_6H_4
f: Ar = m-OH-p-OCH_3-C_6H_4
g: Ar = p-Cl-C_6H_4
h: Ar = o-Cl-C_6H_4
i: Ar = p-F-C_6H_4
j: Ar = p-NO_2-C_6H_4
k: Ar = m-NO_2-C_6H_4

Scheme-I

yield = 78.2 %; purity of 98.2 %; m.p. 108.4-108.9 °C; $[\alpha]_D^{20}$ = -12.3° (c = 1, $CHCl_3$).

Synthesis of compound 2c: A mixture of **1** (1.38 g, 10 mmol), *p*-hydroxybenzaldehyde (1.83 g, 15 mmol), potassium *tert*-butoxide (3 g, 27 mmol) and *tert*-butanol (30 mL) was refluxed for 7-8 h, other conditions reference **2a**. colourless transparent crystal; yield = 69.3 %; purity of 98.5 %; m.p. 199.6-200.6 °C; $[\alpha]_D^{20}$ = -56.3° (c = 0.6, $CHCl_3$).

Synthesis of compound 2d: A mixture of **1** (1.38 g, 10 mmol), *p*-methoxylbenzaldehyde (2.04 g, 15 mmol), potassium *tert*-butoxide (3 g, 27 mmol) and *tert*-butanol (30 mL) was refluxed for 1-2.5 h, other conditions reference **2a**. colourless transparent crystal; yield = 83.5 %; purity of 98.1 %; m.p. 82.7-83.8 °C; $[\alpha]_D^{20}$ = -43° (c = 0.55, $CHCl_3$).

Synthesis of compound 2e: A mixture of **1** (1.38 g, 10 mmol), vanillin (1.82 g, 12 mmol), potassium *tert*-butoxide (3 g, 27 mmol) and methylbenzene (30 mL) was refluxed for 10-12 h, other conditions reference **2a**. colourless transparent crystal; yield = 38.6 %; purity of 99.3 %; m.p. 173.5-174.2 °C; $[\alpha]_D^{20}$ = -44.7° (c = 0.32, $CHCl_3$).

Synthesis of compound 2f: A mixture of **1** (1.38 g, 10 mmol), *o*-vanillin (1.82 g, 12 mmol), potassium *tert*-butoxide (3 g, 27 mmol) and methylbenzene (30 mL) was refluxed for 20-22 h, other conditions reference **2a**. colourless transparent crystal; yield = 47.1 %; purity of 98.7 %; m.p. 195.2-195.6 °C; $[\alpha]_D^{20}$ = -72.6° (c = 0.24, $CHCl_3$).

Synthesis of compound 2g: A mixture of (+)-nopinone (1.38 g, 10 mmol), *p*-chlorobenzaldehyde (1.68 g, 12 mmol), sodium methoxide (3 g, 56 mmol) and *tert*-butanol (30 mL) was refluxed for 5-8 h, other conditions reference **2a**. colourless transparent crystal; yield = 85.5 %; purity of 99.4 %; m.p. 109.7-110.7 °C; $[\alpha]_D^{20}$ = -22.9° (c = 0.31, $CHCl_3$).

Synthesis of compound 2h: A mixture of **1** (1.38 g, 10 mmol), *o*-chlorobenzaldehyde (1.68 g, 12 mmol), sodium methoxide (1.62 g, 30 mmol) and methanol (30 mL) was refluxed for 1 h, other conditions reference **2a**. colourless transparent crystal; yield = 91.2 %; purity of 99 %; m.p. 107.7-108.2 °C; $[\alpha]_D^{20}$ = -125.4° (c = 0.5, $CHCl_3$).

Synthesis of compound 2i: A mixture of **1** (1.38 g, 10 mmol), *p*-fluorobenzaldehyde (1.24 g, 10 mmol), sodium ethoxide (1.36 g, 20 mmol) and ethanol (30 mL) was refluxed for 1 h, other conditions reference **2a**. colourless transparent crystal; yield = 90 %; purity of 98.6 %; m.p. 90.8-91.5 °C; $[\alpha]_D^{20}$ = -91° (c = 0.5, $CHCl_3$).

Synthesis of compound 2j: A mixture of **1** (1.38 g, 10 mmol), *p*-nitrobenzaldehyde (1.81 g, 12 mmol), NaOH (0.60 g, 15 mmol) and ethanol (30 mL) was reacted for 1 h at room temperature, other conditions reference **2a**. colourless transparent crystal; yield = 62.7 %; purity of 98.8 %; m.p. 151.2-151.6 °C; $[\alpha]_D^{20}$ = -101.8° (c = 0.5, $CHCl_3$).

Synthesis of compound 2k: A mixture of **1** (1.38 g, 10 mmol), *m*-nitrobenzaldehyde (1.81 g, 12 mmol), NaOH (0.60 g, 15 mmol) and ethanol (30 mL) was reacted for 1 h at room temperature, other conditions reference **2a**. colourless transparent crystal; yield = 73.1 %; purity of 98.1 %; m.p. 123.1-124 °C; $[\alpha]_D^{20}$ = -12.8° (c = 0.5, $CHCl_3$).

