



Research Article

SYNTHESIS AND ANTIBACTERIAL SCREENING OF NOVEL (E)-3-(3-(2-(4-FLUOROPHENYL)-4-METHYLTHIAZOL-5-YL)-1-PHENYL-1H-PYRAZOL-4-YL)-1-(2-HYDROXYPHENYL)PROP-2-EN-1-ONES

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Article Received on: 22/04/19 Approved for publication: 12/05/19

DOI: 10.7897/2230-8407.1005189

ABSTRACT

A novel series of chalcone 3a-e was prepared by conventional Claisen–Schmidt condensation of 3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde 1 with substituted 2-hydroxyacetophenones using 40 % aq. KOH in ethanol. The starting material 3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde 1 was synthesized by reacting 1-[2-(4-fluorophenyl)-4-methyl-1,3-thiazol-5-yl]ethan-1-one with phenyl hydrazine followed by reaction with DMF/ POCl₃. The structures of all newly synthesized compounds were assigned on the basis of spectral data such as IR, ¹H-NMR and mass. These compounds 3a-e were evaluated for their antibacterial activity against gram-negative *Pseudomonas fluorescens* and *Escherichia coli* and gram-positive bacteria, *Bacillus subtilis* and *Staphylococcus aureus*. Compounds 3a-e showed good activity against gram positive bacterial strain of *Bacillus subtilis* compared to the standard drug Ampicillin at a concentration of 100 µg/mL also compounds 3a, 3c, 3d and 3e showed good activity at a concentration of 30 µg/mL but none of them was as active as standard Ampicillin.

Keywords: 1,3-Thiazole, Pyrazole, Antibacterial, Chalcones.

INTRODUCTION

1,3-Thiazole is well known sulphur and nitrogen containing five member heterocyclic compound found in many clinically used drugs like Meloxicam, Nizatidine, Tiazofurin, Ritonavir, Bleomycin, etc. Molecules containing thiazole nucleus are attractive targets for medicinal chemistry because of their wide spectrum of biological activities such as anti-inflammatory^{1,2}, antibacterial², human adenosine A₃ receptor antagonists³, antiproliferative⁴, adenosine receptor antagonists⁵, C-aryl glucoside SGLT2 inhibitors⁶.

Chalcone is generally found in plant pigments and it is an intermediate involved in the synthesis of many biologically active heterocyclic compounds. A large number of chalcones have been studied mainly due to their various pharmacological properties. Chalcones and their derivatives are known to have antidiabetic⁷, anticancer⁸, anti-parasitic⁹, antileishmanial¹⁰, anti-inflammatory¹¹, antimicrobial¹², antimalarial¹³, antiplasmodial¹⁴, acetylcholinesterase inhibitor¹⁵ activities.

Fluorine and fluorinated compounds have attracted many researchers due to their pharmacological importance. Fluorine substitution has been extensively investigated in drug designing and development as a means of enhancing pharmacological activity and increasing metabolic or chemical stability. Fluorine containing compounds possess fungicidal¹⁶, herbicidal¹⁷, antiviral¹⁸, cytotoxic¹⁹, antipyretic²⁰, insecticidal²¹ and analgesic²² activities.

