Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(8):39-43

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

An easy route to synthesis of thiophene tagged pyrimidin-2-thiones as antibacterial agents

V. K. Shruthi, C. B. Vagish and *K. Ajay Kumar

Department of Chemistry, Yuvaraja's College, University of Mysore, Mysore, India

---

ABSTRACT

A series of substituted pyrimidin-2-thiones tagged with thiophene moiety was synthesized by an easy procedure. The reaction of chalcones 1-5 and thiourea 6 in the presence potassium hydroxide in ethanol yielded 6-aryl-4-(thiophen-2-yl) -5,6-dihydropyrimidin-2(1H) -ones, 7-11 in good yields. The synthesized new compounds were characterized by ^{1}H NMR, ^{13}C NMR, Mass spectral studies and elemental analysis and were screened for their antifungal susceptibility against different bacteria species.

Key words: Antibacterial, cyclocondensation, inhibition, Pyrimidine, thiourea.

INTRODUCTION

The exploitation of a simple molecule with different functionalities for the synthesis of heterocycles is a worthwhile contribution to heterocyclic chemistry [1]. Among the different classes of heterocycles, pyrimidines play a prominent role for their diverse pharmaceutical applications. Various methodologies have been demonstrated in the literature for the synthesis of pyrimidines, among them cyclocondensation of α,β-unsaturated ketones or chalcones with substituted or unsubstituted amides is more commonly employed method [2]. α,β-unsaturated ketones or chalcones were considered as useful synthons for the construction of bioactive molecules such as pyrazolines [3], thiazepines [4], isoxazoles [5] etc.

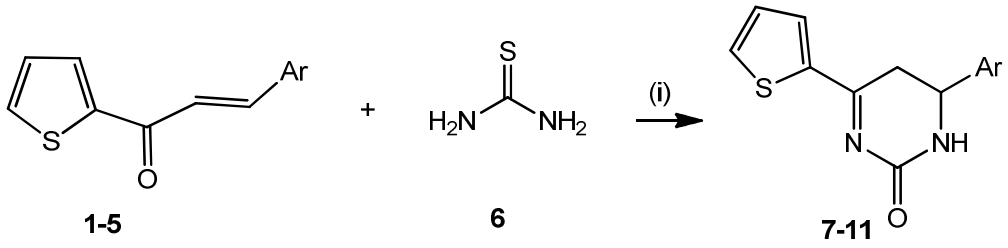
Three component reactions of 2-Hydroxymethylene-3-ketosteroid, aromatic aldehyde and ammonium acetate under MW conditions produced 2-arylsteroidal[3,2-d]pyrimidines [6]. Chalcones prepared from 4-acetylpyridine and substituted benzaldehyde undergoes cyclocondensation with urea to yield pyrimidines [7]. A three-component reaction of malononitrile, aldehydes and N-unsubstituted amidines forms 4-amino-5-pyrimidinecarbonitrile derivatives [8]. An efficient synthesis of pyrimido[4,5-d]pyrimidine-2,4-dione derivatives through the reaction of 6-aminouracils and N,N-bis(arylmethylidene)arylmethane in the presence of molecular iodine as a readily available and feasible catalyst [9].

In view of the enormous quantity of synthetic and biological applications associated with the pyrimidines, we herein report the synthesis of a series of novel pyrimidin-2-thione analogues with an access procedure and the results of their antibacterial susceptibility.

EXPERIMENTAL SECTION

Melting points were determined by open capillary method and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Agilent-NMR 400 MHz and 100 MHz spectrophotometer respectively in $CDCl_3$ with TMS as an internal standard. The Chemical shifts are expressed in δ ppm. Mass spectra were obtained on Mass Lynx SCN781 spectrophotometer TOF mode. Elemental analysis was performed on a Thermo Finnigan Flash EA 1112 CHN analyzer. Chromatographic separations were carried out on silica gel (70-230 mesh, Merck) column using hexane: ethyl acetate (4:1) as eluent.

