Original Article

Design, synthesis, and evaluation of pyrimidine bridged chalcone derivatives of naphthalene as antibacterial agents

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ABSTRACT

Pyrimidines, due to their very distinct and unique place in our lives, have provoked significant interest of medicinal chemists in the development of novel antibacterial agents. Thus, with the aim to discover new potentially active antibacterial agents, we have synthesized some new pyrimidine bridged chalcone derivatives of naphthalene and investigated their antimicrobial activities against pathogenic microbial strains, *Bacillus subtilis* (MTCC 2451), *Pseudomonas aeruginosa* (MTCC 2642), and *Escherichia coli* (MTCC 82) by disk diffusion method. The compounds were found to possess moderate activity against all tested strains. In general, the new synthesized compounds showed a good antimicrobial activity against these microorganisms.

Keywords: Antibacterial, pyrimidine derivatives, chalcone, naphthalene derivatives

INTRODUCTION

The bacterial infections are still an excessive challenge to medicinal chemist from therapeutic point of view because of factors such as emerging infectious diseases and multidrug resistant. Although a large number of antibiotics and chemotherapeutics drugs are available for treatment, the development of antibiotic-resistant bacterial strains in recent years has posed new challenges for the treatment of bacterial infections and thus led to an urgent need to develop new classes of antibacterial agents.[1] Due to fast emerging resistance issues, major pharmaceutical companies are intended to modify the structures of the already established antimicrobial agents with modification.[2] However, due to advanced techniques available and current need, the researchers will soon reach to end point of structural alterations possible for currently available collection of chemotherapeutics. Thus, the development of new structurally different drugs that can avoid drug resistance is the need of time for the treatment of bacterial infections.

The pyrimidines, heterocyclic aromatic compounds, represent one of the most active classes of heterocyclic molecules having wide range of pharmacological profile.[3,4] Substituted purines and pyrimidines occur widely in living organisms and were some of the first compounds studied by the organic chemists.[5] In literature, a number of reports are available on the biological activities of molecules containing pyrimidine scaffold which includes antibacterial,[6,7] antidiabetic,[8,9] antifungal,[10,11] antileishmanial,[12,13] anti-inflammatory,[7,14] analgesic,[15] antihypertensive,[16] antiviral,[17] anticonvulsant,[18] antioxidant,[19] anticancer,[20-22] anti-Parkinson's,[23] and central nervous system -depressant activities.[24,25] Trisubstituted pyrimidines are reported to possess potent antimicrobial activity.[26,27] Pyrimidine bridged chalcone scaffold is key molecule to possess wide range of activities.

Thus, in view of above discussed facts and as need to discover new potentially active antibacterial agents, we have synthesized some new pyrimidine bridged chalcone derivatives of naphthalene. The synthesized intermediate chalcones and pyrimidine derivatives were characterized using nuclear magnetic resonance (NMR), mass, and infrared (IR) data and were tested for their antimicrobial activities against pathogenic microbial strains, *Bacillus subtilis* (MTCC 2451), *Pseudomonas aeruginosa* (MTCC 2642), and *Escherichia coli* (MTCC 82) by disk diffusion method.

EXPERIMENTAL

Chemistry

General synthetic procedure of chalcone (3)

1-acetylnaphthalene **1** (2 g, 0.011 mol) was dissolved in methanol (25 mL) in 100 mL round bottom flask. To the solution, substituted

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benzaldehyde **2** (0.011 mol) followed by 10% methanolic NaOH solution (5 mL) was added. The reaction mixture was under ice-cold conditions. The progress of reaction was monitored by thin-layer chromatography (TLC) (20% ethyl acetate in hexane). After completion of the reaction, mixture was poured into ice; precipitated solid was filtered and recrystallized from methanol.

General synthetic procedure of pyrimidine derivatives (4)

A mixture of chalcones **3** (0.01mol), guanidine hydrochloride (0.02 mol), and NaOH (0.02 mol) was refluxed in ethanol (25 mL) for 6 h until the reactants were completely consumed. After completion of the reaction as indicated by the TLC, the reaction mixture was quenched on ice cubes. Precipitated solid was filtered and purified by column chromatography or recrystallized from methanol to give pure product 4.