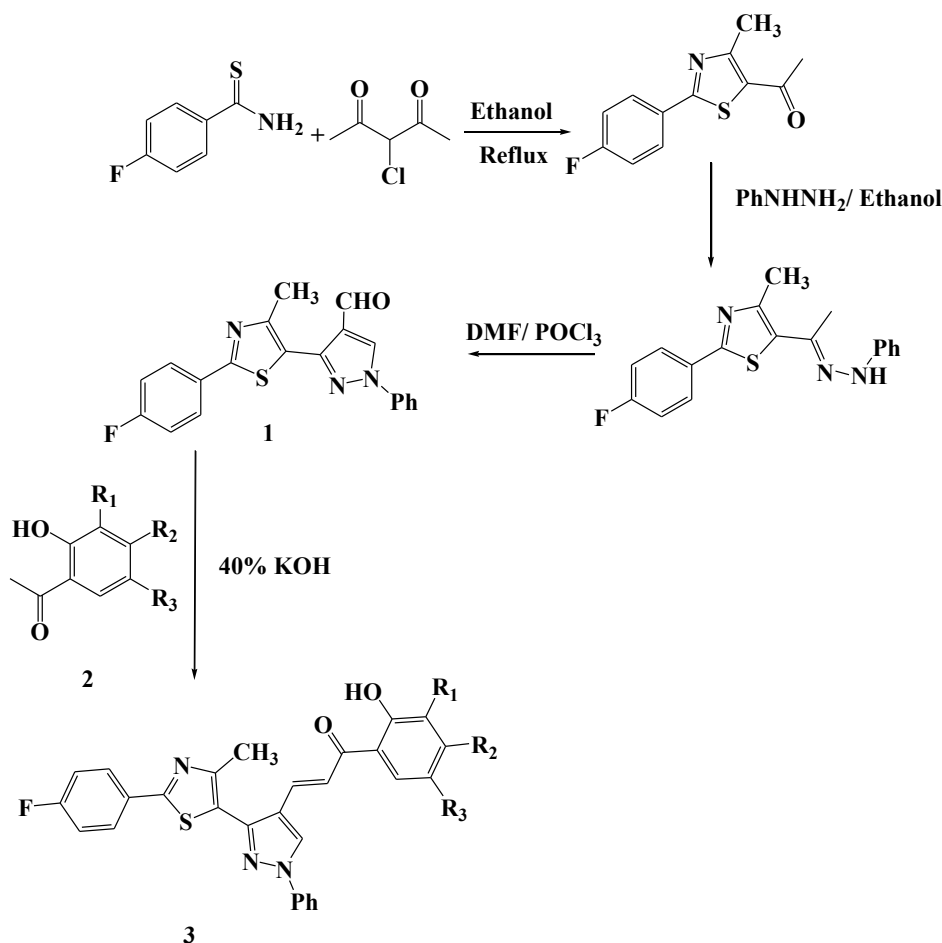
Activities associated with thiazole and fluorine containing compounds prompted us to synthesize thiazole and fluorine anchored novel chalcone derivatives.

MATERIALS AND METHODS

The synthetic route adopted to obtain the chalcone derivatives 3a-e is shown in scheme-1. The starting material 3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde 1 was synthesized by reacting 1-[2-(4-fluorophenyl)-4-methyl-1,3-thiazol-5-yl]ethan-1-one with phenyl hydrazine followed by reaction with DMF/ POCl₃. Chalcone 3a-e was prepared by conventional Claisen–Schmidt condensation of 3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde 1 with substituted 2-hydroxyacetophenones using 40 % aq. KOH in ethanol. The structures of all newly synthesized compounds were assigned on the basis of spectral data such as IR, ¹H-NMR and mass. These compounds were evaluated for their antibacterial activity against gram-negative *Pseudomonas fluorescens* and *Escherichia coli* and gram-positive bacteria, *Bacillus subtilis*, *Staphylococcus aureus*.

RESULTS AND DISCUSSION

All organic solvents were acquired from commercial sources and used as received. The melting points were measured on a DBK melting point apparatus and are uncorrected. IR spectra were recorded on Shimadzu IR Affinity 1S (ATR) FTIR spectrophotometer. ¹H NMR (400 MHz) spectra were recorded on Varian 400 spectrophotometer using TMS as an internal standard and DMSO-d₆ as solvent and chemical shifts were expressed as δ ppm units. Mass spectra were obtained on Shimadzu (LC-MS) mass spectrometer.



