



SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME CHALCONE DERIVATIVES

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ABSTRACT

In an effort to develop antibacterial agents, a few chalcones were prepared by aldol condensation of appropriate acetophenones with appropriate aromatic aldehydes in the presence of aqueous potassium hydroxide and ethanol at room temperature. Then novel chalcone derivatives were prepared further by coupling with methyl 4-(1-(aminomethyl)cyclopentyl)benzoate (**7**), which is prepared via Grubbs metathesis. The structures of compounds (**i-iv**) were elucidated on the basis of spectral and chemical studies. All the compounds were tested for their antibacterial activities by the paper disc method.

Key words: Chalcone, Grubbs metathesis, HATU, Flavone, Antibacterial.

INTRODUCTION

Chalcones are well known intermediates for synthesizing various heterocyclic compounds. The compounds with the backbone of chalcones have been reported to possess various biological activities such as antimicrobial¹, anti-inflammatory², analgesic³, antiplatelet⁴, antiulcerative⁵, antimalarial⁶, anticancer⁷, antiviral⁸, antileishmanial⁹, antioxidant¹⁰, antitubercular¹¹, antihyperglycemic¹², immunomodulatory¹³, inhibition of chemical mediators release¹⁴, inhibition of leukotriene B₄¹⁵, inhibition of tryptophanase¹⁶ and inhibition of aldose reductase¹⁷ activities. The presence of α , β -unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity¹⁸. In the present communication, we report Grubbs metathesis to prepare novel amine, which is coupled with chalcones prepared by aldol condensation of acetophenone and aromatic aldehydes. All coupled products were screened for their antibacterial activity.

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EXPERIMENTAL

All reagents and solvents were purchased from Srinivasa Traders, Hyderabad, India. TLC (pre-coated silica gel 60 F₂₅₄, Merck) was used to monitor the progress of the reaction and the products were isolated by short column chromatography on silica gel (100-200 mesh) using ethyl acetate/hexane mixtures as eluent. ¹H NMR were recorded in CDCl₃ and DMSO-d₆ with 200 MHz instrument. TMS was used as an internal standard.

4-(Bromomethyl) benzoic acid (2)

To a suspended solution of 4-methyl benzoic acid (**1**) (5 g, 36.7 mmol) in nitrobenzene (7.5 mL) bromine (6.47 g, 40.44 mmol) was added at 180 °C for 45 min. The reaction mixture was allowed to room temperature and then diluted with hexane. The precipitated solids were filtered; dried under vacuum. The crude material was crystallized in EtOH to afford 4-(bromomethyl) benzoic acid (**2**) (5.0 g, 65% yield). Mass (e/z) 216 (M+1). ¹H NMR (CDCl₃, 200 MHz): δ 13.01 (br s, 1H), 7.99 (dd, *J* = 2, 6.8 Hz, 2H), 7.59 (dd, *J* = 2.1, 6.8 Hz, 2H), 4.77 (s, 2H). Anal. Calcd for C₈H₇BrO₂: C, 44.68; H, 3.28; Br, 37.16; O, 14.88.

Methyl 4-(bromomethyl) benzoate (3)

To a solution of 4-(bromomethyl) benzoic acid (**2**) (4.5 g, 20.9 mmol) in MeOH (40 mL) was added conc. H₂SO₄ (0.4 mL) at room temperature. The reaction mixture was heated to reflux and then stirred for 4h. The volatiles were concentrated under vacuum and residue was diluted with ethyl acetate and water. The organic layer was separated, washed with sat. NaHCO₃ solution, dried (anhy. Na₂SO₄) and concentrated under vacuum to afford methyl 4-(bromomethyl)benzoate (**3**) (2.39 g, 50% yield) as a syrup. Mass (e/z) 230 (M+1). ¹H NMR (CDCl₃, 200 MHz): δ 7.89 (dd, *J* = 2, 6.6 Hz, 2H), 7.55 (dd, *J* = 2.1, 6.8 Hz, 2H), 4.75 (s, 2H), 3.88 (s, 3H). Anal. Calcd for C₉H₉BrO₂: C, 47.19; H, 3.96; Br, 34.88; O, 13.97.