Synthetic scheme

Reaction conditions: (a) 10% aq. NaOH, methanol, 2 h, stirring; (b) guanidine, NaOH, ethanol, reflux,6 h.

Spectral data

(E)-1-(naphthalen-1-yl)-3-(4-chlorophenyl)prop-2-en-1-one (3a)

Yellow solid; yield 85%; 100–102°C; IR (KBr, cm^{-1}) 3008 (aromatic C-H str), 1655 (C=O str), 1602 (aliphatic C=C str), 1488 (aromatic C=C str), 777 (C-Cl str); ^{1}H-NMR (300 MHz, $CDCl_3$, TMS=0) δ 8.32 (1H, dd, *J*=2.4, 7.8 Hz), 8.00 (1H, d, *J*=8.4 Hz), 7.91 (1H, d, *J*=2.4, 7.7 Hz), 7.77 (1H, d, *J*=7.2 Hz), 7.58 (1H, d, *J*=16.2 Hz), 7.56–7.53 (3H, m), 7.50 (2H, d, *J*=8.4 Hz), 7.37 (2H, d, *J*=8.4 Hz), 7.25 (1H, d, *J*=16.2 Hz); M^+ ($C_{19}H_{13}ClO$) m/z: 292, 294.

(E)-1-(naphthalen-1-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (3b)

Yellow solid; yield 83%; 109–111°C; IR (KBr, cm^{-1}) 3002 (aromatic C-H str), 2938 (aliphatic C-H str), 1662 (C=O str), 1590 (aliphatic C=C str), 1452 (aromatic C=C str), 1253 (C-O str); ^{1}H-NMR (300MHz, $CDCl_3$, TMS=0) δ 8.25 (1H, d, *J*=8.2 Hz), 8.09 (1H, d, *J*=8.1 Hz), 7.81 (1H, d, *J*=7.1 Hz), 7.78 (1H, d, *J*=7.8 Hz), 7.66 (1H, d, *J*=15.9 Hz), 7.58-7.21 (3H, m), 7.16 (1H, d, *J*=15.9 Hz), 6.79 (2H, s), 3.81 (9H,s); M^+ ($C_{22}H_{20}O_4$) m/z: 348.

(E)-1-(naphthalen-1-yl)-3-(4-dimethylaminophenyl)prop-2-en-1-one (3c)

Yellowish-orange solid; yield 91%; 83–85°C; IR (KBr, cm^{-1}) 3056 (aromatic C-H str), 2846 (aliphatic C-H str), 1649 (C=O str), 1608 (aliphatic C=C str), 1431 (aromatic C=C str); ^{1}H-NMR (300MHz, $CDCl_3$, TMS=0) δ 8.14 (1H, d, *J*=8.4 Hz), 8.01 (1H, d, *J*=8.1 Hz), 7.84 (1H, d, *J*=8.1 Hz), 7.66 (1H, d, *J*=7.6 Hz), 7.54 (1H, d, *J*=16.2 Hz), 7.48-7.25 (3H, m), 7.10 (1H, d, *J*=16.2 Hz), 6.98 (2H, d, *J*=8.4 Hz), 6.54 (2H, d, *J*=8.4 Hz), 2.95 (6H, s); M^+ ($C_{21}H_{19}NO$) m/z: 301.

4-(4-chlorophenyl)-6-(naphthalen-1-yl)-pyrimidin-2-amine (4a)

Off white solid; yield 55%; 138–140°C; IR (KBr, cm^{-1}) 3492 (N-H asymmetric str), 3293 (N-H symmetric str), 3190 (N-H bend overtone), 3010 (aromatic C-H str), 1635 (C=N str), 1595 (N-H bend), 1450 (aromatic C=C str), 1090 (C-N str), 777 (C-Cl str); ^{1}H-NMR (300MHz, $CDCl_3$, TMS=0) δ 8.18 (1H, d, *J*=8.1 Hz), 8.01 (2H, d, *J*=8.6 Hz), 7.95 (1H, d, *J*=8.2 Hz), 7.91 (1H, d, *J*=8.4 Hz), 7.66 (1H, dd, *J*=1.2,7.1 Hz), 7.56–7.49 (3H, m), 7.45 (2H, d, *J*=8.6 Hz), 7.29 (1H, s), 5.40 (2H, s); M^+ ($C_{20}H_{14}ClN_3$) m/z: 331, 333.

