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Research Article

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Synthesis and antifungal activity of novel pyrimidin-2-one analogues

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ABSTRACT

*A series of thiophene appended substituted pyrimidin-2-one analogues were synthesized by an accessible approach. The reaction of chalcones **1(a-e)** and urea **2** in the presence potassium hydroxide in ethanol yielded 6-aryl-4-(thiophen-2-yl)-5,6-dihydropyrimidin-2(1H)-ones, **3(a-e)** 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 fungi species.*

Key words: Antifungal, cyclocondensation, inhibition, pyrimidine, urea.

INTRODUCTION

The exploitation of a simple molecule with different functionalities to the synthesis of heterocycles is a worthwhile contribution in heterocyclic chemistry [1]. Literature reveals many synthetic strategies for the pyrimidine derivatives and their biological potency. For instance, 2-Arylsteroidal[3,2-d]pyrimidines were prepared from 2-Hydroxymethylene-3-ketosteroid, aromatic aldehyde and ammonium acetate mixed with silica gel under MW conditions [2]. An unprecedented approach to 4,5-disubstituted pyrimidine derivatives by a $ZnCl_2$-catalyzed three-component coupling reaction [3]. A mixture of 4-acetylpyridine and substituted benzaldehydes reacts in the presence of KOH to form chalcones, which undergoes cyclocondensation with urea to yield substituted pyrimidines [4]. α,β-unsaturated ketones or chalcones were considered as useful synthons for the construction of bioactive molecules such as pyrimidines [3], pyrazolines [5.6], thiazepines [7,8], isoxazoles [9] etc.

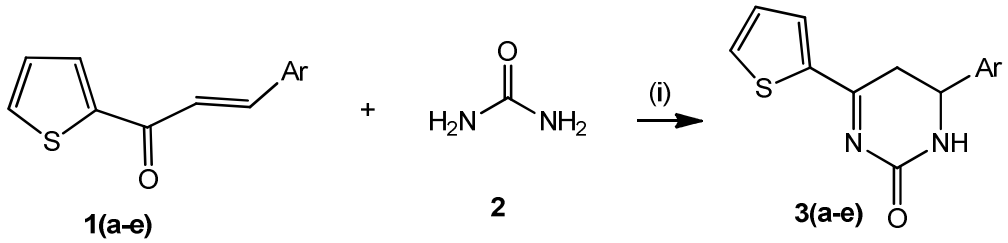
Hassan and co-workers [10] reported the synthesis of 4-amino-5-pyrimidinecarbonitrile derivatives by a three-component reaction of malononitrile, aldehydes and N-unsubstituted amidines. A new and efficient synthesis of pyrimido[4,5-d]pyrimidine-2,4-dione derivatives through the reaction of 6-aminouracils and N,N-bis(arylmethylidene)arylmethane in the presence of molecular iodine as a readily available and feasible catalyst [11]. Copper/6-methylpicolinic acid catalyzed coupling reaction of substituted 5-bromopyrimidin-4-amines with alkynes and subsequent cyclization took place in DMSO afford 2-chloro-pyrrolo[2,3-d]pyrimidines in moderate to excellent yields [12].

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-one analogues by an accessible procedure and the results of their antifungal 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 spectrophotomer 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(1H)-ones, 3(a-e): A mixture of substituted chalcones **1(a-e)** (0.001mol) and urea **2** (0.001mol) and potassium hydroxide (0.02 mol) in ethyl alcohol (20 mL) was refluxed on a water bath for 6-8 hrs. 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 **3(a-e)** in good yields. The reaction pathway is depicted in scheme-1.



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

a) Ar = 4-FC_6H_4; b) Ar = 4-$CH_3C_6H_4$; c) Ar = 3,4-$(OCH_3)_2C_6H_3$;
d) Ar = 4-$NO_2C_6H_4$; e) Ar = Furan-2-yl.

Scheme-1: Synthetic route for the pyrimidine analogues

Antifungal activity of the synthesized compounds was done by paper disc diffusion method [13, 14]. The test compounds **3(a-e)** at the concentration of 50 µg/mL in methanol in the nutrient agar media were screened for their antifungal activity against fungi species *Aspergillus niger*, *Aspergillus flavus*, *Fusarium oxysporium*. The antibiotic nystatin was used as the standard drug against fungi species.