Methyl 4-(cyanomethyl)benzoate (4)

To a solution of methyl 4-(bromomethyl)benzoate (**3**) (2 g, 8.73 mmol) in methanol (20 mL), a solution of sodium cyanide (642 mg, 13.1 mmol) in water was added dropwise at room temperature. The reaction mixture was heated to 50 °C, and then stirred for 1 h. The reaction mixture was concentrated under vacuum and residue was diluted with water. The precipitated solids were filtered, washed with water (25 mL), dried under vacuum to afford methyl 4-(cyanomethyl) benzoate (**4**) (733 mg, 48% yield) as a solid. Mass (e/z) 176 (M+1). ¹H NMR (CDCl₃, 200 MHz): δ 8.06 (dd, *J* = 2, 6.6 Hz, 2H), 7.43 (dd, *J* = 2 Hz, 7.8 Hz, 2H), 3.93 (s, 3H), 3.82 (s, 2H). Anal. Calcd for C₁₀H₉NO₂: C, 68.56; H, 5.18; N, 8.00; O, 18.27.

Methyl 4-(4-cyanohepta-1,6-diene-4-yl)benzoate (5)

To a solution of methyl 4-(cyanomethyl)benzoate (**4**) (700 mg, 4 mmol) in anhy. THF (10 mL), LiHMDS (1 M solution in THF) (9.5 mL, 9.5 mmol) was added dropwise at 0°C and stirred for 30 mins at room temperature. Then propargyl bromide (1.04 g, 8.8 mmol) was added at 0°C dropwise, and stirred for 3 h at room temperature. The reaction mixture was quenched with sat. NH₄Cl (10 mL). Then volatiles were concentrated under vacuum and product was extracted into ethyl acetate (25 mL). The organic layer was dried (anhy. Na₂SO₄) and concentrated under vacuum. The crude material was purified through column chromatography, eluted product with 7% ethyl acetate/hexanes to afford methyl 4-(4-cyanohepta-1,6-diene-4-yl)benzoate (**5**) (683 mg, 67% yield) as a solid. Mass (e/z) 256 (M+1). ¹H NMR (CDCl₃, 200 MHz): δ 8.12 (dd, *J* = 2, 6.8 Hz, 2H), 7.43 (dd, *J* = 2.2 Hz, 7.8 Hz, 2H), 5.78-5.46 (m, 2H), 5.20 (s, 2H), 5.15 (d, 2H), 3.86 (s, 3H), 2.78-2.65 (m, 4H). Anal. Calcd for C₁₆H₁₇NO₂: C, 75.27; H, 6.71; N, 5.49; O, 12.53.

Methyl 4-(1-cyano cyclopent-3-enyl)benzoate (6)

To a solution of methyl 4-(4-cyanohepta-1,6-diene-4-yl)benzoate (**5**) (600 mg, 2.35 mmol) in dichloromethane (20 mL), grubbs catalyst (second generation) (10 mg) was added at room temperature. The reaction mixture was heated to 50 °C, and then stirred for 4 h. The reaction mixture was filtered through celite, washed with dichloromethane (20 mL), the filtrate was washed with water, dried (anhy. Na₂SO₄) and concentrated under vacuum to afford methyl 4-(1-cyano cyclopent-3-enyl)benzoate (**6**) (480 mg, 90% yield) as a solid. Mass (e/z) 228 (M+1). ¹H NMR (CDCl₃, 200 MHz): δ 8.03 (dd, *J* = 2, 6.8 Hz, 2H), 7.43 (dd, *J* = 2, 6.8 Hz, 2H), 5.83 (s, 2H), 3.92 (s, 3H), 3.35 (d, *J* = 15.2, 2H), 2.97 (d, *J* = 15 Hz, 2H). Anal. Calcd for C₁₄H₁₃NO₂: C, 73.99; H, 5.77; N, 6.16; O, 14.08.