General procedure for the synthesis of 6-Aryl-3-(thiophen-2-yl)-5,6-dihydropyrimidin-2(^{1}H)-ones, 7-11: A mixture of substituted chalcones 1-5 (0.001mol) and thiourea 6 (0.001mol) and potassium hydroxide (0.02 mol) in ethyl alcohol (20 mL) was refluxed on a water bath for 6-8 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice cold water and stirred. The solid separated was filtered, washed with ice cold water and recrystallized from ethyl alcohol to obtain target molecules 7-11 in good yields. The reaction pathway is depicted in scheme-1



1-5 **6** **7-11**

Reagents and condition: (i) KOH/C_2H_5OH Reflux, 3-4 hr

1. Ar = 4-FC_6H_4; 2. Ar = 4-$CH_3C_6H_4$; 3. Ar = 3,4-$(OCH_3)_2C_6H_3$;
4. Ar = 4-$NO_2C_6H_4$; 5. Ar = Furan-2-yl.

Scheme-1: Synthetic route for the pyrimidin-2-thione analogues

Antimicrobial activity of the synthesized compounds was done by paper disc diffusion method [10, 11]. The test compounds 7-11 at the concentration of 50 µg/mL in methanol/water on the nutrient agar media were screened for their antibacterial activity against bacteria species Escherichia coli, Salmonella typhimurium, Bacillus substilis. The antibiotic Ciprofloxacin was used as the standard drug against bacteria species.

RESULTS AND DISCUSSION

6-(4-Fluorophenyl)-4-(thiophen-2-yl)-5,6-dihydropyrimidine-2(1H)-thione, 7: Obtained from 3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one, 1 (0.001 mol) and thiourea, 6 (0.001 mol) as white solid in 78% yield, m.p. 171-174 ºC. ^{1}H NMR (CDCl3): δ 1.582-1.638 (dd, 1H, C5-Ha), 1.893-1.968 (dd, 1H, C5-Hb), 2.130 (s, 1H, -NH), 4.104-4.227 (dd, 1H, C6-H), 7.176 (dd, 2H, Ar-H), 7.285 (dd, 2H, Ar-H), 7.350-7.680 (m, 3H, thiophene ring-H). ^{13}C NMR (CDCl3): δ 41.88 (1C, C-5), 56.30 (1C, C-6), 114.31 (2C, Ar-C), 124.90 (1C, 5m ring-C), 125.55 (1C, 5m ring-C), 127.40 (1C, 5m ring-C), 127.86 (1C, 5m ring-C), 128.48 (2C, Ar-C), 138.13 (1C, Ar-C), 159.20 (1C, Ar-C), 163.60 (1C, C-4), 182.94 (1C, C=S). MS (m/z): 290 (M+, 100). Anal. Calcd. for C14H11FN2S2: C, 57.91; H, 3.82; N, 9.65%; Found: C, 57.81; H, 3.66; N, 9.47%.

4-(Thiophen-2-yl)-6-(p-tolyl)-5,6-dihydropyrimidine-2(1H)-thione, 8: Obtained from 3-(4-methylphenyl)-1-(thiophen-2-yl)prop-2-en-1-one, 2 (0.001 mol) and thiourea, 6 (0.001 mol) as white solid in 84% yield, m.p. 130-132 ºC. MS (m/z): 286 (M+, 100). Anal. Calcd. for C15H14N2S2: C, 62.90; H, 4.93; N, 9.78%; Found: C, 62.76; H, 4.85; N, 9.62%.

6-(3,4-Dimethoxyphenyl)-4-(thiophen-2-yl)-5,6-dihydropyrimidine-2(1H)-thione, 9: Obtained from 3-(3,4-dimethoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one, 3 (0.001 mol) and thiourea, 6 (0.001 mol) as white solid in 74% yield, m.p. 142-146 ºC.