6-(4-Fluorophenyl)-4-(thiophen-2-yl)-5,6-dihydropyrimidin-2(1H)-one, **3a**: Obtained from 3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one, **1a** (0.001 mol) and urea, **2** (0.001 mol) as white solid in 72% yield, m.p. 165-168 ºC. MS (m/z): 275 (M+H, 15), 274 (M+, 100). Anal. Calcd. for $C_{14}H_{11}FN_2OS$: C, 61.30; H, 4.04; N, 10.21%; Found: C, 61.12; H, 4.09; N, 10.09%.

4-(Thiophen-2-yl)-6-(p-tolyl)-5,6-dihydropyrimidin-2(1H)-one, **3b**: Obtained from 3-(4-methylphenyl)-1-(thiophen-2-yl)prop-2-en-1-one, **1b** (0.001 mol) and urea, **2** (0.001 mol) as white solid in 78% yield, m.p. 118-122 ºC. ^{1}H NMR ($CDCl_3$): δ 1.550-1.602 (dd, 1H, C_5-H_a), 1.811-1.868 (dd, 1H, C_5-H_b), 2.289 (s, 1H, CH_3), 4.810-4.846 (dd, 1H, C_6-H), 7.120 (dd, 2H, Ar-H), 7.229 (dd, 2H, Ar-H), 7.346-7.658 (m, 3H, thiophene ring-H), 8.134 (s, 1H, -NH). ^{13}C NMR ($CDCl_3$): δ 21.22 (1C, CH_3), 43.86 (1C, C-5), 46.32 (1C, C-6), 123.30 (2C, Ar-C), 124.34 (1C, 5m ring-C), 125.60 (1C, 5m ring-C), 127.32 (1C, 5m ring-C), 127.80 (1C, 5m ring-C), 128.68 (2C, Ar-C), 135.10 (1C, Ar-C), 139.36 (1C, Ar-C), 162.14 (1C, C=O), 164.12 (1C, C-4). MS (m/z): 271 (M+H, 12), 270 (M+, 100). Anal. Calcd. for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36%; Found: C, 66.47; H, 5.13; N, 10.14%.

6-(3,4-Dimethoxyphenyl)-4-(thiophen-2-yl)-5,6-dihydropyrimidin-2(1H)-one, **3c**: Obtained from 3-(3,4-dimethoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one, **1c** (0.001 mol) and urea, **2** (0.001 mol) as white solid in 77% yield, m.p. 135-137 ºC. ^{1}H NMR ($CDCl_3$): δ 1.523-1.614 (dd, 1H, C_5-H_a), 1.832-1.873 (dd, 1H, C_5-H_b), 3.856 (s, 6H, OCH_3), 4.824-4.858 (dd, 1H, C_6-H), 6.981-7.582 (m, 6H, Ar-H, thiophene ring-H), 8.105 (s, 1H, -NH). ^{13}C NMR ($CDCl_3$): δ 43.60 (1C, C-5), 46.83 (1C, C-6), 55.78 (2C, OCH_3), 108.14 (1C, Ar-C), 118.10 (1C, Ar-C), 120.07 (1C, Ar-C), 124.44 (1C, 5m ring-C), 125.70 (1C, 5m ring-C), 127.42 (1C, 5m ring-C), 127.89 (1C, 5m ring-C), 135.10

(1C, Ar-C), 146.52 (1C, Ar-C), 147.64 (1C, Ar-C), 162.20 (1C, C=O), 164.56 (1C, C-4). MS (m/z): 317 (M+H, 22), 316 (M+, 100). Anal. Calcd. for $C_{16}H_{16}N_2O_3S$: C, 60.74; H, 5.10; N, 8.85%; Found: C, 60.54; H, 5.00; N, 8.66%.