Methyl 4-(1-(aminomethyl)cyclopentyl)benzoate hydrochloride (7)

To a solution of 4-(1-cyano cyclopent-3-enyl)benzoate (**6**) (400 mg, 1.76 mmol) in MeOH (20 mL), Raney Ni (400 mg) was added at room temperature and stirred for 12 h at room temperature under H₂ balloon pressure. The reaction mixture was filtered through celite bed, washed with methanol. Then 1N dioxane-HCl (1.7 mL) was added and concentrated under vacuum. The crude material was titrated with hexanes and then concentrated under vacuum to afford methyl 4-(1-(aminomethyl)cyclopentyl)benzoate hydrochloride (**7**) (356 mg, 75% yield) as a white solid. Mass (e/z) 234 (M+1). ¹H NMR (DMSO-d₆, 200 MHz): δ 7.93 (d, *J* = 8.2 Hz, 2H), 7.78 (br s, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 3.03 (s, 2H), 2.01-1.87 (m, 4H), 1.72-1.59 (m, 4H). Anal. Calcd for C₁₄H₂₀ClNO₂: C, 62.33; H, 7.47; Cl, 13.14; N, 5.19; O, 11.86.

1-(2-Methyl *H*-imidazo [1, 2-*a*] pyridin-3-yl) ethanone (17)

A mixture of 2-amino pyridine (**15**) (10 g, 106 mmol) and 3-chloropentane-2, 4-dione (**16**) (21.3 g; 159 mmol) in ethanol (100 mL) was refluxed at 80 °C for 24 h. The volatiles were concentrated under reduced pressure. The crude material was purified through silica gel column chromatography and eluted product with 80% ethylacetate/hexanes afforded 1-(2-methyl*H*-imidazo [1, 2-*a*] pyridin-3-yl) ethanone (**17**) (8.5 g; 46% yield) as a solid. Mass (*e/z*): 175 (*M*+1). ¹H NMR (200 MHz, CDCl₃-d₆): δ 9.75 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.50 (t, *J* = 7 Hz, 1H), 7.03 (t, *J* = 7 Hz, 1H), 2.80 (s, 3H), 2.63 (s, 3H). Anal. Calcd for C₁₀H₁₀N₂O: C, 68.95; H, 5.79; N, 16.08; O, 9.18.

2-(4-Ethoxy-phenyl)-4-oxo-4H-chromene-6-carboxylic acid (19)

Bromine (26 mg; 0.16 mmol) was added to a solution of the chalcone (**13**) (25 mg; 0.08 mmol) in acetic acid (5 mL) at room temperature. After the solution was stirred at ambient temperature for 3 h, 1% aqueous NaHSO₃ (5 mL) was added slowly. The resulting precipitate was filtered, washed with water and suspended in ethanol (5 mL). Then KOH (18 mg; 0.32 mmol) dissolved in water was added, and stirring was continued for 4 h. The reaction mixture was acidified by using 2N HCl to pH = 4 and stirred for 15 min, filtered; precipitated solid was then purified through column chromatography, eluted with 8% methanol/dichloromethane to afford flavone (**19**) (10.6 mg; 41% yield) as a yellow solid. Mass (*e/z*) 310 (*M*+1). ¹H NMR 200 MHz (DMSO-d₆): δ 8.56 (s, 1H), 8.26 (dd, *J* = 2.8 Hz, 2.7 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 2H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.99 (s, 1H), 4.10 (q, 2H), 1.34 (t, *J* = 6.6 Hz, 3H). Anal. Calcd for C₁₈H₁₄O₅: C, 69.67; H, 4.55; O, 25.78.

