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SYNTHESIS AND ANTIBACTERIAL ACTIVITIES OF NEW 6-ARYL-4-OXO-1,4-DIHYDROPYRIMIDINE DERIVATIVES

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ABSTRACT

Pyrimidine derivatives are an important class of compounds in medicinal chemistry. In this study, a series of 6-aryl-4-oxo-1,4-dihydropyrimidine-5-carbonitrile derivatives were synthesized using a multicomponent reaction, followed by *S*-alkylation with different halogenated derivatives, and then evaluated for their antibacterial activities. Ciprofloxacin was used as the reference antibiotic. The prepared compounds were characterized by ^{1}H, ^{13}C NMR, FT-IR spectroscopy, and LC-and HR-MS spectrometry. All compounds were screened *in vitro* against *Pseudomonas aeruginosa* and *Escherichia coli* (Gram-negative bacteria), as well as *Staphylococcus aureus* and *Enterococcus faecalis* (Gram-positive bacteria). The results showed that *S*-alkylation is beneficial in improving the antibacterial activity of the thiouracil derivatives offering a few compounds with antibacterial activity against Gram-positive bacteria.

Keywords: 1,4-Dihydropyrimidine, Thiouracil, Synthesis, Medicinal Chemistry, Antibacterial Activity

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INTRODUCTION

Among chemical compounds currently registered as commercial drugs, about two-thirds contain heterocyclic systems in their structures.[1] In particular, nitrogen-containing heterocycles are of great importance in the pharmaceutical field or medicinal chemistry.[2] Indeed, these compounds are found in many bioactive structures patented in recent years.[3,4] This is the case of pyrimidine, an unsaturated six-membered ring containing nitrogen atoms at 1,3 positions. Heterocycles containing pyrimidine moiety are of great interest because they represent an important class of natural products such as nucleic acid, uracil, cytosine, and thymine. In addition, structural pyrimidine subunits are present in various synthetic compounds, many of which have beneficial biological activities and clinical applications.[5-7] For instance, they showed many medicinal properties which are antimicrobial,[8] antitumors,[9] anti-inflammatory agents,[10] antihypertensive,[11] and antituberculosis.[12] We have recently described some 1,6-dihydropyrimidine-5-carbonitriles as SecA inhibitors.[13-15] Several studies have been done showing that SecA is a central component of the bacterial protein secretion (Sec) pathway and essential for bacterial survival.[16-18] Since SecA is a conserved and essential protein in all bacteria that can be inhibited by pyrimidine derivatives, we are developing compounds containing this structural subunit as antibacterial agents. In this article, we report the synthesis and biological evaluation of new 1,4-dihydro pyrimidine derivatives as potential antibacterial agents.

EXPERIMENTAL

Material and Methods

All the reactions were monitored by thin-layer chromatography (TLC) using silica gel (60 F254) plates and the compounds were visualized by UV irradiation. Flash column chromatography was performed on silica gel 60. Melting points (M.p. [°C]) were measured from samples in open capillary tubes. The infrared spectra

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(IR) of compounds are given in cm^{-1} and were recorded on a Fourier Transformer-IR Thermo Scientific Nicolet iS10. ^1H and ^{13}C NMR spectra were recorded at 250 MHz (^{13}C, 62.9 MHz) or 400 MHz (^{13}C, 100.7 MHz) with a Bruker spectrometer. Chemical shifts are given in parts per million using tetramethylsilane (TMS) as an internal standard. (Multiplicity: s = singlet, d = doublet, dd = double doublet, dt = double triplet, t = triplet, q = quartet, m = multiplet …). High-resolution mass spectrometry (HRMS) was performed on a quadrupole analyzer. Mass spectra (LCMS) were recorded on a UHPLC-DAD/MS Thermo U3000 + MSQ Instrument.

General Procedure

General Procedure for the Synthesis of Compounds (4a, b)

To a flask containing absolute ethanol (50 mL), appropriate aldehyde (9.86 mmol, 1 equiv.), ethyl cyanoacetate (9.86 mmol, 1.068 mL, 1 equiv.), thiourea (9.86 mmol, 0.751 g, 1 equiv.) and piperidine (19.72 mmol, 2 equiv.) were successively added. The mixture was then refluxed under magnetic stirring overnight. After cooling, the precipitate was filtered under a vacuum and washed several times with ethanol, and dried at room temperature. After drying, the residue was dissolved in 30-50 mL NaOH solution (0.5 M) and acidified with HCl (1M) to pH ≈ 2. The precipitate formed was washed several times with water and dried.

2-mercapto-4-oxo-6-phenyl-1,4-dihydropyrimidine-5-carbonitrile (**4a**) recrystallized from methanol, yellow solid, yield 33%, M.p. 259-260°C. IR $\bar{\nu}$ (cm^{-1}): 3244.37 (NH), 2221.12 (CN), 1722.36 (CO). ^1H NMR (400 MHz, DMSO-d_6) δ 7.54−7.68 (m, 5H, Ar− H), 13.16 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO-d_6) δ 90.8 (−C−C≡N, pyrimidine), 114.8 (−C≡N), 128.6 - 128.8 (4x−CH−), 129.4 (−C−, Ar), 132.3 (−CH−), 158.6 (−C=N, pyrimidine), 161.1 (−C=O), 176.3 (−C=C−, pyrimidine). Mass (LCMS): m/z for $C_{11}H_7N_3OSNa^+$ $[M+Na]^+$: calcd 252.2, found 252.2.