Scheme-1

General procedure for the synthesis of (E)-3-(3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-phenyl-1H-pyrazol-4-yl)-1-(2-hydroxyphenyl) prop-2-en-1-one

A mixture of 3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde **1** (0.015 mol) and 2-hydroxyacetophenone **2** (0.015 mol) was dissolved in 25 mL of ethanol and 10 mL of 40 % KOH solution. The reaction mixture was stirred at RT for 10 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents were poured over crushed ice and acidified with conc. HCl. The solid product thus obtained was filtered and re-crystallized from ethanol to get compound **3a-e**.

(E)-1-(5-Fluoro-2-hydroxyphenyl)-3-(3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-phenyl-1H-pyrazol-4-yl) prop-2-en-1-one **3a**

Yellow solid; Yield: 73 %; M.P. = 226°C; IR: 3151, 1637, 1561, 1170 cm^{-1} ; ^1H NMR: δ 2.54 (s, 3H), 7.10 (t, 2H, $J = 8\text{Hz}$), 7.22-8.30 (m, 12H), 9.51 (s, 1H), 12.35 (s, 1H); Mass: m/z 500 $[\text{M}+\text{H}]^+$.

(E)-1-(5-Chloro-2-hydroxyphenyl)-3-(3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-phenyl-1H-pyrazol-4-yl) prop-2-en-1-one **3b**

Yellow solid; Yield: 69 %; M.P. = 250 °C; IR: 3153, 1638, 1560, 1171 cm^{-1} ; ^1H NMR: δ 2.53 (s, 3H), 7.11 (t, 2H, $J = 8\text{Hz}$), 7.16-8.23 (m, 12H), 9.52 (s, 1H), 12.33 (s, 1H); Mass: m/z 516 $[\text{M}+\text{H}]^+$.

(E)-1-(5-Bromo-2-hydroxyphenyl)-3-(3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-phenyl-1H-pyrazol-4-yl) prop-2-en-1-one **3c**

Yellow solid; Yield: 77 %; M.P. = 264 °C; IR: 3154, 1637, 1562, 1170 cm^{-1} ; ^1H NMR: δ 2.54 (s, 3H), 7.08 (t, 2H, $J = 8.4\text{Hz}$), 7.19-8.30 (m, 12H), 9.53 (s, 1H), 12.34 (s, 1H); Mass: m/z 560 $[\text{M}+\text{H}]^+$.

(E)-1-(3,5-Dichloro-2-hydroxyphenyl)-3-(3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-phenyl-1H-pyrazol-4-yl) prop-2-en-1-one **3d**

Yellow solid; Yield: 75 %; M.P. = 270°C; IR: 3152, 1636, 1564, 1169 cm^{-1} ; ^1H NMR: δ 2.54 (s, 3H), 7.10 (t, 2H, $J = 8.4\text{Hz}$), 7.17-8.28 (m, 11H), 9.54 (s, 1H), 12.31 (s, 1H); Mass: m/z 550 $[\text{M}+\text{H}]^+$.

(E)-1-(5-Chloro-2-hydroxy-4-methylphenyl)-3-(3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-phenyl-1H-pyrazol-4-yl) prop-2-en-1-one 3e

Yellow solid; Yield: 72 %; M.P.=256 °C; IR: 3153, 1638, 1560, 1170 cm⁻¹; ¹H NMR: δ 2.31 (s, 3H), 2.52 (s, 3H), 7.10 (t, 2H, J=8Hz), 7.22-8.30 (m, 11H), 9.51 (s, 1H), 12.35 (s, 1H); Mass: m/z 530 [M+H]⁺.

Antibacterial screening

The antibacterial activity of synthesized compounds was against the standard Gram-negative bacteria, *Pseudomonas fluorescens* (NCIM 2059), *Escherichia coli* (NCIM 2576) and Gram-positive bacteria, *Bacillus subtilis* (NCIM 2162), *Staphylococcus aureus* (NCIM 2602). Ampicillin served as positive control for antibacterial activity. The *in vitro* preliminary screening values (% inhibition) against microorganisms tested are summarized in Table 1.