General procedure for chalcone synthesis

To a solution of aldehyde (**8-10**) (1.1 mole) and 3-acetyl-4-hydroxy benzoic acid (**11**) (1 mol) or 1-(2-methyl *H*-imidazo [1, 2-*a*] pyridin-3-yl) ethanone (**17**) (1 mol) in ethanol, 40% KOH (aq) solution (15 mL) was added slowly dropwise at 0 °C for 20 min. Then the reaction was stirred for 48 h at ambient temperature. The reaction mixture was quenched with ice-cold water and pH was adjusted to 5 by using 4N HCl at 20°C; stirred for 15 min, filtered. The solid was washed with water, dried under vacuum and recrystallized in ethanol to afford chalcone (**12-14**, **17**) as a yellow solid. (~60% yield).

4-Hydroxy-3-(3-(4-methoxy-phenyl)-acryloyl) benzoic acid (12)

As a yellow solid. Mass (*e/z*) 298 (*M*+1). ¹H NMR 200 MHz (DMSO-d₆): δ 12.5-12.9 (bs, 1H), 8.55 (s, 1H), 8.03 (d, *J* = 10.6 MHz, 1H), 7.83 (t, *J* = 8.8 Hz, 4H), 7.04 (t, *J* = 8.8 Hz), 3.82 (s, 3H). Anal. Calcd for C₁₇H₁₄O₅: C, 68.45; H, 4.73; O, 26.82.

3-(3-(4-Ethoxy-phenyl)-acryloyl)-4-hydroxy-benzoic acid (13)

Yellow solid Mass (e/z) 312 (M+1). ¹H NMR 200MHz (DMSO-d₆): δ 12.85 (bs, 1H), 12.77 (bs, 1H), 8.55 (s, 1H), 8.04 (d, *J* = 10.6MHz, 1H), 7.83 (t, *J* = 7.6 Hz, 4H), 6.9-7.08 (m, 3H), 4.10 (q, 2H), 1.33 (t, *J*=7Hz, 3H). Anal. Calcd for C₁₈H₁₆O₅: C, 69.22; H, 5.16; O, 25.61.

3-(4-Ethoxy phenyl)-1-(2-methyl H-imidazol[1,2-a]pyridin-3-yl)prop-2-en-1-one (iii)

As a yellow solid. Mass (e/z) 307 (M+1). ¹H NMR (200 MHz, DMSO-d₆): δ 1.36 (t, 3H), 2.81 (s, 3H), 4.15 (q, 2H), 6.99-7.22 (m, 2H), 7.4-7.85 (m, 6H), 9.63 (d, 1H). Anal. Calcd for C₁₉H₁₈N₂O₂: C, 74.49; H, 5.92; N, 9.14; O, 10.44.

General amide coupling procedure with HATU¹⁹ reagent

The appropriated chalcone acid derivative (**12 & 13**) (1 mol) or flavones acid (**19**) (1 mol) was added to a solution of the appropriated amines (**19**) (1.1 mol) in dry DMF (0.2 mL/mg) followed by HATU (1.2 mol) & DIPEA (2 mol) at 0°C. The reaction mixture was stirred for overnight at room temperature, and then reaction mixture was poured into water. The precipitated solid was filtered, purified through silica gel column chromatography; eluted product with 5-7% methanol/dichloromethane afforded (**i, ii, iv**) (ca. 45-65% yield).

Amide (i) : as a yellow solid Mass (e/z) 514 (M+1). ¹H NMR (DMSO-d₆, 200 MHz): 8.36 (s, 1H), 8.18-8.15 (m, 1H), 7.90-7.77 (m, 6H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.03 (t, *J* = 6.4 Hz, 3H), 3.89 (s, 3H), 3.77 (s, 3H), 3.49 (d, *J* = 5.2 Hz, 2H), 2.15-1.63 (m, 8H). Anal. Calcd for C₃₁H₃₁NO₆: C, 72.50; H, 6.08; N, 2.73; O, 18.69.

