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Synthesis, characterization and antibacterial evaluation of chalcones containing thiazole moiety

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Abstract: Chalcones **(5a-j)** containing thiazole moiety were synthesized by Claisen-Schmidt condensation between 1-(4-methyl-2-(pyridine-3-yl)thiazol-5-yl)ethanone **(3)** and variously substituted aryl/heteryl aldehydes **(4a-j)** in good yield. All the synthesized compounds were characterized by FTIR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis data. The synthesized compounds were evaluated for their *in vitro* antibacterial activity against Gram-positive and Gram-negative bacteria and showed moderate to good antibacterial activity.

Keywords: Thiazole, Chalcone, Antibacterial, Synthesis, Aldehydes.

Introduction

High chemical reactivity, appearance of different colors, various pharmacological properties and easy accessibility of chalcones provides several routes to chemist and pharmacologist to synthesize varieties of heterocyclic compounds like pyrazolines [1], pyrimidines [2], coumarines [3], benzothiazepines [4], benzodiazepines [5] etc, using chalcone precursors. Presence of reactive α,β-unsaturated carbonyl system in chalcones plays an important role in construction of several biodynamic structures. Literature survey reveals that the potential activity of chalcones was modified several times when these are in connection with other heterocyclic system [6]. Thiazoles are well known five membered nitrogen and sulfur containing heterocyclic compounds and have been reported to possess different biological activities like antimicrobial [7], anticonvulsant [8], antioxidant [9], antitumor [10], anticancer [11] etc.

Keeping in mind the importance of chalcones and thiazoles, an attempt has been made to synthesize chalcones containing thiazole moiety.

Several researchers have reported synthesis of fused chalcone-thiazole in a single molecule exhibiting diverse pharmacological activities [12]. We have tried to synthesize chalcones containing thiazole ring at position 1 of α,β-unsaturated carbonyl system using medicinally important nicotinamide or niacin which is also known as vitamin B_3 as a starting material [13].

Results and discussion

The aim of our present work is intended to synthesize of potentially active chalcones. Thus, chalcones containing thiazole moiety were synthesized by Claisen-Schmidt condensation of 1-(4-methyl-2-(pyridine-3-yl)thiazol-5-yl)ethanone **(3)** with variously substituted aryl/heteryl aldehydes **(4a-j)** (Scheme **1**). The compound **(3)** required for the synthesis was prepared by reaction of pyridine-3-carbothioamide **(1)**

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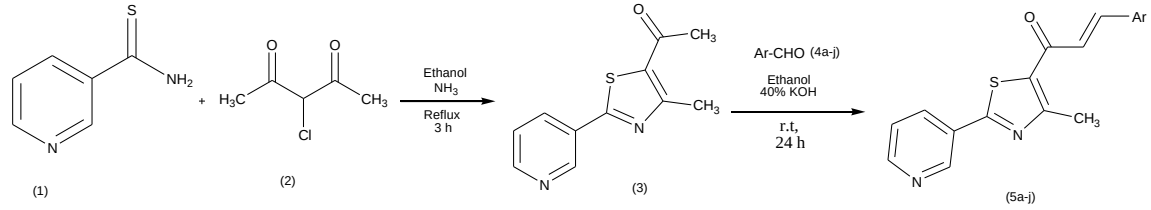
and 3-chloropentane-2,3-dione **(2)** in ethanol. The formation of compound **(3)** containing acetyl group at position 5 of thiazole ring was confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. The IR spectrum of compound **(3)** displayed band at 1627 cm^{-1} for carbonyl stretching, ^{1}H NMR spectrum displayed singlet peak at δ 2.59 for three –$COCH_3$ protons attached at position 5 of thiazole and singlet peak at δ 2.80 for three -CH_3 protons attached at position 4 of thiazole ring, four aromatic protons displayed multiplate peaks at δ 7.28-8.01, ^{13}C NMR spectrum displayed peak at δ 190.60 for carbonyl carbon, peak at δ 30.90 for methyl carbon and peak at δ 18.48 for acetyl carbon, the mass spectrum displayed (M^+) peak at m/z = 218 and (M+1) peak at m/z = 219, which confirms the formation of 1-(4-methyl-2-(pyridine-3-yl)thiazol-5-yl)ethanone **(3)**. Physical data of synthesized compounds **(5a-j)** is given in Table **1.** The compounds **(5a-j)** were characterized by spectral and elemental analyses which are in good agreement with the proposed structure of chalcones. For example, the IR spectrum of compound (**5j)** exhibited sharp peak at 1657 cm^{-1} for carbonyl stretching, ^{1}H NMR spectrum displayed singlet peak at δ 2.89 for three protons of –CH_3 group attached to position four of thiazole ring and multiplate peaks in the region δ 6.55-9.24 for nine aromatic and vinylic protons, the ^{13}C NMR spectrum of the same compound displayed peak at δ 18.61 for methyl carbon and peak at δ 182.52 carbonyl carbon, mass spectrum displayed peak at m/z = 296 (M^+), 297 (M+1). The spectral data is in good agreement with the proposed structure.



