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

Hemantkumar Akolkar *, Bhausaheb Karale, Nirmala Darekar

P.G. Department of Chemistry, Radhabai Kale Mahila Mahavidyalaya, Ahmednagar, Maharashtra, India,

*Corresponding Author Email: hemantakolkar@gmail.com

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 = 8Hz), 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 = 8Hz), 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 = 8.4Hz), 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 = 8.4Hz), 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.

REFERENCES

- Helal MHM, Salem MA, El-Gaby MSA, Aljahdali M. Synthesis and biological evaluation of some novel thiazole compounds as potential anti-inflammatory agents. European Journal of Medicinal Chemistry 2013; 65: 517-26.
- Aggarwal R, Kumar S, Kaushik P, Kaushik D, Gupta GK. Synthesis and pharmacological evaluation of some novel 2-(5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-yl)-4-(coumarin-3-yl)thiazoles. European Journal of Medicinal Chemistry 2013; 62: 508-14.
- Jung KY, Kim SK, Gao ZG, Gross AS, Melman N, Jacobson KA *et al.* Structure-activity relationships of thiazole and thiadiazole derivatives as potent and selective human adenosine A3 receptor antagonists. Bioorganic Medicinal Chemistry 2004; 12 Suppl 3: 613-23.
- Grozav A, Gaina LI, Pileczki V, Crisan O, Silaghi Dumitrescu L, Therrien B *et al.* The synthesis and anti proliferative activities of new arylidene-hydrazinyl-thiazole derivatives. International Journal of Molecular Sciences 2014; 15 Suppl 12: 22059-72.
- Muijlwijk Koezen JE, Timmerman H, Vollinga RC, Drabbe Kunzel JF, de Groote M, Visser S *et al.* Thiazole and thiadiazole analogues as a novel class of adenosine receptor antagonists. Journal of Medicinal Chemistry 2001; 44 Suppl 5: 749-62.
- Song K, Lee SH, Kim MJ, Seo HJ, Lee J, Lee S *et al.* Synthesis and SAR of Thiazolylmethylphenyl Glucoside as Novel C-Aryl Glucoside SGLT2 Inhibitors. ACS Medicinal Chemistry Letters 2011; 2 Suppl 2: 182-87.
- Hsieh CT, Hsieh TJ, El-Shazly M, Chuang DW, Tsai YH, Yen CT *et al.* Synthesis of chalcone derivatives as potential anti-diabetic agents Bioorganic Medicinal Chemistry Letters 2012; 22 Suppl 12: 3912-15.
- Lawrence NJ, Patterson RP, Ooi LL, Cook D, Ducki S. Effects of α -substitutions on structure and biological activity