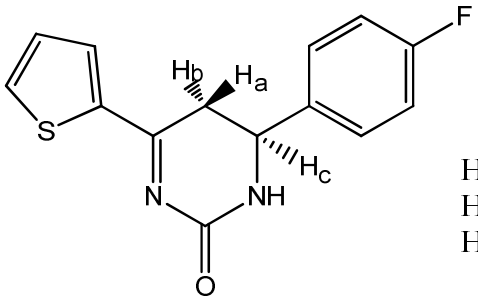
***6-(4-Nitrophenyl)-4-(thiophen-2-yl)-5,6-dihydropyrimidin-2(1H)-one,* 3d**: Obtained from 3-(4-Nitrophenyl)-1-(thiophen-2-yl)prop-2-en-1-one, **1d** (0.001 mol) and urea, **2** (0.001 mol) as white solid in 82% yield, m.p. 115-118 ºC. ^{1}H NMR ($CDCl_3$): δ 1.536-1.632 (dd, 1H, C_5-H_a), 1.832-1.865 (dd, 1H, C_5-H_b), 4.811-4.847 (dd, 1H, C_6-H), 7.334-7.502 (m, 3H, thiophene ring-H), 7.598 (dd, 2H, Ar-H), 8.108 (s, 1H, -NH), 8.230 (dd, 2H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 43.12 (1C, C-5), 46.33 (1C, C-6), 1234.30 (2C, Ar-C), 124.64 (2C, Ar-C), 124.98 (1C, 5m ring-C), 125.53 (1C, 5m ring-C), 127.32 (1C, 5m ring-C), 127.78 (1C, 5m ring-C), 148.10 (1C, Ar-C), 149.20 (1C, Ar-C), 162.26 (1C, C=O), 163.65 (1C, C-4). MS (m/z): 302 (M+H, 19), 302 (M+, 100). Anal. Calcd. for $C_{14}H_{11}N_3O_3S$: C, 55.80; H, 3.68; N, 13.95%; Found: C, 55.54; H, 3.48; N, 13.76%.

***6-(Furan-2-yl)-4-(thiophen-2-yl)-5,6-dihydropyrimidin-2(1H)-one,* 3e**: Obtained from 3-(Furan-2-yl)-1-(thiophen-2-yl)prop-2-en-1-one, **1e** (0.001 mol) and urea, **2** (0.001 mol) as white solid in 66% yield, m.p. 160-164 ºC. ^{1}H NMR ($CDCl_3$): δ 1.592-1.646 (dd, 1H, C_5-H_a), 1.872-1.910 (dd, 1H, C_5-H_b), 5.011-5.052 (dd, 1H, C_6-H), 6.551-7.442 (m, 6H, thiophene furan ring-H), 8.120 (s, 1H, -NH). ^{13}C NMR ($CDCl_3$): δ 43.09 (1C, C-5), 46.32 (1C, C-6), 108.13 (1C, 5m ring-C), 109.92 (1C, 5m ring-C), 123.87 (1C, 5m ring-C), 124.02 (1C, 5m ring-C), 126.96 (1C, 5m ring-C), 127.24 (1C, 5m ring-C), 138.10 (1C, 5m ring-C), 151.10 (1C, 5m ring-C), 162.30 (1C, C=O), 163.25 (1C, C-4). MS (m/z): 247 (M+H, 16), 246 (M+, 100). Anal. Calcd. for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37%; Found: C, 58.35; H, 4.01; N, 11.23%.

RESULTS AND DISCUSSION

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 **2a** as the representative compound. In its ^{1}H NMR spectra, H_a, H_b and H_c protons of the pyrimidine ring appeared as a doublet of doublet. The doublets of H_a appeared in the region δ 1.556-1.608 ppm; doublets of H_b appeared in the region δ 1.802-1.870 ppm; and that of H_c in the region δ 4.815-4.852 ppm. Doublets of H_a and H_b are due to diastereotopic nature of methylene protons. Among H_a, H_b and H_c protons, H_c is the most deshielded due to its close proximity to electronegative NH function. H_c couples not only with H_a but also with H_b and appears as doublet of doublet instead of a triplet; exhibited a typical ABX spin system with H_c as a doublet of doublets (Fig-1). NH proton is highly deshielded due to electron withdrawing adjacent C=O group and appears as singlet at δ 8.125 ppm. Due to para substitution, two aromatic protons each appeared as doublet of doublet at δ 7.021 ppm. and δ 7.228 ppm. Three thiophene ring protons appeared as multiplet in the region δ 7.341-7.612 ppm. All the synthesized compounds **2**(**b-e**) showed the similar ^{1}H NMR signals.