Synthesis of compound 2l: A mixture of **1** (1.38 g, 10 mmol), furfural (1.15 g, 12 mmol), NaOH (3 g, 75 mmol) and ethanol (30 mL) was refluxed for 4 h, other conditions reference **2a**. yellow liquid; yield = 85.5 %; purity of 97.3 %; $[\alpha]_D^{20}$ = -8.34° (c = 0.50, $CHCl_3$).

Synthesis of pinanyl-2-amino pyrimidines

Synthesis of 3a: A 50 mL dried flash equipped with a agitator, thermometer and condenser was charged with **2a** (1.20 g, 5 mmol), guanidine hydrochloride (0.95 g, 10 mmol), NaOH (1.20 g, 30 mmol) and distilled water (1.20 g) in 30 mL of ethanol under nitrogen atmosphere and the resulting mixture was refluxed for 9 h until the conversion ratio of **2a** reached over 95 % (monitored with GC) and then water was added. The mixture was extracted with ethyl acetate for three times and the combined organic layers were washed with water and saturated brine to neutrality, dried over Na_2SO_4 and concentrated to afford the yellow crude product, which was purified by recrystallization in acetone and ethanol to provide 1.25 g of compound **3a** as a colourless transparent crystal; yield = 89.6 %; purity of 98.7 %; m.p. 106.7-107.3 °C; $[\alpha]_D^{20}$ = -121.8° (c = 0.5, CH_3OH). IR (KBr, ν_{max}, cm^{-1}): 3316, 3187 (ν_{N-H}, NH_2), 1704 ($\nu_{C=N}$), 1625 (δ_{N-H}, NH_2), 1566, 1552 ($\nu_{C=C}$, C_6H_4-), 1274, 1215 (ν_{C-C}), 1071 (ν_{C-N}), 774, 700 (δ_{C-H}, C_6H_4-); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.78 (s, 3H, 10-CH_3), 1.32 (d, *J* = 9.8 Hz, 1H, 6-CH), 1.41 (s, 3H, 11-CH_3), 2.32 (t, *J* = 2.8 Hz, 1H, 8-CH), 2.42 (s, 3H, Ar-CH_3) 2.66-2.83 (m, 4H, 9, 5-CH_2), 6.27 (s, 2H, NH_2), 7.28 (t, *J* = 1.2 Hz, 2H, 3', 5'-CH), 7.47 (d, *J* = 8.1 Hz, 2H, 2', 6'-CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm): 21.24, 21.36, 25.76, 29.28, 29.78, 38.80, 40.24, 48.97, 113.58, 128.30, 128.99, 134.50, 139.21, 160.37, 164.35, 176.20; MS *m/z* (% relative intensity): 279 (M^+, 55), 278 (48), 264 (33), 250 (11), 236 (45), 223 (13), 211 (18), 147 (7), 119 (100), 117 (12), 91 (16), 77 (15), 65 (9); Anal. Calcd for $C_{18}H_{21}N_3$: C, 77.37; N, 15.04; H, 7.59. Found: C, 77.32; N, 15.06; H, 7.63.

Synthesis of compound 3b: A mixture of **2b** (1.13 g, 5 mmol), guanidine hydrochloride (0.95 g, 10 mmol), NaOH (1.20 g, 30 mmol), distilled water (1.20 g) and ethanol (30 mL) was refluxed for 12 h, other conditions reference **3a**. Colourless transparent crystal; yield = 90.1 %; purity of 98.2 %; m.p. 98.8-99.5 °C; $[\alpha]_D^{20}$ = -120° (c = 0.5, CH_3OH). IR (KBr, ν_{max}, cm^{-1}): 3320, 3191 (ν_{N-H}, NH_2), 1704 ($\nu_{C=N}$), 1625 (δ_{N-H}, NH_2), 1566, 1552 ($\nu_{C=C}$, C_6H_5-), 1271, 1216 (ν_{C-C}), 1071 (ν_{C-N}), 774, 700 (δ_{C-H}, C_6H_5-); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.78 (s, 3H, 10-CH_3), 1.31 (d, *J* = 9.8 Hz, 1H, 6-CH), 1.40 (s, 3H, 11-CH_3), 2.30 (m, 1H, 9α-CH), 2.63-2.68 (m, 1H, 9β-CH_2), 2.74 (t, *J* = 2.6 Hz, 2H, 5-CH_2), 2.82 (t, *J* = 5.5 Hz, 1H, 8-CH), 6.59 (s, 2H, NH_2), 7.43-7.47 (m, 3H, 3', 4', 5'-CH), 7.53 (t, *J* = 2.1 Hz, 2H, 2', 6'-CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm): 21.16, 25.66, 29.00, 29.67, 38.73, 40.09, 48.65, 113.40, 128.18, 128.22, 129.12, 137.02, 160.31, 164.44, 176.16; MS *m/z* (% relative intensity): 265 (M^+, 52), 264 (45), 250 (29), 236 (11), 222 (48), 209 (14), 197 (14), 119 (100), 115 (13), 104 (10), 91 (8), 77 (28), 51 (7); Anal. Calcd for $C_{17}H_{19}N_3$: C, 76.93; N, 15.84; H, 7.23. Found: C, 76.86; N, 15.82; H, 7.34.