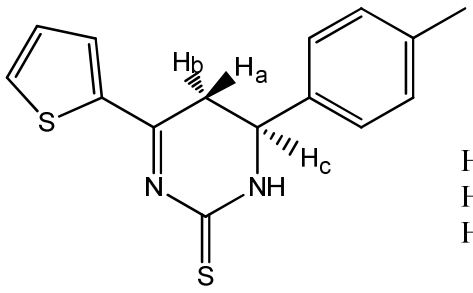
^{1}H NMR (CDCl3): δ 1.556-1.636 (dd, 1H, C5-Ha), 1.868-1.882 (dd, 1H, C5-Hb), 2.185 (s, 1H, -NH), 3.855 (s, 6H, OCH3), 3.964-4.018 (dd, 1H, C6-H), 6.976-7.524 (m, 6H, Ar-H, thiophene ring-H). ^{13}C NMR (CDCl3): δ 41.66 (1C, C-5), 55.56 (2C, OCH3), 56.88 (1C, C-6), 108.20 (1C, Ar-C), 118.80 (1C, Ar-C), 120.12 (1C, Ar-C), 124.40 (1C, 5m ring-C), 125.74 (1C, 5m ring-C), 127.48 (1C, 5m ring-C), 127.90 (1C, 5m ring-C), 135.19 (1C, Ar-C), 146.50 (1C, Ar-C), 147.62 (1C, Ar-C), 164.51 (1C, C-4), 183.24 (1C, C=S). MS (m/z): 332 (M+, 100). Anal. Calcd. for C16H16N2O2S2: C, 57.81; H, 4.85; N, 8.43%; Found: C, 57.64; H, 4.75; N, 8.30%.

6-(4-Nitrophenyl)-4-(thiophen-2-yl)-5,6-dihydropyrimidine-2(1H)-thione, 10: Obtained from 3-(4-Nitrophenyl)-1-(thiophen-2-yl)prop-2-en-1-one, 4 (0.001 mol) and thiourea, 6 (0.001 mol) as white solid in 80% yield, m.p. 123-126 ºC. ^{1}H NMR (CDCl3): δ 1.571-1.646 (dd, 1H, C5-Ha), 1.896-1.944 (dd, 1H, C5-Hb), 2.176 (s, 1H, -NH), 3.918-4.047 (dd, 1H, C6-H), 7.320-7.492 (m, 3H, thiophene ring-H), 7.526 (dd, 2H, Ar-H), 8.223 (dd, 2H, Ar-H). ^{13}C NMR (CDCl3): δ 41.82 (1C, C-5), 56.34 (1C, C-6), 123.32 (2C, Ar-C), 124.68 (2C, Ar-C), 124.92 (1C, 5m ring-C), 125.50 (1C, 5m ring-C), 127.44 (1C, 5m ring-C), 127.26 (1C, 5m ring-C), 148.13 (1C, Ar-C), 149.24 (1C, Ar-C), 163.61 (1C, C-4), 182.90 (1C, C=S). MS (m/z): 317 (M+, 100). Anal. Calcd. for C14H11N3O2S2: C, 52.98; H, 3.49; N, 13.24%; Found: C, 52.87; H, 3.33; N, 13.14%.

6-(Furan-2-yl)-4-(thiophen-2-yl)-5,6-dihydropyrimidin-2(1H)-thione, 11: Obtained from 3-(Furan-2-yl)-1-(thiophen-2-yl) prop-2-en-1-one, 5 (0.001 mol) and thiourea, 6 (0.001 mol) as white solid in 62% yield, m.p. 166-168 ºC. ^{1}H NMR ($CDCl_3$): δ 1.610-1.692 (dd, 1H, C5-Ha), 1.890-1.934 (dd, 1H, C5-Hb), 2.185 (s, 1H, -NH), 4.012-4.150 (dd, 1H, C6-H), 6.650-7.541 (m, 6H, thiophene furan ring-H). ^{13}C NMR (CDCl3): δ 41.66 (1C, C-5), 56.78 (1C, C-6), 108.10 (1C, 5m ring-C), 109.96 (1C, 5m ring-C), 123.81 (1C, 5m ring-C), 124.10 (1C, 5m ring-C), 126.88 (1C, 5m ring-C), 127.62 (1C, 5m ring-C), 139.70 (1C, 5m ring-C), 151.18 (1C, 5m ring-C), 163.98 (1C, C-4), 1832.30 (1C, C=S). MS (m/z): 262 (M+, 100). Anal. Calcd. for C12H10N2OS2: C, 54.94; H, 3.84; N, 10.68%; Found: C, 54.84; H, 3.70; N, 10.56%.