Amide (ii): as a yellow solid. Mass (e/z) 529 (M+1). ¹H NMR (DMSO-d₆, 200 MHz): δ 8.37 (s, 1H), 8.17-8.10 (m, 1H), 7.96-7.78 (m, 6H), 7.50-7.43 (m, 3H), 7.03 (dd, *J* = 1.8, 7.2 Hz, 2H), 4.14-4.08 (m, 2H), 3.77 (s, 3H), 3.48 (d, *J* = 5.6 Hz, 2H), 2.12-1.62 (m, 8H), 1.39-1.31 (m, 3H). Anal. Calcd for C₃₂H₃₃NO₆: C, 72.85; H, 6.30; N, 2.65; O, 18.19.

Amide (iv): as a yellow solid. Mass (e/z) 526 (M+1). ¹H NMR 200 MHz (DMSO-d₆): 8.41 (d, *J* = 2 Hz, 1H), 8.12-8.05 (m, 3H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 9.2 Hz, 2H), 6.99 (s, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 3.48 (d, *J* = 5.8 Hz, 2H), 2.12-1.63 (m, 8H), 1.36 (t, *J* = 6.8 Hz, 3H). Anal. Calcd for C₃₂H₃₁NO₆: C, 73.13; H, 5.94; N, 2.66; O, 18.26.

In vitro antibacterial screening

The synthesized compounds were subjected to antibacterial screening by paper disc

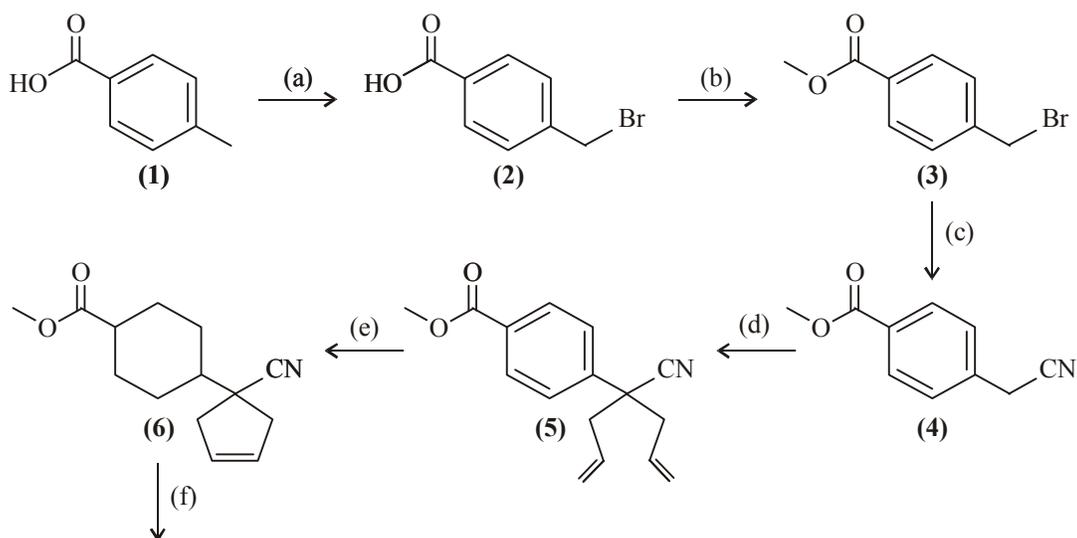
method²⁰ for zone of inhibition. The antibacterial activity tested against Gram positive bacteria (*Bacillus sphericus*) and Gram negative bacteria (*E.Coli*). The results are described in the Table 1.

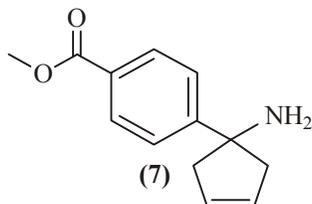
Table 1: Anti bacterial activity of chalcone derivatives (Zone of inhibition in mm)