Synthesis of compound 3c: A mixture of **2c** (1.21 g, 5 mmol), guanidine hydrochloride (0.95 g, 10 mmol), potassium *tert*-butoxide (2.24 g, 20 mmol), methylbenzene (30 mL) and ethanol (5 mL) was refluxed for 10 h, other conditions reference **3a**. colourless transparent crystal; yield = 80.3 %; purity of 98.3 %; m.p. 272.4-273.1 °C; $[\alpha]_D^{20}$ = -168.2° (c = 0.5,

CH_3OH). IR (KBr, ν_{max}, cm^{-1}): 3488 (ν_{O-H}), 3416 (fermi resonance of 2 δ_{N-H} and $\nu_{as\ N-H}$), 3294, 3165 (ν_{N-H}, NH_2), 1627 ($\nu_{C=N}$), 1610 (δ_{N-H}, NH_2), 1556, 1514 ($\nu_{C=C}$, C_6H_4-), 1380 (ν_{C-O}), 1279 (ν_{C-C}), 1230 (ν_{C-N}), 842, 800 (δ_{C-H}, C_6H_4-); ^{1}H NMR (300 MHz, DMSO) δ (ppm): 0.68 (s, 3H, 10-CH_3), 1.23 (d, *J* = 8.6 Hz, 1H, 6-CH), 1.35 (s, 3H, 11-CH_3), 2.30 (t, *J* = 2.6 Hz, 1H, 8-CH), 2.50-2.64 (m, 2H, 9-CH_2), 2.71-2.88 (m, 2H, 5-CH_2), 6.19 (s, 2H, NH_2), 6.83 (d, *J* = 8.6 Hz, 2H, 3', 5'-CH), 7.57 (d, *J* = 8.6 Hz, 2H, 2', 6'-CH), 9.67 (s, 1H, Ar-OH); ^{13}C NMR (300 MHz, DMSO) δ (ppm): 21.54, 26.11, 29.82, 29.89, 38.61, 40.87, 50.07, 111.82, 115.20, 129.92, 130.51, 158.41, 161.76, 162.65, 175.56; MS *m/z* (% relative intensity): 281 (M^+, 75), 280 (68), 266 (40), 252 (14), 239 (40), 238 (53), 225 (17), 213 (26), 172 (4), 147 (9), 131 (7), 119 (100), 91 (8), 77 (17), 65 (10), 51 (4); Anal. Calcd for $C_{17}H_{19}N_3O$: C, 72.56; N, 14.94; H, 6.82. Found: C, 72.53; N, 14.90; H, 6.89.

Synthesis of compound 3d: A mixture of **2d** (1.28 g, 5 mmol), guanidine hydrochloride (0.95 g, 10 mmol), NaOH (1.20 g, 30 mmol), distilled water (1.20 g) and ethanol (30 mL) was refluxed for 12 h, other conditions reference **3a**. colourless transparent crystal; yield = 73.4 %; purity of 99 %; m.p. 175.5-176.1 °C; $[\alpha]_D^{20}$ = -152.8° (c = 0.5, CH_3OH). IR (KBr, ν_{max}, cm^{-1}): 3311, 3186 (ν_{N-H}, NH_2), 1735 ($\nu_{C=N}$), 1609 (δ_{N-H}, NH_2), 1581, 1560 ($\nu_{C=C}$, C_6H_4-), 1512 ($\nu_{as\ C-O-C}$), 1250 ($\nu_{s\ C-O-C}$), 1196, 1174 (ν_{C-C}), 1037 (ν_{C-N}), 834, 801 (δ_{C-H}, C_6H_4-); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.75 (s, 3H, 10-CH_3), 1.32 (d, *J* = 9.7 Hz, 1H, 6-CH), 1.38 (s, 3H, 11-CH_3), 2.32 (m, 1H, 9α-CH), 2.63 (m, 1H, 9β-CH), 2.75 (t, *J* = 5.5 Hz, 1H, 8-CH), 2.84 (m, 2H, 5-CH_2), 3.84 (s, 3H, Ar-OCH_3), 5.19 (s, 2H, NH_2), 6.96 (m, 2H, 3', 5'-CH), 7.60 (m, 2H, 2', 6'-CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm): 21.21, 25.79, 29.58, 29.89, 38.71, 40.41, 50.29, 55.27, 113.60, 113.76, 129.88, 131.00, 160.06, 160.79, 163.16, 176.43; MS *m/z* (% relative intensity): 295 (M^+, 74), 294 (66), 280 (40), 266 (13), 252 (49), 239 (15), 227 (29), 208 (5), 147 (9), 134 (8), 119 (100), 91 (7), 77 (14), 65 (4), 51 (3); Anal. Calcd for $C_{18}H_{21}N_3O$: C, 73.18; N, 14.23; H, 7.18. Found: C, 73.24; N, 14.14; H, 7.27.