The general synthetic pathway employed is depicted in the scheme-1. The structure proof of the products was provided by ^{1}H NMR, ^{13}C NMR, MS studies and elemental analysis.

The structural assignments were made by NMR analysis by considering compound 4-(Thiophen-2-yl) -6-(p-tolyl) -5,6-dihydropyrimidine-2(1H) -thione, 8 as the representative compound. In its 1H NMR spectra, Ha, Hb and Hc protons of the pyrimidine ring appeared as a doublet of doublet. The doublets of Ha appeared in the region δ 1.576-1.622 ppm; doublets of Hb appeared in the region δ 1.898-1.928 ppm; and that of Hc in the region δ 4.016-4.218 ppm. Doublets of Ha and Hb are due to diastereotopic nature of methylene protons. Among Ha, Hb and Hc protons, Hc is the most deshielded due to its close proximity to electronegative NH and C=S functions. Hc couples not only with Ha but also with Hb and appears as doublet of doublet instead of a triplet; exhibited a typical ABX spin system with Hc as a doublet of doublets (Fig-1). NH proton is shielded due to adjacent C=S group and appears as singlet at δ 2.124 ppm. The signal appeared as singlet at δ 2.280 ppm. For three protons were assigned to aromatic CH_3 protons. Due to para substitution, two aromatic protons each appeared as doublet of doublet at δ 7.130 ppm. and δ 7.246 ppm. Three thiophene ring protons appeared as multiplet in the region δ 7.342-7.664 ppm. All the synthesized compounds 7, 9, 10 and 11 showed the similar ^{1}H NMR signals.



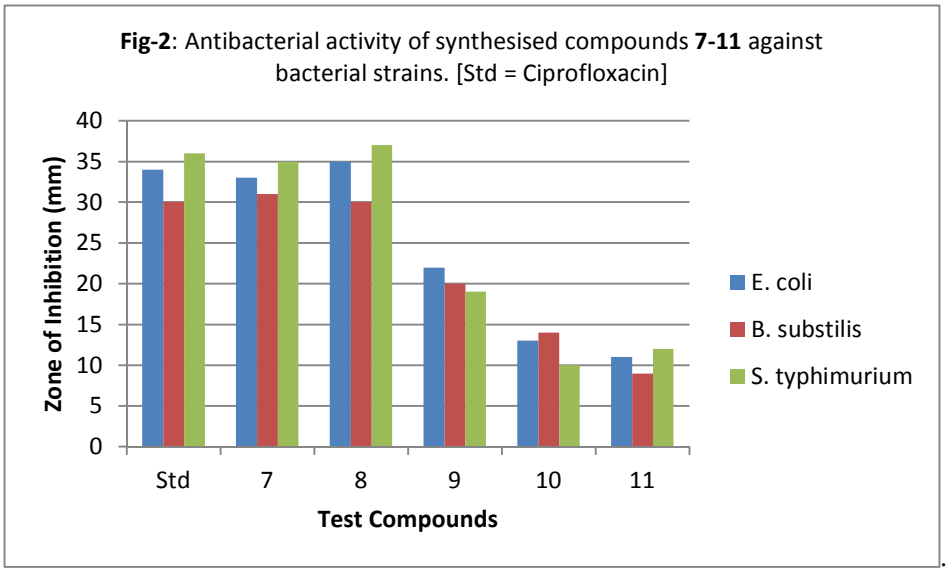
Ha: 1.576-1.622 (dd, 1H; *J=8.1, 19.0*Hz)
Hb: 1.898-1.928 (dd, 1H; *J=10.8, 20.0*Hz)
Hc: 4.016-4.218 (dd, 1H; *J=9.3, 19.0*Hz)