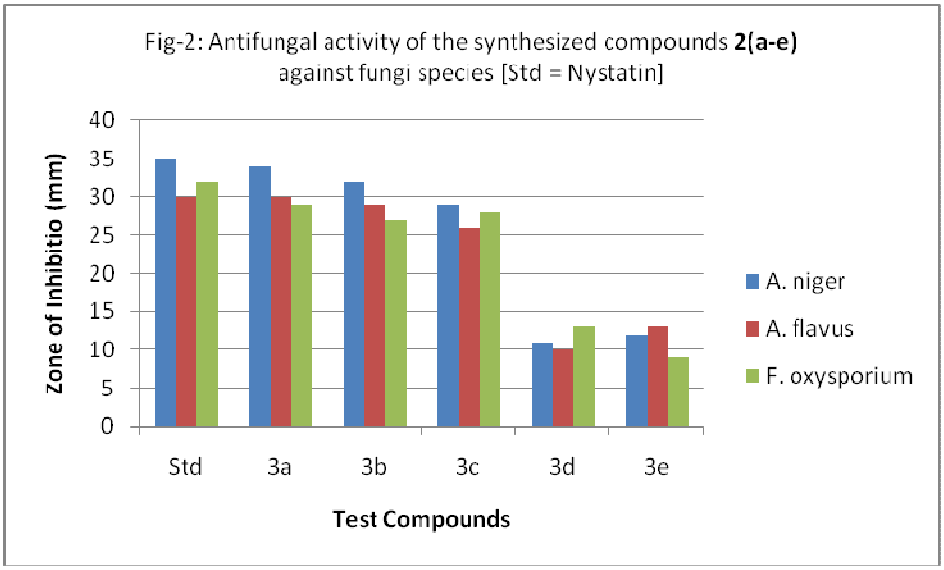
Ha: 1.556-1.608 (dd, 1H; *J=8.9, 19.6*Hz)
Hb: 1.802-1.870 (dd, 1H; *J=10.2, 20.1*Hz)
Hc: 4.815-4.852 (dd, 1H; *J=9.8, 19.2*Hz)

Fig-1: Proton chemical shifts and couplings of **2a**

In ^{13}C NMR, the compound **2a** showed signals due to C-5-atom at δ 43.72 ppm, for the C-6 atom at δ 46.51 ppm. The C-4 atom signal appeared at δ 163.20 ppm. An intense signal appeared at δ 162.33 ppm was due to C=O carbon atom. An array of signals appeared at δ 114.32 and 128.60 ppm. for two carbon each, and at δ 124.03, 125.64, 127.40, 127.86, 138.10 and 159.13 ppm. for one carbon each was assigned to aromatic and thiophene ring carbons. The synthesized compounds **2**(**b-e**) showed similar consistent pattern signal in the ^{13}C NMR spectra, which strongly

support the structure of the products. All new compounds gave stable molecular mass MH^+ peak and a base peak at corresponding M^+ ion. Satisfactorily elemental analysis further supports structure of the products.

Antimicrobial activity: The results of antifungal activity of the synthesized compounds **2**(**a-e**) against different fungi species were depicted in Fig-2.



The results of the study revealed that synthesized new compounds **2**(**a-e**) have shown moderate to good antifungal activity against all the tested organisms. The compounds **2a, 2b** and **2c** showed remarkable inhibition effect on all the tested organisms in comparison with the standard drug. The compounds **2d** and **2e** having strong electron withdrawing $–NO_2$ substitution and furan ring showed moderate inhibition against all the fungi strains tested.

CONCLUSION

The easy and accessible procedure for the synthesis of novel pyrimidin-2-ones, the efficacy of some of the synthesized molecules as antifungal agents validates the significance of this study. Among the series of the compounds reported, the compounds **2a, 2b** and **2c** can be used as potential antifungal agents.

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