Synthesis of compound 3e: A mixture of **2e** (1.36 g, 5 mmol), guanidine hydrochloride (0.95 g, 10 mmol), potassium *tert*-butoxide (2.24 g, 20 mmol), methylbenzene (30 mL) and ethanol (5 mL) was refluxed for 13 h, other conditions reference **3a**. colourless transparent crystal; yield = 62.1 %; purity of 98.8 %; m.p. 222.8-223.5 °C; $[\alpha]_D^{20}$ = -69.0° (c = 0.1, CH_3OH). IR (KBr, ν_{max}, cm^{-1}): 3465 (ν_{O-H}), 3440 (fermi resonance f 2 δ_{N-H} and $\nu_{as\ N-H}$), 3310, 3184 (ν_{N-H}, NH_2), 1637 ($\nu_{C=N}$), 1608 (δ_{N-H}, NH_2), 1566, 1514 ($\nu_{C=C}$, C_6H_3-), 1370 (ν_{C-O}), 1270 (ν_{C-C}), 1232 (ν_{C-N}), 806, 778 (δ_{C-H},C_6H_3-); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.77 (s, 3H, 10-CH_3), 1.33 (d, *J* = 9.7 Hz, 1H, 6-CH), 1.39 (s, 3H, 11-CH_3), 2.34 (t, *J* = 2.8 Hz, 1H, 8-CH), 2.61-2.90 (m, 4H, 9, 5-CH_2), 3.92 (s, 3H, Ar-OCH_3), 5.98 (s, 2H, NH_2), 6.92-6.95 (d, *J* = 8.0 Hz, 1H, 3'-CH), 7.13-7.26 (m, 2H, 2', 6'-CH), 9.19 (s, 1H, Ar-OH); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 21.20, 25.72, 29.63, 29.78, 38.74, 40.30, 49.29, 55.96, 111.49, 113.52, 114.08, 122.05, 129.56, 146.59, 160.30, 163.57, 175.79, 176.35; MS *m/z* (% relative intensity): 311 (M^+, 100), 296 (54), 282 (15), 268 (71), 253 (21), 243 (22), 236 (7), 224 (6), 119 (93), 115 (7), 91 (9), 77 (15), 65 (5), 51 (5); Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.42; N, 13.50; H, 6.81. Found: C, 69.39; N, 13.57; H, 6.83.

Synthesis of compound 3f: A mixture of **2f** (1.36 g, 5 mmol), guanidine hydrochloride (0.95 g, 10 mmol), potassium *tert*-butoxide (2.24 g, 20 mmol), methylbenzene (30 mL) and ethanol (5 mL) was refluxed for 4 h, other conditions reference **3a**. colourless transparent crystal; yield = 66.2 %; purity of 99.3 %; m.p. 223.7-224.4 °C; $[\alpha]_D^{20}$ = -59.0° (c = 0.1, CH_3OH). IR (KBr, ν_{max}, cm^{-1}): 3385 (ν_{O-H}), 3311, 3172 (ν_{N-H}, NH_2), 1699 ($\nu_{C=N}$), 1639 (δ_{N-H}, NH_2), 1561 ($\nu_{C=C}$, C_6H_3-), 1382 (ν_{C-O}), 1283, 1241 (ν_{C-C}), 1192 (ν_{C-N}), 736, 608 (δ_{C-H}, C_6H_3-); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.77 (s, 3H, 10-CH_3), 1.33 (d, *J* = 9.7 Hz, 1H, 6-CH), 1.39 (s, 3H, 11-CH_3), 2.35 (m, 1H, 8-CH), 2.61-2.68 (m, 1H, 9α-CH), 2.80 (t, *J* = 5.6 Hz, 1H, 9β-CH), 2.92 (d, *J* = 2.8 Hz, 2H, 5-CH_2), 3.91 (s, 3H, Ar-OCH_3), 5.88 (s, 2H, NH_2), 6.83-6.95 (m, 2H, 2', 3'-CH), 7.23 (t, *J* = 1.3 Hz, 1H, 6'-CH), 11.16 (s, 1H, Ar-OH); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 21.18, 25.68, 29.66, 30.17, 38.74, 40.22, 49.71, 56.11, 112.82, 114.46, 118.29, 121.33, 147.52, 148.48, 158.70, 161.91, 175.81, 177.59; MS *m/z* (% relative intensity): 311 (M^+, 88), 310 (29), 296 (66), 268 (100), 252 (24), 238 (8), 196 (6), 167 (3), 119 (13), 77 (10), 65 (4), 51 (3); Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.42; N, 13.50; H, 6.81. Found: C, 69.38; N, 13.47; H, 6.87.