Fig-1: Proton chemical shifts and couplings of **8**

In ^{13}C NMR, the compound 8 showed signals due to C-5-atom at δ 41.86 ppm, for the C-6 atom at δ 56.35 ppm. The C-4 atom signal appeared at δ 164.56 ppm. An intense signal appeared at δ 183.14 ppm was due to C=S carbon atom. An array of signals appeared at δ 123.34 and 128.60 ppm. for two carbon each, and at δ 124.30, 125.64,

127.34, 127.88, 135.15 and 139.40 ppm. For one carbon each was assigned to aromatic and thiophene ring carbons. A signal appeared at δ 21.20 ppm. Was assigned to aromatic CH_3 substituent carbon. All the synthesized compounds 7, 9, 10 and 11 showed the similar consistent pattern signals in their ^{13}C NMR spectra, which strongly supports the structure of the products. All new compounds gave M+ ion as the base peak corresponding to their molecular mass. The satisfactorily elemental analysis further supports structure of the products.

Antibacterial activity: The results of antibacterial activity of the synthesized compounds 7-11 against different bacterium were depicted in Fig-2.



The results of the study revealed that synthesized new compounds 7-11 have shown moderate to good antibacterial activity against all the tested organisms. Compounds 7 and 8 showed excellent inhibition effect on all the tested organisms in comparison with the standard drug. The compound 9 having dimethoxy substitution on the aromatic ring showed moderate inhibition effect. The compounds 10 and 11 having strong electron withdrawing $–NO_2$ substitution and furan ring showed lesser inhibition against all the bacterium tested.

CONCLUSION

Synthesis of novel pyrimidin-2-thiones by an easy procedure and the efficacy of some of the synthesized molecules as antibacterial agents validate the significance of this study. Among the series of the compounds reported, compounds 7 and 8 can be used as potential antibacterial agents.

Acknowledgements
The authors are grateful to IOE Instrumentation facility. University of Mysore, for recording spectra of the compounds reported.

REFERENCES

[1] CN Thilak Kumar; N Renuka; G Vasanth Kumar; K Ajay Kumar, *J Chem and Pharma Res.*, **2015**, 7(3), 1845-1849.
[2] R Aggarwal; E Masan; P Kaushik; D Kaushik; C Sharma; KR Aneja, *J Fluorine Chem*., **2014**, 17-23.
[3] K Ajay Kumar; M Govindaraju, *Int J of ChemTech Res*, **2015**, 8(1), 313-322.
[4] M Manjula; BC Manjunath; N Renuka; K Ajay Kumar; NK Lokanath, *Acta Crystallographica Section E*, **2013**, E69 Part 11, o1608-o1608.
[5] K Ajay Kumar; KM Lokanatha Rai; KB Umesha; K Rajasekhara Prasad; *Indian Journal of Chemistry*, **2001**, 40B, 269-273.
[6] S Toshiaki; F Kobayashi; N Sakai; T Konakahara, *Org Lett.*, **2009**, 11(10), 2161-2164.

[7] K Monica; P Rakesh; Y Yadav, *Der Pharma Chem.*, **2014**, 6(2), 352-359.
[8] S Hassan; AS Saljoogi; A Bazgir; Arkivoc, **2008**, (ii), 115-123.
[9] FM Moghaddam; MR Khodabakhshi; M Aminaee, *Tetrahedron Lett.*, **2014**, 55, 4720-4723.
[10] K Ajay Kumar; M Govindaraju; G Vasantha Kumar, *Indian Journal of Heterocyclic Chemistry*, **2010**, 20, 183-184.
[11] P Jayaroopa; G Vasanth Kumar; N Renuka; MA Harish Nayaka; K Ajay Kumar, *Int J of PharmTech Res*, **2013**, 5(1), 264-270.