5a = Ar = -Ph, 5b = Ar = *p*-ClPh, 5c = Ar = *p*-FPh, 5d = Ar = *p*-BrPh, 5e = Ar = *o*-ClPh,

5f = Ar = *p*-NO_2Ph, 5g = Ar = *p*-MeOPh, 5h = Ar = *p*-MePh, 5i = Ar = 2-Thiophene, 5j = Ar = 2-Furan

Scheme 1: Synthesis of thiazolyl chalcones

Table 1: Physical data of thiazolyl chalcones[a] (**5a-j**).

Sr. No.	Product[b]	Molecular formula	Molecular weight (g)	Melting point (°C)	Yield (%)
1	5a	$C_{18}H_{14}N_2OS$	306	150-152	82
2	5b	$C_{18}H_{13}ClN_2OS$	340	160-162	86
3	5c	$C_{18}H_{13}FN_2OS$	324	158-160	87
4	5d	$C_{18}H_{13}BrN_2OS$	383	156-158	80
5	5e	$C_{18}H_{13}ClN_2OS$	340	166-168	86
6	5f	$C_{18}H_{13}N_3O_3S$	351	146-148	72
7	5g	$C_{19}H_{16}N_2O_2S$	336	154-156	82
8	5h	$C_{19}H_{16}N_2OS$	320	162-164	76
9	5i	$C_{16}H_{12}N_2OS_2$	312	152-154	78
10	5j	$C_{16}H_{12}N_2O_2S$	296	148-150	84

[a]1-(4-methyl-2-(pyridine-3-yl)thiazol-5-yl) ethanone (2.18 g, 0.01 mol), aromatic/heteryl aldehydes (0.01 mol), 40% KOH (10 mL), ethanol (50 ml) were stirred at room temperature for about 24 h.
[b]All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry.

Antibacterial activity:

All the synthesized compounds were screened *in vitro* for their antibacterial activity against gram-positive bacteria viz. *Staphylococcus aureus*, *Bacillus subtilis* and gram-negative bacteria viz. *Escherichia coli*, *Pseudomonas aeruginosa* using ciprofloxacin as standard antibacterial. The antibacterial activity was determined by the cup plate method on agar nutrient media at the concentration of 100 µg per disk using DMSO solvent. The results of the antibacterial activity are presented in Table **2**. An examination of antibacterial activity data revealed that the compounds 5b, 5c, 5e, 5g and 5h having *p*-Cl, *p*-F, *o*-Cl, *p*-OCH_3 and *p*-CH_3 substituents respectively have showed significant activities against both gram-positive and gram-negative bacteria.