Synthesis of compound 3g: A mixture of **2g** (1.30 g, 5 mmol), guanidine hydrochloride (0.95 g, 10 mmol), NaOH (1.20 g, 30 mmol), distilled water (1.20 g) and ethanol (30 mL) was refluxed for 9 h, other conditions reference **3a**. colourless transparent crystal; yield = 90.2 %; purity of 99.4 %; m.p. 111.8-112.1 °C; $[\alpha]_D^{20}$ = -117.6° (c = 0.5, CH_3OH). IR (KBr, ν_{max}, cm^{-1}): 3316, 3191 (ν_{N-H}, NH_2), 1701 ($\nu_{C=N}$), 1624 (δ_{N-H}, NH_2), 1578, 1560 ($\nu_{C=C}$, C_6H_4-), 1269 (ν_{C-C}), 1089 (ν_{C-N}), 833, 800 (δ_{C-H}, C_6H_4-); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.76 (s, 3H, 10-CH_3), 1.31 (d, *J* = 9.8 Hz, 1H, 6-CH), 1.40 (s, 3H, 11-CH_3), 2.32 (m, 1H, 9α-CH), 2.66 (m, 1H, 9β-CH), 2.75 (t, *J* = 3.2 Hz, 2H, 5-CH_2), 2.81 (t, *J* = 5.5 Hz, 1H, 8-CH), 6.06 (s, 2H, NH_2), 7.42 (m, 2H, 3', 5'-CH), 7.52 (m, 2H, 2', 6'-CH); ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm): 21.24, 25.73, 29.18, 29.77, 38.80, 40.19, 49.20, 113.65, 128.56, 129.78, 135.23, 136.06, 160.52, 162.99, 175.95; MS *m/z* (% relative intensity): 299 (M^+, 41), 284 (25), 270 (9), 256 (37), 243 (11), 231 (11), 221 (6), 147 (7), 138 (5), 119 (100), 91 (5), 77 (13), 51 (4); Anal. Calcd for $C_{17}H_{18}N_3Cl$: C, 68.10; N, 14.02; H, 6.06. Found: C, 68.15; N, 13.93; H, 6.12.

Synthesis of compound 3h: A mixture of **2h** (1.30 g, 5 mmol), guanidine hydrochloride (0.95 g, 10 mmol), sodium ethoxide (1.36 g, 20 mmol) and ethanol (30 mL) was refluxed for 4 h, then $KMnO_4$ (0.79 g, 5 mmol) was added for another 2 h, other conditions reference **3a**. colourless transparent crystal; yield = 75.9 %; purity of 98.7 %; m.p. 107.8-108.6 °C; $[\alpha]_D^{20}$ = -143.0° (c = 0.1, CH_3OH). IR (KBr, ν_{max}, cm^{-1}): 3318, 3200 (ν_{N-H}, NH_2), 1708 ($\nu_{C=N}$), 1640 (δ_{N-H}, NH_2), 1577 ($\nu_{C=C}$, C_6H_4-), 1264 (ν_{C-C}), 760 (δ_{C-H}, C_6H_4-); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.78 (s, 3H, 10-CH_3), 1.33 (d, *J* = 9.8 Hz, 1H, 6-CH), 1.39 (s, 3H, 11-CH_3), 2.25 (s, 1H, 8-CH), 2.48 (s, 2H, 5-CH_2), 2.65-2.70 (m, 1H, 9α-CH), 2.80 (t, *J* = 5.3 Hz, 1H, 9β-CH), 5.97 (s, 2H, NH_2), 7.26 (t, *J* = 5.6 Hz, 1H, 3'-CH), 7.35 (m, 2H, 4', 5'-CH), 7.46 (t, *J* = 3.9 Hz, 1H, 6'-CH); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 21.18, 25.90, 27.92, 30.03, 39.29, 39.97, 49.18, 115.17, 126.96, 129.29, 129.66, 129.90, 136.60, 160.33, 163.11, 175.72, 176.50; MS *m/z* (%

relative intensity): 299 (M^+, 46), 284 (26), 264 (20) 256 (41), 221 (6), 192 (2), 147 (8), 119 (100), 77 (11), 51 (3); Anal. Calcd. for $C_{17}H_{18}N_3Cl$: C, 68.10; N, 14.02; H, 6.06. Found: C, 68.08; N, 14.06; H, 6.15.

Synthesis of compound 3i: A mixture of **2i** (1.21 g, 5 mmol), guanidine hydrochloride (0.95 g, 10 mmol), NaOH (1.20 g, 30 mmol) and ethanol (30 mL) was refluxed for 16 h, other conditions reference **3a**. colourless transparent crystal; yield = 57.9 %; purity of 99.2 %; m.p. 182.4-183 °C; $[\alpha]_D^{20}$ = -178.0° (c = 0.1, CH_3OH). IR (KBr, ν_{max}, cm^{-1}): 3324, 3189 (ν_{N-H}, NH_2), 1705 ($\nu_{C=N}$), 1644 (δ_{N-H}, NH_2), 1602, 1572 ($\nu_{C=C}$, C_6H_4-), 1380 (ν_{C-F}), 1271 (ν_{C-C}), 1223 (ν_{C-N}), 845 (δ_{C-H}, C_6H_4-); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.78 (s, 3H, 10-CH_3), 1.33 (d, *J* = 9.8 Hz, 1H, 6-CH), 1.41 (s, 3H, 11-CH_3), 2.31-2.35 (m, 1H, 9α-CH), 2.66–2.70 (m, 1H, 9β-CH), 2.76 (d, *J* = 2.0 Hz, 2H, 5-CH_2), 2.82 (t, *J* = 5.5 Hz, 1H, 8-CH), 6.23 (s, 2H, NH_2), 7.11-7.18 (m, 2H, 3', 5'-CH), 7.55-7.59 (m, 2H, 2', 6'-CH); ^{13}C NMR (300 MHz, $CDCl_3$) ν (ppm): 21.22, 25.72, 29.21, 29.76, 38.79, 40.20, 49.02, 113.55, 115.21, 115.50, 130.42, 133.48, 160.43, 164.84, 176.21; MS *m/z* (% relative intensity): 283 (M^+, 57), 282 (46), 268 (34), 254 (12), 240 (51), 227 (16), 215 (16), 184 (3), 147 (10), 133 (13), 119 (100), 95 (8), 77 (12), 51 (3); Anal. Calcd for $C_{17}H_{18}N_3F$: C, 72.05; N, 14.83; H, 6.42. Found: C, 72.10; N, 14.88; H, 6.48.