4-(3,4,5-trimethoxyphenyl)-6-(naphthalen-1-yl)-pyrimidin-2-amine (4b)

Yellow solid; yield 60%; 124–126°C; IR (KBr, cm^{-1}) 3492 (N-H asymmetric str), 3293 (N-H symmetric str), 3173 (N-H bend overtone), 3001 (aromatic C-H str), 2938 (aliphatic C-H str), 1626 (C=N str), 1586 (N-H bend), 1466 (aromatic C=C str), 1127 (C-N str); ^{1}H-NMR (300MHz, $CDCl_3$, TMS=0) δ 8.17(1H, d, *J*=8.1 Hz), 7.94 (2H, d, *J*=8.7 Hz), 7.66 (1H, d, *J*=7.2 Hz), 7.60–7.50 (3H, m), 7.31 (2H, s), 7.28 (1H, s), 5.23 (2H, s), 3.95 (9H, s); M^+ ($C_{23}H_{21}N_3O_3$) m/z: 388.

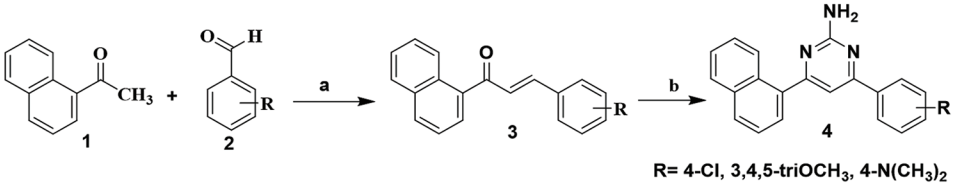
4-(4-(dimethyamino)phenyl)-6-(naphthalen-1-yl)-pyrimidin-2-amine (4c)

Yellow solid; yield 53%; 118–120°C; IR (KBr, cm^{-1}) 3467 (N-H asymmetric str), 3286 (N-H symmetric str), 3154 (N-H bend overtone), 3010 (aromatic C-H str), 2910 (aliphatic C-H str), 1631 (C=N str), 1577 (N-H bend), 1444 (aromatic C=C str), 1192 (C-N str); ^{1}H-NMR (300MHz, $CDCl_3$, TMS=0) δ 8.21 (1H, d, *J*=8.2 Hz), 8.00 (2H, d, *J*=8.8 Hz), 7.93–7.89 (2H, d, *J*=7.6 Hz), 7.66 (1H, d, *J*=8 Hz), 7.57–7.47 (4H,m), 6.76 (2H, d, *J*=8.2 Hz), 5.13 (2H,s), 3.04 (6H,s); M^+ ($C_{22}H_{20}N_4$) m/z: 340.

Biological studies

Antibacterial assay

Synthesized compounds were assessed for their antibacterial activity against pathogenic microbial strains, *B. subtilis* (MTCC 2451), *P. aeruginosa* (MTCC 2642), and *E. coli* (MTCC 82) by disk diffusion method.[28] The antibacterial activity of synthetics was determined by observing the zone of inhibition in comparison to standard antibiotic (ciprofloxacin) disc. Test compounds were dissolved in dimethyl sulfoxide (DMSO) to make a stock solution of 1 mg/mL. The fresh subculture of strains of bacteria