- of anticancer chalcones. Bioorganic Medicinal Chemistry Letters 2006; 16 Suppl 22: 5844-48.
9. Roussaki M, Hall B, Lima SC, da Silva AC, Wilkinson S, Detsi A. Synthesis and anti-parasitic activity of a novel quinolinone-chalcone series. Bioorganic Medicinal Chemistry Letters 2013; 23 Suppl 23: 6436-41.
 10. Suryawanshi SN, Chandra N, Kumar P, Porwal J, Gupta S. Chemotherapy of *leishmaniasis* part-VIII: Synthesis and bio evaluation of novel chalcones. European Journal of Medicinal Chemistry 2008; 43 Suppl 11: 2473-78.
 11. Cheng JH, Hung CF, Yang SC, Wang JP, Won SJ, Lin CN. Synthesis and cytotoxic, anti-inflammatory, and anti-oxidant activities of 2',5'-dialkoxylchalcones as cancer chemo preventive agents. Bioorganic Medicinal Chemistry 2008; 16 Suppl 15: 7270-76.
 12. Ngainia Z, Fadzillah SMH, Hussain H. Synthesis and antimicrobial studies of hydroxylated chalcone derivatives with variable chain length. Natural Product Research 2012; 26 Suppl 10: 892-902.
 13. Dominguez JN, Leon C, Rodrigues J, de Dominguez N G, Gut J, Rosenthal PJ. Synthesis and Evaluation of New Anti malarial Phenylurenyl Chalcone Derivatives. Journal of Medicinal Chemistry 2005; 48 Suppl 10: 3654-58.
 14. Raj R, Saini A, Gut J, Rosenthal PJ, Kumar V. Synthesis and *in vitro* anti plasmodial evaluation of 7-chloroquinoline-chalcone and 7-chloroquinoline-ferrocenylchalcone conjugates. European Journal of Medicinal Chemistry 2015; 95 Suppl C: 230-39.
 15. Liu H, Liu X, Fan H, Tang J, Gao X, Liu W. Design, synthesis and pharmacological evaluation of chalcone derivatives as acetylcholinesterase inhibitors. Bioorganic Medicinal Chemistry 2014; 22 Suppl 21: 6124-33.
 16. Guan A, Liu C, Huang G, Li H, Hao S, Xu Y *et al.* Synthesis and fungicidal activity of fluorine-containing chlorothalonil derivatives. Journal of Fluorine Chemistry 2014; 160: 82-87.
 17. Wang W, He H, Zuo N, Zhang X, Lin J, Chen W *et al.* Synthesis and herbicidal activity of 2-(substituted phenoxyacetoxy)alkyl-5,5-dimethyl-1,3,2-dioxaphosphinan-2-one containing fluorine. Journal of Fluorine Chemistry 2012; 142: 24-28.
 18. Chen H, Huang S, Xie J. A simple and efficient method for synthesis of fluorine-containing saccharide esters and antiviral activity. Journal of Fluorine Chemistry 2006; 127 Suppl 8: 1130-36.
 19. Kielbasinski P, Quczak J, Cierpial T, Blaszczyk J, Sieron L, Wiktorska K *et al.* New enantiomeric fluorine-containing derivatives of sulforaphane: Synthesis, absolute configurations and biological activity. European Journal of Medicinal Chemistry 2014; 76: 332-42.
 20. Kucukguzel SG, Rollas S, Erdeniz H, Kiraz AC, Ekinci M, Vidin A. Synthesis, characterization and pharmacological properties of some 4-arylhydrazono-2-pyrazoline-5-one derivatives obtained from heterocyclic amines. European Journal of Medicinal Chemistry 2000; 35 Suppl 7-8: 761-71.
 21. Zheng XM, Li Z, Wang YL, Chen WD, Huang QC, Liu CX *et al.* Syntheses and insecticidal activities of novel 2,5-disubstituted 1,3,4-oxadiazoles. Journal of Fluorine Chemistry 2003; 123 Suppl 2: 163-69.
 22. Gregory TP, Darlene CD, David MS. Structure-Activity Relationships for the Action of Dihydropyrazole Insecticides on Mouse Brain Sodium Channels. Pesticide Biochemistry and Physiology 1998; 60 Suppl 3:177-85.
 23. Singh R, Nawale L, Arkile M, Shedbalkar U, Wadhwani S, Sarkar D *et al.* Chemical and biological metal nanoparticles as anti mycobacterial agents: A comparative study. International Journal of Antimicrobial Agents 2015; 46 Suppl 2: 183-88.
 24. Ciapetti G, Cmni E, Pratelli L, Pizzoferrato A. *In vitro* evaluation of cell/biomaterial interaction by MTT assay. Biomaterials 1993; 14 Suppl 5: 359-64.
 25. Abhale YK, Shinde A, Deshmukh KK, Nawale L, Sarkar D, Mhaske PC. Synthesis, anti tubercular and antimicrobial potential of some new thiazole substituted thiosemicarbazide derivatives. Medicinal Chemistry Research 2017; 26 Suppl 10: 2557-67.

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

Disclaimer: IRJP is solely owned by Moksha Publishing House - A non-profit publishing house, dedicated to publish quality research, while every effort has been taken to verify the accuracy of the content published in our Journal. IRJP cannot accept any responsibility or liability for the site content and articles published. The views expressed in articles by our contributing authors are not necessarily those of IRJP editor or editorial board members.