Synthesis of compound 3j: A mixture of **2j** (1.35 g, 5 mmol), guanidine hydrochloride (0.95 g, 10 mmol), potassium *tert*-butoxide (1.68 g, 15 mmol) and *tert*-butyl alcohol (30 mL) was reacted for 2 h at room temperature, other conditions reference **3a**. yellow solid; yield = 57.2 %; purity of 98.7 %; m.p. 253.1-255.0 °C; $[\alpha]_D^{20}$ = -108° (c = 0.05, CH_3OH). IR (KBr, ν_{max}, cm^{-1}): 3313, 3186 (ν_{N-H}, NH_2), 1689 ($\nu_{C=N}$), 1625 (δ_{N-H}, NH_2), 1553 ($\nu_{C=C}$, C_6H_4-), 1456 ($\nu_{as\ N=O}$, NO_2), 1217, 1198 (ν_{C-C}), 856, 801 (ν_{C-H}, C_6H_4-); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.77 (s, 3H, 10-CH_3), 1.31 (d, *J* = 9.8 Hz, 1H, 6-CH), 1.40 (s, 3H, 11-CH_3), 2.35 (s, 1H, 8-CH), 2.66-2.83 (m, 4H, 9,5-CH_2), 5.15 (s, 2H, NH_2), 7.81 (d, *J* = 8.2 Hz, 2H, 3', 5'-CH), 8.28 (d, *J* = 8.2 Hz, 2H, 2', 6'-CH); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 21.25, 25.73, 29.15, 29.84, 38.81, 40.22, 50.34, 114.37, 123.49, 129.47, 144.77, 147.92, 160.74, 161.15, 177.50; MS *m/z* (% relative intensity): 310 (M^+, 50), 309 (30), 295 (28), 281 (7), 267 (52), 254 (10), 221 (14), 190 (2), 154 (4), 119 (100), 77 (12), 51 (3); Anal. Calcd. for $C_{17}H_{18}N_4O_2$: C, 65.78; N, 18.05; H, 5.86. Found: C, 65.82; N, 18.08; H, 5.87.

Synthesis of compound 3k: A mixture of **2k** (1.35 g, 5 mmol), guanidine hydrochloride (0.95 g, 10 mmol), potassium *tert*-butoxide (1.68 g, 15 mmol) and *tert*-butyl alcohol (30 mL) was reacted for 2 h at room temperature, other conditions reference **3a**. yellow solid; yield = 57.9 %; purity of 99 %; m.p. 110.8-111.7 °C; $[\alpha]_D^{20}$ = -90° (c = 0.1, CH_3OH). IR (KBr, ν_{max}, cm^{-1}): 3322, 3188 (ν_{N-H}, NH_2), 1706 ($\nu_{C=N}$), 1646 (δ_{N-H}, NH_2), 1570, 1532 ($\nu_{C=C}$, C_6H_4-), 1468 ($\nu_{as\ N=O}$, NO_2), 1217, 1199 (ν_{C-C}), 716, 696 (ν_{C-H}, C_6H_4-); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.79 (s, 3H, 10-CH_3), 1.35 (d, *J* = 9.8 Hz, 1H, 6-CH), 1.42 (s, 3H, 11-CH_3), 2.35-2.38 (m, 1H, 9α-CH), 2.66-2.73 (m, 1H, 9β-CH_2), 2.81 (d, *J* = 2.5 Hz, 2H, 5-CH_2), 2.84 (d, *J* = 5.5 Hz, 1H, 8-CH), 5.94 (s, 2H, NH_2), 7.63-7.68 (t, *J* = 7.9 Hz, 1H, 5'-CH), 7.96 (d, *J* = 7.7 Hz, 1H, 4'-CH), 8.31 (d, *J* = 8.2 Hz, 1H, 6'-CH), 8.50 (s, 1H, 2'-CH); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 21.28, 25.72, 29.11, 29.77, 38.85, 40.16, 49.40, 113.85, 123.59, 123.83, 129.42, 134.47, 139.48, 160.68, 161.31, 175.85, 177.29; MS *m/z* (% relative intensity): 310 (M^+, 50), 309 (34), 295 (30), 281 (8), 267 (58), 254 (10), 221 (13), 180 (4), 154 (4), 119 (100), 77 (12), 51 (3); Anal. Calcd for $C_{17}H_{18}N_4O_2$: C, 65.78; N, 18.05; H, 5.86. Found: C, 65.70; N, 18.11; H, 5.87.