Table 2: Antibacterial activity of compound (5a-j)

Compound	Zone of inhibition (in mm)			
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*
5a	10	12	12	12
5b	23	23	24	23
5c	21	22	23	23
5d	21	20	22	23
5e	23	22	24	23
5f	20	19	21	21
5g	21	20	22	23
5h	21	21	22	20
5i	12	10	12	13
5j	12	10	12	12
Ciprofloxacin	32	34	35	34
DMSO	---	---	---	---

(S. aureus = Staphylococcus aureus, B. subtilis = Bacillus subtilis, E. coli = Escherchia coli, P. aeruginosa = Pseudomonas aeruginosa)

Conclusion

In summary, we have synthesized and fully characterized a series of chalcones containing thiazole moiety by simple Claisen-Schmidt condensation. The compounds having *p*-Cl, *p*-F, *o*-Cl, *p*-OCH_3 and *p*-CH_3 substituents showed significant antibacterial activities against gram-positive and gram-negative bacteria. We hope that, these chalcones can be used as precursors for the synthesis of varieties of heterocyclic compounds containing thiazole moiety. In our work, we have used these chalcones as an intermediate for the synthesis of 1,5-benzothiazepines containing thiazole moiety.

Experimental

Melting points were determined on MEL-TEMP capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkine Elmer FTIR spectrometer. The samples were examined as KBr discs 5% w/w. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker AC (300 MHz for ^{1}HNMR and 75MHz for ^{13}CNMR) spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Perkin Elmer SQ 300 vectro model. Elemental analyses were performed on the EURO EA3000 Vector model. Precoated aluminium sheets (silica gel 60 F254, Merk Germany) were used for thin-layer chromatography

(TLC) and spots were visualized under UV light. All other chemicals were of commercial grade and used without further purification.

Synthesis of 1-(4-methyl-2-(pyridine-3-yl)thiazol-5-yl) ethanone **(3):**

A mixture of pyridine-3-carbothioamide **(1)** (1.38 g, 0.1 mol) and 3-chloropentane-2,3-dione **(2)** (11.21 ml, 0.1 mol) in ethanol (75 ml) was refluxed for 3 hours. It was then cooled and alcohol removed by evaporation. The separated solid was washed with diethyl ether in order to remove unreacted 3-chloropentane-2,3-dione. The product solid hydrochloride was then treated with ammonia solution. It was then filtered, dried and crystallized form ethanol as pale yellow solid with 80% yield. mp: 192-194 ^{o}C; FT-IR (KBr): ν = 1627, 1541, 1311, 1272, 1244 cm^{-1}; ^{1}HNMR (300MHz, DMSO-d_6): δ 2.59 (s, 3H, -$COCH_3$), 2.80 (s, 3H, thiazole 4'-CH_3), 7.28-8.01 (m, 4H, ArH): ^{13}CNMR (75 MHz, DMSO-d_6): δ 190.6, 168.4, 158.9, 148.2, 143.7, 138.7, 79.7, 79.2, 78.8, 30.9, 18.4 ppm; MS (EI): m/z 218 (M^+), 219 (M+1); Anal. Calcd. for $C_{11}H_{10}N_2OS$: %C, 60.53; %H, 4.62; %N, 12.83. Found: % C, 60.59; % H, 4.65; %N, 12.87.

General procedure for the synthesis of (E)-1-(4-methyl-2-(pyridine-3-yl)thiazol-5-yl)-3-aryl/heterylprop-2-en-ones **(5a-j):**

A mixture of 1-(4-methyl-2-(pyridine-3-yl)thiazol-5-yl)ethanone **(3)** (2.18 g, 0.01 mol) and aromatic/heteryl aldehydes (0.01 mol) in ethanol (50 mL) was added a solution of 40% KOH (10 mL) in portions keeping the temperature below 10^{0}C. The reaction flask was corked and allowed to stir at room temperature for 24 h. The progress of the reaction was monitored by thin layer chromatography. The contents of the flask were then poured over ice (100 g). The solid product obtained was then washed with water, filtered and crystallized from ethanol.