All bacterial cultures were first grown in Luria Burtony media at 37°C at 180 rpm. Once the culture reaches 1 O.D., it is used for

anti-bacterial assay. Bacterial strains *Pseudomonas fluorescens* (NCIM 2059), *Escherichia coli* (NCIM 2576) as Gram-negative and *Bacillus subtilis* (NCIM 2162), *Staphylococcus aureus* (NCIM 2602) as Gram-positive. The bacterial strains were obtained from NCIM (NCL, Pune) and the bacterial strains were grown in Luria Burtony medium from Hi Media, India. The assay was performed in 96 well plates after 8 h and 12 h for Gram negative and Gram positive bacteria respectively²³. For the screening inoculated culture 0.1 % of 1 O.D. culture at 620 nm was used and added into each well of 96 well plates which contains the compounds to be tested.^{24,25} Optical density for each plate was measured at 620 nm after 8 h for Gram-negative bacteria and after 12 h for Gram-positive bacteria.

All the synthesized compounds were found to be inactive against gram negative bacterial strains of *P. fluorescens* and *E. coli* and gram positive bacterial strains of *S. aureus*. Compounds 3a-e showed good activity against gram positive bacterial strain of *B. subtilis* compared to the standard drug Ampicillin at a concentration of 100 µg/mL also compounds 3a, 3c, 3d and 3e showed good activity at a concentration of 30 µg/mL.

Table 1: Antibacterial screening of some synthesized compounds (% inhibition)

Comp	Gram Negative						Gram Positive					
	<i>P. fluorescens</i>			<i>E. coli</i>			<i>S. aureus</i>			<i>B. subtilis</i>		
	100	30	10	100	30	10	100	30	10	100	30	10
3a	13.4	1.6	-	13.3	11.2	8.7	-	-	-	85.4	73.4	-
3b	13.0	-	-	22.7	20.7	13.6	4.7	0.8	-	80.2	64.1	29.9
3c	20.1	2.1	-	40.9	33.9	23.5	3.6	-	-	86.0	84.7	73.4
3d	14.7	0.8	-	27.6	2.3	-	-	-	-	86.0	85.9	20.6
3e	14.5	-	-	24.5	26.0	28.3	-	-	-	87.1	80.6	43.1
AMP	97.0	95.2	92.2	96.6	92.0	92.1	95.0	93.8	91.1	98.5	95.0	90.5

AMP - Ampicillin; Concentrations in µg/mL

CONCLUSION

A series of novel (E)-3-(3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-phenyl-1H-pyrazol-4-yl)-1-(2-hydroxyphenyl) prop-2-en-1-one 3a-e was synthesized and their antibacterial activities were reported. Compounds 3a-e showed good activity against gram positive bacterial strain of *B. subtilis* compared to the standard drug Ampicillin at a concentration of 100 µg/mL also compounds 3a, 3c, 3d and 3e showed good activity at a concentration of 30 µg/mL but none of them was as active as standard ampicillin.

ACKNOWLEDGMENTS

The authors are thankful to Rayat Shikshan Sanstha's Radhabai Kale Mahila Mahavidyalaya, Ahmednagar and Department of Science and Technology (FIST) for providing financial assistance. The authors are also thankful to Dr. Dhiman Sarkar, National Chemical Laboratory, Pune for providing antibacterial screening of the synthesized compounds.

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Cite this article as:

Hemantkumar Akolkar *et al.* Synthesis and Antibacterial screening of novel (E)-3-(3-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)-1-phenyl-1h-pyrazol-4-yl)-1-(2-hydroxyphenyl)prop-2-en-1-ones. Int. Res. J. Pharm. 2019; 10(5):196-199 <http://dx.doi.org/10.7897/2230-8407.1005189>

Source of support: Rayat Shikshan Sanstha's Radhabai Kale Mahila Mahavidyalaya, Ahmednagar and Department of Science and Technology (FIST), Conflict of interest: None Declared

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