Synthesis of compound 3l: A mixture of **2l** (1.08 g, 5 mmol), guanidine hydrochloride (0.95 g, 10 mmol), potassium *tert*-butoxide (1.12 g, 10 mmol) and *tert*-butanol (30 mL) was refluxed for 14 h, other conditions reference **3a**. brown transparent crystal; yield = 50.2 %; purity of 97.8 %; m.p. 147.8-149.1 °C; $[\alpha]_D^{20}$ = -133.5° (c = 0.1, CH_3OH). IR (KBr, ν_{max}, cm^{-1}): 3318, 3187 (ν_{N-H}, NH_2), 1631 ($\nu_{C=N}$), 1597 (δ_{N-H}, NH_2), 1564 ($\nu_{C=C}$, C_4H_3O), 1363 (ν_{C-O}), 1221,1199 (ν_{C-C}), 1070 (ν_{C-N}), 807, 797(δ_{C-H}, C_4H_3O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.74 (s, 3H, 10-CH_3), 1.32 (d, *J* = 9.7 Hz, 1H, 6-CH), 1.40 (s, 3H, 11-CH_3), 2.38-2.42 (m, 1H, 9α-CH), 2.64-2.67 (m, 1H, 9β-CH), 2.76 (t, *J* = 5.6 Hz, 1H, 8-CH), 2.92-3.09 (m, 2H, 5-CH_2), 5.12 (s, 2H, NH_2), 6.54 (m, 1H, 4'-CH), 7.08 (d, *J* = 3.5 Hz, 1H, 5'-CH), 7.61 (t, *J* = 1.1 Hz, 1H, 3'-CH); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 21.16, 25.84, 29.97, 29.99, 38.85, 40.20, 50.33, 111.76, 112.21, 113.50, 144.11, 151.93, 152.38, 160.48, 177.27; MS *m/z* (% relative intensity): 255 (M^+, 80), 240 (38), 226 (20), 212 (88), 200 (13), 199 (18), 187 (29), 170 (9), 120 (11), 119 (100), 91 (11), 77 (26), 65 (10), 51(11); Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.55; N, 16.46; H, 6.72. Found: C, 70.50; N, 16.43; H, 6.81.

Test of antimicrobial activity

Materials and microorganisms: Pinanyl-2-amino pyrimidine compounds **3a-3l**, purified; beef extract and peptone, biochemical reagent; glucose, agar, NaCl and NaOH were commercially available, analytical grade; potato were purchased from agriculture market of Suo Jincun.

The organisms used were: fungus namely *Canidia albicans*, *Aspergillus niger* and *Candida tropicalis*, bacteria namely *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Pseudomonas fluorescens*. These microorganisms were obtained from Microbiology Laboratory of Chemical Engineering College of Nanjing Forestry University.

Preparation of culture medium: The preparation of potato glucose agar medium (PDA medium): Weigh 200 g washed and peeled diced potatoes in 1000 mL of water, boil for 0.5 h, filter with 4 layers of gauze, then add 20 g glucose and 18 g agar, heated to melt and then supply water to 1000 mL, pH nature, packed in Erlenmeyer flask, respectively, stuffed with cotton plug, sterilized at 121 °C for 20 min and set aside.

The preparation of beef extract peptone medium (NA medium): Weigh 5 g beef extract, 10 g peptone, 1 g glucose, 5 g NaCl and 18 g agar was added to 1000 mL water, heated and dissolved, adjust pH to 7-7.2 with 10 % NaOH solution, packed in Erlenmeyer flask, respectively, stuffed with cotton plug, sterilized at 121 °C for 20 min and set aside.

Preparation of bacterium suspension: The test fungi and bacteria were inoculated in sterile PDA and NA agar medium. To culture fungi in the constant temperature of 28 °C box for 72 h, bacteria for 24 h. Picking a little activated thalli

in a PDA or NA liquid medium in tubes by inoculating loop, shaking it, to make a series of 10^6-10^7 CFU mL^{-1} bacterium suspension.

Test of minimum inhibitory concentration (MIC): The antimicrobial activities of the compounds were evaluated through the determination of the minimum inhibitory concentration (MIC) by the method of twofold serial dilutions. From the second to the twelfth holes were added 75 µL sterile water, the newly synthesized compounds (**3a-3l**) and ketoconazole and kanamycin were dissolved in dimethyl sulfoxide (DMSO), respectively, to prepare chemicals of stock solutions of 500 µg mL^{-1}, taking 150 µL to the first hole and making a series of concentration gradient (250-0.244 µg mL^{-1}) from the first to the twelfth holes by the method of twofold serial dilutions on the 96 hole plate, containing 75 µL in each hole. In order to ensure that the solvent per se had no effect on bacterial growth, a control test was also performed containing inoculated broth supplemented with only DMSO at the same dilutions used in our experiments and found inactive in culture medium. Then adding 75 µL prepared bacterium suspension, shake well. Last, to culture fungi in the constant temperature of 28 °C box for 48 h, bacteria for 24 h. All of the compounds were tested for their *in vitro* growth inhibitory activity against different bacteria and fungi.