(E)-1-(4-methyl-2-(pyridine-3-yl)thiazol-5-yl)-3-phenylprop-2-en-1-one **(5a):**

Yellow solid; mp 150-152 ^{o}C; FT-IR (KBr): ν = 1642, 1590, 1572, 1491, 1403 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 2.64 (s, 3H, thiazole 4'-CH_3), 6.24-9.14 (m, 11H, aromatic and vinylic protons): ^{13}CNMR (75 MHz, $CDCl_3$): δ 182.64, 152.84, 152.39, 151.73, 149.61, 146.28, 136.42, 132.97, 126.45, 126.32, 121.58, 117.94, 18.22 ppm; MS (EI): m/z 306 (M^+); Anal. Calcd. for $C_{18}H_{14}N_2OS$: %C, 70.56; %H, 4.61; %N, 9.14. Found: %C, 70.50; %H, 4.56; %N, 9.09.

(E)-3-(4-chlorophenyl)-1-(4-methyl-2-(pyridine-3-yl)thiazol-5-yl)prop-2-en-1-one **(5b):**

Yellow solid**;** mp 160-162 ^{o}C; FT-IR (KBr): 1661, 1590, 1572, 1415, 1403 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 2.68 (s, 3H, thiazole 4'-CH_3), δ 6.31-9.16 (m, 10H, aromatic and vinylic protons): ^{13}CNMR (75 MHz, $CDCl_3$): δ 182.42, 154.52, 152.24, 151.84, 147.32, 146.23, 135.29, 132.27, 122.65, 121.21, 117.19, 116.36, 18.59 ppm; MS (EI): m/z 340 (M^+); Anal. Calcd. for $C_{18}H_{13}ClN_2OS$: %C, 63.43; %H, 3.84; %N, 8.22. Found: %C, 63.38; %H, 3.79; %N, 8.18.

(E)-3-(4-flurophenyl)-1-(4-methyl-2-(pyridine-3-yl)thiazol-5-yl)prop-2-en-1-one **(5c):**

Yellow solid**;** mp 154-156 ^{o}C ; FT-IR (KBr): 1674, 1592, 1449, 1429 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 2.69 (s, 3H, thiazole 4'-CH_3), 6.27-9.14 (m, 10H, aromatic and vinylic protons): ^{13}CNMR (75 MHz, $CDCl_3$): δ 182.71, 152.17, 151.34, 147.82, 147.57, 146.42, 136.48, 130.67, 121.91, 121.46, 117.73, 116.75, 18.05 ppm; MS (EI): m/z 323 (M^+); Anal. Calcd. for $C_{18}H_{13}FN_2OS$: %C, 66.65; %H, 4.04; %N, 8.64. Found: %C, 66.60; %H, 4.01; %N, 8.59.

(E)-3-(4-bromophenyl)-1-(4-methyl-2-(pyridine-3-yl)thiazol-5-yl)prop-2-en-1-one **(5d):**

Yellow solid**;** mp 156-158 ^{o}C ; FT-IR (KBr): 1654, 1594, 1459, 1432 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$); δ 2.65 (s, 3H, thiazole 4'-CH_3), 6.51-9.21 (m, 9H, aromatic and vinylic protons): ^{13}CNMR (75 MHz, $CDCl_3$); δ 190.85, 162.54, 152.64, 152.54, 151.34, 149.45, 146.46, 136.21, 132.94, 127.02, 126.46, 126.21, 121.54, 117.94, 20.52 ppm; MS (EI): m/z 385 (M+2); Anal. Calcd. for $C_{18}H_{13}BrN_2OS$: %C, 56.11; %H, 3.40; %N, 7.27. Found: %C, 56.06; %H, 3.36; %N, 7.22.