S. No	Sample code	<i>Bacillus sphericus</i>	<i>Escherichia coli</i>
1	i	8	-ve
2	ii	6	-ve
3	iii	-ve	4
4	iv	-ve	4

RESULTS AND DISCUSSION

The bromination of p-methyl benzoic acid (**1**) using bromine in nitrobenzene at 180 °C for 45 min (ca. 65% yield)²¹ and then esterification of bromo acid (**2**) was carried out by using conc. H₂SO₄ in MeOH for 4 h (ca. 50% yield). This bromo ester (**3**) was converted to cyanoester (**4**) by using NaCN in MeOH and H₂O at 50 °C for 1 h (ca. 48% yield). Then dialkylation at α -carbon of cyano compound (**4**) was done with propargyl bromide using LiHMDS in THF at room temperature for 5 h (ca. 67% yield). Grubb's (second generation) catalyst²² was used for ring closing metathesis at both allyl groups of dialkylated product (**5**) in DCM at 50 °C for 4 h (ca. 90% yield). Finally, cyano group was hydrogenated over Raney nickel to give the cyclopropyl amine derivative (**7**) (ca. 75% yield) **Scheme 1**.

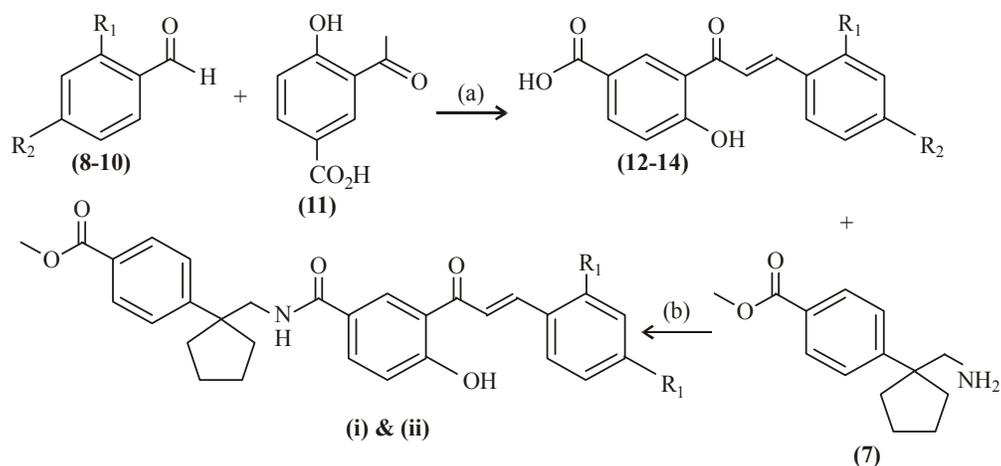




Reagents and conditions: (a) Br₂, Nitrobenzene, 175°C, 45 min (b) MeOH, Conc. H₂SO₄, reflux, 4 h (c) NaCN, water, MeOH, 50°C, 1 h (d) LiHMDS, propargyl bromide, 0°C-Room temperature, 4 h (e) Grubb's second generation, DCM, 40°C, 4 h (f) Raney Ni, H₂, 24 h.

Scheme 1

An aldol condensation of aromatic aldehydes (**8-10**) with keto derivatives (**11**) by using 40% KOH solution in ethanol at room temperature^{20,23} (ca.~60% yield) gave corresponding chalcone derivatives (**12-14**) and further coupling was done with methyl 4-(1-(aminomethyl) cyclopentyl) benzoate (**7**) by using HATU, DIPEA in DMF at 0°C-room temperature for 3 h (~ 65% yield) (**Scheme 2**).