were spread over sterile assay medium (nutrient agar) at 40–45°C in petri plates and allowed to stand for 30 min. Previously marked sterile paper discs (8 mm diameter) were placed on the surface of inoculated agar plates and 30 µL of each compound was pipetted onto the discs. The Petri plates were kept aside for 1 h and then incubated at 37°C for 24 h and zone of inhibition was measured. Antimicrobial activity was determined in triplicates and DMSO was used as negative control. To calculate minimum inhibitory concentration (MIC) of compounds, serial dilution method was used. Different dilutions (1–150 µg/mL) of all selected compounds were prepared in DMSO. A 5 mL of nutrient broth was taken in previously marked test tubes and 100 µL of microbial suspension was added to these test tubes. A 1 mL of different concentration of compounds were added in test tubes and tubes were kept in incubator at 37°C for 24 h and were viewed for assessing MIC of compounds against different test organisms. The concentration showing apparently no growth was considered to be MIC of the respective compound against that strain.

RESULTS AND DISCUSSION

Antibacterial activity

The synthesized intermediate chalcones and pyrimidine final compounds were tested for their antimicrobial activities against highly pathogenic strains; *B. subtilis* (MTCC 2451), *P. aeruginosa* (MTCC 2642), and *E. coli* (MTCC 82) by disk diffusion method. Data obtained for zone of inhibition and MIC value were tabulated in Tables 1 and 2, respectively. In this study, compound 4b was found to have moderate antibacterial activity and the inhibition zone against *B. subtilis* (MTCC 2451), *P. aeruginosa* (MTCC 2642), and *E. coli* (MTCC 82) was found to be 17.5 ± 0.7 mm, 23 ± 1.1 mm, and 16 ± 1.3 mm, respectively [Table 1] as compared to standard drug used ciprofloxacin. Other compounds did not show significant inhibition against these bacterial strains. The chalcone derivatives (3a-c) were found ineffective against *E. coli* at concentration of 30 µg. Comparing to standard antibacterial drug, the target molecules showed less activity as inhibition zone was much smaller as compared to ciprofloxacin.

Table 1: Antibacterial activity of 3a-c and 4a-c (30 µg) in terms of zone of inhibition (in mm)

Compound	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
3a	13.3±0.5	Nd	12.7 ± 0.2
3b	10±0.7	Nd	8±1.3
3 c	9.7±0.6	Nd	Nd
4a	14±0.8	17.5±0.7	14.5±0.7
4b	17.5±0.7	23±1.1	16±1.3
4c	9.5±0.7	Nd	8.5±0.7
Ciprofloxacin	34±2.1	30±0.7	26.5±0.7

n=3; values are given as mean inhibition zone (mm) ± S.D; Nd – no inhibition

Table 2: Minimum inhibitory concentration of 3a-c and 4a-c (µg/mL)

Compound	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
3a	125	125	62.5
3b	125	125	62.5
3c	NA	62.5	31.25
4a	31.25	62.5	125
4b	7.8	15.6	15.6
4c	31.25	125	62.5
Ciprofloxacin	0.25	0.20	0.32

As indicated from above table of zone inhibition, compound 4b showed MIC value of 7.8 µg/mL, 17.8 µg/mL, and 15.6 µg/mL against *B. subtilis* (MTCC 2451), *P. aeruginosa* (MTCC 2642), and *E. coli* (MTCC 82) bacterial strains, respectively [Table 2]. The intermediate chalcones were found to be less effective as compared to final target compounds having pyrimidine scaffold in structure. Thus, we can conclude that pyrimidine ring also plays some role in antibacterial activity of target compounds. Although, the final target compounds were found to have very moderate antibacterial activity as compared to standard ciprofloxacin.

CONCLUSION

Pyrimidines, due to their very distinct and unique place in our lives, have provoked significant interest of medicinal chemists in the development of novel antibacterial agents which make them occupy a very distinct and unique place in our lives. Thus, with the aim to discover new potentially active antibacterial agents, we have synthesized some new pyrimidine bridged chalcone derivatives of naphthalene and investigated for their antimicrobial activities against pathogenic microbial strains, *B. subtilis* (MTCC 2451), *P. aeruginosa* (MTCC 2642), and *E. coli* (MTCC 82) by disk diffusion method. The compounds were found to have moderate activity against all tested strains. In general, the new synthesized compounds showed a good antimicrobial activity against these microorganisms.

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