(E)-3-(2-chlorophenyl)-1-(4-methyl-2-(pyridine-3-yl)thiazol-5-yl)prop-2-en-1-one **(5e):**

Yellow solid**;** mp 166-168 ^{o}C; FT-IR (KBr): 1629, 1599, 1489, 1456 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 2.67 (s, 3H, thiazole 4'-CH_3), δ 6.34-9.29 (m, 10H, aromatic and vinylic protons): ^{13}CNMR (75 MHz, $CDCl_3$): δ 188.98, 157.76, 153.54, 151.23, 148.75, 147.06, 136.43, 135.22, 132.87, 132.04, 122.23, 121.74, 118.17, 117.39, 116.42, 18.22 ppm; MS (EI): m/z 342 (M+2); Anal. Calcd. for $C_{18}H_{13}ClN_2OS$: %C, 63.43; %H, 3.84; %N, 8.22. Found: %C, 63.39; %H , 3.79; %N, 8.19.

(E)-1-(4-methyl-2-(pyridine-3-yl)thiazol-5-yl)-3-(4-nitrophenyl)prop-2-en-1-one **(5f):**

Yellow solid**;** mp 146-148 ^{o}C ; FT-IR (KBr): 1651, 1601, 1485, 1423 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 2.63 (s, 3H, thiazole 4ˈ-CH_3), 6.29-9.11 (m, 10H, aromatic and vinylic protons): ^{13}CNMR (75 MHz, $CDCl_3$): δ 189.20, 167.21, 152.95, 152.64, 151.42, 147.21, 147.01, 146.87, 146.75, 136.54, 131.29, 130.67, 121.41, 121.34, 117.85, 116.27, 18.65 ppm; MS (EI): m/z 352 (M+1); Anal. Calcd. for $C_{18}H_{13}N_3O_3S$: %C, 61.53; %H, 3.73; %N, 11.96. Found: %C, 61.48; %H, 3.69; %N, 11.93.

(E)-3-(4-methoxyphenyl)-1-(4-methyl-2-(pyridine-3-yl)thiazol-5-yl)prop-2-en-1-one **(5g):**

Yellow solid**;** mp 158-160 ^{o}C ; FT-IR (KBr): 1657, 1606, 1514, 1443, 1418 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$); δ 2.60 (s, 3H, thiazole 4ˈ-CH_3), 2.80 (s, 3H, -OCH_3), 7.41-9.19 (m, 10H, aromatic and vinylic protons): ^{13}CNMR (75 MHz, $CDCl_3$); δ 182.54, 151.62, 151.16, 147.63, 145.27, 135.20, 134.36, 123.72, 121.63, 117.12, 116.20, 59.13, 18.21 ppm; MS (EI): m/z 336 (M^+); Anal. Calcd. for $C_{19}H_{16}N_2O_2S$: %C, 67.84; %H, 4.79; %N, 8.33. Found: %C, 67.87; %H, 4.82; %N, 8.36.

(E)-1-(4-methyl-2-(pyridine-3-yl)thiazol-5-yl)-3-p-tolylprop-2-en-1-one **(5h):**

Yellow solid**;** mp 162-164 ^{o}C ; FT-IR (KBr): 1687, 1602, 1554, 1466, 1412 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$); δ 2.62 (s, 3H, thiazole 4ˈ-CH_3), 2.86 (s, 3H, -CH_3), 7.39-9.07 (m, 10H, aromatic and vinylic protons): ^{13}CNMR (75 MHz, $CDCl_3$); δ 187.23, 161.34, 151.16, 151.01, 147.87, 145.41, 139.04, 135.45, 134.38, 124.33, 121.86, 117.35, 116.34, 21.49, 18.47 ppm; MS (EI): m/z 321 (M+1); Anal. Calcd. for $C_{19}H_{16}N_2OS$: %C, 71.22; %H, 5.03; %N, 8.74. Found: %C, 71.17; %H, 4.98; %N, 8.69.

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