RESULTS AND DISCUSSION

Structural characterization of 3a-3l: Assignment of the products **3a-3l** were based on elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral date. ^{1}H NMR spectrum of **3a-3l** displayed multiplet signals at δ 6.95-7.61 ppm for aromatic protons, exchangeable protons at δ 5.19-6.59 ppm for NH_2. Besides, the structure of **3a** was also confirmed by the presence of a broad singlet at δ 2.42 ppm due to Ar-CH_3 protons, **3d**, **3e** and **3f** were confirmed by the presence of a broad singlet at 3.84, 3.80 and 3.80 ppm due to Ar-OCH_3 protons and sharp singlet signals centered at δ 9.67 ppm due to Ar-OH protons of **3c**, **3d, 3e** and **3f**. The IR spectrum showed the absence of the carbonyl band and the presence of bands in 3300-3200 cm^{-1} region due to NH_2 stretching, the presence of bands at about 1700 cm^{-1} due to C=N stretching and the presence of bands at about 1560 cm^{-1} due to benzene ring skeleton stretching.

Minimum inhibitory concentration (MIC) of 3a-3l: The *in vitro* antimicrobial activity of the twelve synthesized compounds **3a-3l** using twofold serial dilutions method was given in Table-1. While its date represented MIC of the tested compounds in comparing to the reference drugs. Compounds **3a-3l** had different degrees of antibacterial activity against fungi and bacteria and inhibition of fungi is better than that of bacteria. Table-1 investigated that the tested compounds show almost the same inhibitory effect against bacteria (MIC = 31.25, 62.50 µg mL^{-1}), in addition, **3d** have better inhibitory effect against *Escherichia coli* (MIC = 15.62 µg mL^{-1}). Broadly, The antibacterial activity against fungi of tested compounds is 4'-Cl > 4'-CH_3 >2' -Cl > 4'-OH > 4'-NO_2 > 3'-NO_2. Among, **3a** and **3g** have very strong inhibition effect against *Candida albicans*, the value of MIC was 3.90 µg mL^{-1}, **3c**, **3h**, **3j** and **3k** was 7.81 µg mL^{-1}; **3g** has very strong inhibition effect against *Aspergillus niger*, the value of MIC was 3.90 µg mL^{-1}, **3a**, **3h** and **3j** was 7.81 µg mL^{-1}; While **3g** has strong inhibition effect against *Candida tropicalis*, the value of MIC was 7.81 µg mL^{-1}.

Structure analysis show that, the substituent on the benzene ring has important influence on the antibacterial activity of compounds, the introduction of Cl, CH_3, OH and NO_2 in benzene ring can improve the affinity of compounds and virus in different degree, so as to improve the antibacterial activity.

So the results showed that, pinene-2-alkyl amino pyrimidines have a broad spectrum antibacterial activity against different strains and were potential antifungal, antibacteria compounds. In order to achieving the promotion and application of these compounds, we should do further study in the field tests, toxicological tests and so on. In addition, we can also study the antitumor and hypoglycemic activity, in order to screen bioactive compounds. The paper provides a certain reference value for designing novel nitrogen containing heterocyclic compounds and analysis of structure-activity relationship.

TABLE-1
MIC OF THE SYNTHESIZED COMPOUNDS **3a-3l**

Compound	MIC (µg mL^{-1})						
	C. albicans	*A. niger*	*G. tropicalis*	*E. coli*	*S. aureus*	*B. subtilis*	*P. fluorescens*
3a	3.90	7.81	15.62	31.25	62.50	31.25	31.25
3b	15.62	15.62	15.62	31.25	62.50	31.25	31.25
3c	7.81	15.62	15.62	62.50	62.50	62.50	31.25
3d	15.62	15.62	15.62	15.62	62.50	62.50	31.25
3e	15.62	15.62	15.62	62.50	62.50	62.50	31.25
3f	15.62	15.62	15.62	31.25	31.25	31.25	31.25
3g	3.90	3.90	7.81	31.25	31.25	31.25	31.25
3h	7.81	7.81	15.62	31.25	31.25	31.25	31.25
3i	15.62	15.62	15.62	31.25	31.25	31.25	31.25
3j	7.81	7.81	15.62	31.25	31.25	31.25	31.25
3k	7.81	15.62	15.62	31.25	31.25	31.25	31.25
3l	15.62	15.62	15.62	31.25	31.25	31.25	31.25
PC[a]	0.98	3.90	3.90	0.98	0.49	1.95	0.98

Nate: Positive control fungi with ketoconazole, bacterial with kanamycin

Conclusion

In conclusion, a series of new pinene-2-alkyl amino pyrimidines **3a-3l** were synthesized in good yield, their structure were identified by ^{1}H NMR, ^{13}C NMR, GC-MS, IR spectra and elemental analysis and their antibacterial activity have been evaluated. Broadly, The antibacterial activity against fungi of tested compounds is 4'-Cl > 4'-CH_3 > 2'-Cl > 4'-OH > 4'-NO_2 > 3'-NO_2. Among, **3a** and **3g** have very strong inhibition effect against *Candida albicans*, **3g** has very strong inhibition effect against *Aspergillus niger*, While **3g** also has strong inhibition effect against Candida tropicalis. Structure analysis show that, the introduction of Cl, CH_3, OH and NO_2 in benzene ring can improve the antibacterial activity. The paper provides a certain reference value for designing novel nitrogen containing heterocyclic compounds and analysis of structure-activity relationship.

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