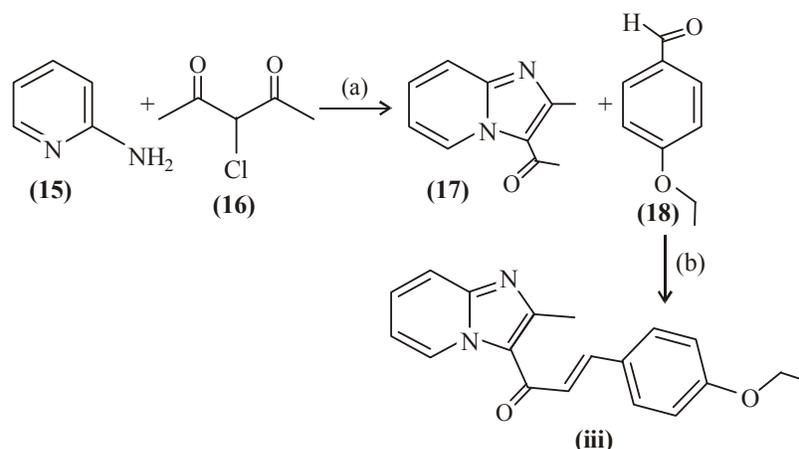
8: R₁ = H, R₂ = OCH₃; **9:** R₁ = H, R₂ = OCH₂CH₃; **10:** R₁ = CH₃, R₂ = H
12: R₁ = H, R₂ = OCH₃; **13:** R₁ = H, R₂ = OCH₂CH₃; **14:** R₁ = CH₃, R₂ = H
(i): R₁ = H, R₂ = OCH₃; **(ii):** R₁ = H, R₂ = OCH₂CH₃

Reagents and conditions: (a) 40% KOH, EtOH, Room temperature, 12h (b) HATU, DIPEA, DMF, 0°C-room temperature, 12 H

Scheme 2

The keto derivative (**17**) was prepared by cyclization of 2-amino pyridine (**15**) with

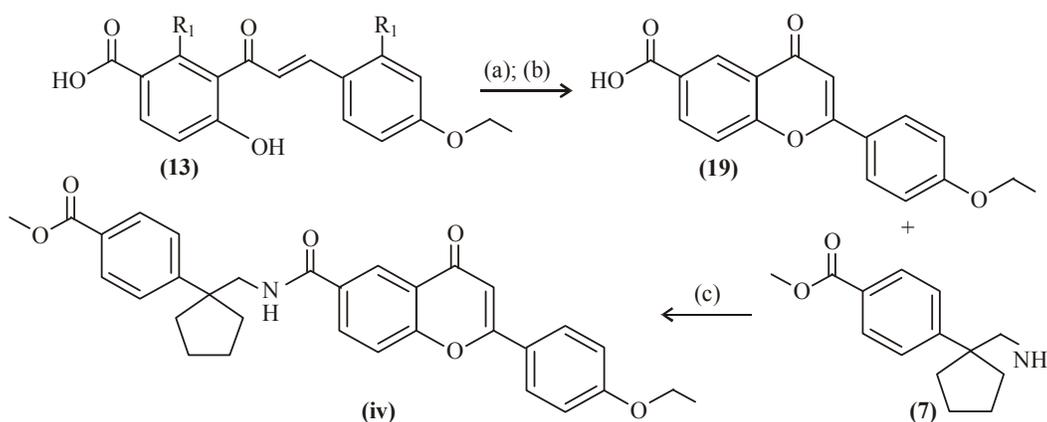
3-chloropentane-2, 4-dione (**16**) in ethanol for 24 h at 80°C (ca. 46% yield). Then further chalcone derivative (**iii**) was prepared by aldol condensation with 4-ethoxy benzaldehyde (**18**) to give (ca. 58% yield) (**Scheme 3**)



Reagents and conditions: (a) EtOH, reflux, 40% KOH, EtOH, Room temperature, 12h

Scheme 3

Flavone (**19**) was prepared by bromination using bromine in acetic acid at room temperature for 3h. Further cyclization was carried out using KOH in ethanol at room temperature for 5h (ca. 41% yield)^{24,25}. Then compound (**iv**) was prepared by coupling of flavones (**19**) with (**7**) using HATU, DIPEA in DMF at room temperature for 12 h. (ca. 48% yield) (**Scheme 4**).



Reagents and conditions: (a) Br₂, AcOH, Room temperature, 3 h (b) KOH, EtOH, Room temperature, 5 h (c) HATU, DIPEA, DMF, 0°C-Room temperature, 12 h

Scheme 4

All the synthesized compounds were screened for their antibacterial activities. Compounds (i) and (ii) showing activity with *Bacillus spericus* and (iii), (iv) on *Escherichia coli* cultures.

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