2-mercapto-6-(4-methoxyphenyl)-4-oxo-1,4-dihydropyrimidine-5-carbonitrile (**4b**) recrystallized from methanol, yield 35%, Yellow solid, M.p. 260-261°C. IR $\bar{\nu}$ (cm^{-1}): 3245.80 (NH), 2830.12 (O−CH_3), 2260.00 (CN), 1620.69 (CO). ^1H NMR (400 MHz, DMSO-d_6) δ 7.09−7.11 (d, J = 8.9 Hz, 2H, Ar−H), 7.63−7.66 (d, J = 8.9 Hz, 2H, Ar−H), 13.09 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO-d_6) δ 55.80 (O−CH_3), 89.87 (−C−C≡N, pyrimidine), 114.13 (−CH−), 115.30 (−C≡N), 121.23 (−C−, Ar), 131.05 (−CH−), 158.91 (−C−OCH_3, Ar), 160.72 (−C=N, pyrimidine), 162.59 (−C=O), 176.39 (−C=C−, pyrimidine). Mass (LCMS): m/z for $C_{12}H_9N_3O_2SNa^+$ $[M+Na]^+$: calcd 282.3, found 282.3.

General Procedure for the Synthesis of Compounds (4c-e)

To a flask containing absolute ethanol (50 mL), added successively the appropriate aldehyde (9.86 mmol, 1 equiv.), ethyl cyanoacetate (9.86 mmol, 1.068 ml, 1 equiv.), thiourea (9.86 mmol, 0.751 g, 1 equiv.) and K_2CO_3 (9.86 mmol, 1.363 g, 1 equiv.). The mixture was refluxed under magnetic stirring overnight. After cooling, the mixture was filtered and the solvent evaporated under vacuum. The residue obtained was washed several times with ethanol and dried at room temperature. After drying, the residue was added to 20-30 mL of water and heated until a clear solution was obtained. A few drops of acetic acid were added until pH = 7 was reached. The precipitate formed was washed several times with water, dried, and recrystallized.

2-mercapto-4-oxo-6-(pyridin-2-yl)-1,4-dihydropyrimidine-5-carbonitrile (**4c**) recrystallized from the mixture (water-methanol), yellow solid, yield 33%, M.p. 306-308°C. IR $\bar{\nu}$ (cm^{-1}): 3268.57 (NH), 3148.13 (SH), 2221.00 (CN), 1649.60 (CO). ^1H NMR (400 MHz, DMSO-d_6) δ 7.50 (s, 1 H, Ar−H), 7.93 (s, 2 H, Ar−H), 8.64 (s, 1 H, Ar−H), 10.02 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 85.60 (−C−C≡N, pyrimidine), 117.9 (−C≡N), 122.9 (−CH−), 125.0 (−CH−), 136.7 (−CH−), 148.4 (−CH−), 154.7 (−C−, pyridine), 162.9 (−C=N, pyrimidine), 164.6 (−C=O), 182.7 (−C=C−, pyrimidine), HRMS (ESI) for $C_{10}H_7N_4OS$ $[M+H]^+$: calcd 231.0341, found 231.0334.

6-(3-benzyloxy)phenyl-2-mercapto-4-oxo-1,4-dihydropyrimidine-5-carbonitrile (**4d**) recrystallized from methanol, yellow solid, yield 45%, M.p. 279-281°C. IR $\bar{\nu}$ (cm^{-1}): 3389.01 (NH), 3248.96 (NH), 2209.79 (CN), 1655.20 (CO), 1543.16 (C=S). ^1H NMR (400 MHz, DMSO-d_6) δ 5.17 (s, 2 H, CH_2–O), 7.26−7.51

(m, 9 H, Ar− H), 13.18 (s, 1 H, NH), 13.26 (s, 1 H, NH). ^{13}C NMR (101 MHz, DMSO-d_6) δ 69.6 (O−CH_2), 90.8 (−C−C≡N, pyrimidine), 114.5 (−C≡N), 115.2 (−CH−), 118.5 (−CH−), 121.1 (−CH−), 127.7 (2x−CH−), 128.0 (−CH−), 128.5 (2x−CH−), 129.8 (−CH−), 130.4 (−C−, Ar), 136.5 (−CH_2−C=C−, Ar), 157.9, (−O−C=C−, Ar), 158.4 (−C=O), 160.4 (−C=C−, pyrimidine), 176.1 (−NH−C=S, pyrimidine). HRMS (ESI) for $C_{18}H_{14}N_3O_2S$ $[M+H]^+$: calcd 336.0807, found 336.0802.

2-mercapto-4-oxo-6-(thiophen-2-yl)-1,4-dihydropyrimidine-5-carbonitrile (**4e**) salmon powder, yield 42%, M.p. 200-202°C. IR $\bar{\nu}$ (cm^{-1}): 3244.37 (NH), 2221.12 (CN), 1722.36 (CO).^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21−7.23 (m, 1H, Ar−H), 7.84−7.85 (d, *J* = 4.9 Hz, 1H, Ar−H), 8.08−8.09 (d, *J* = 3.5 Hz, 1H, Ar−H), 11.67 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO-d_6) δ 81.9 (−C−C≡N, pyrimidine), 118.8 (−C≡N), 128.3 (−CH−), 129.7 (−CH−), 132.2 (−CH−), 140.8 (−C−, thiophene), 157.8 (−C=N, pyrimidine), 162.2 (−C=O), 181.7 (−C=C−, pyrimidine). Mass (LCMS): m/z for $C_9H_5N_3OS_2Na^+$ **[**$M+Na]^+$: calcd 258.3, found 258.3.

General Procedure for the Synthesis of Compounds (5a-q)

To a flask containing 3-5 mL of DMF, compounds **4a-e** (0.2 g, 1 equiv.), K_2CO_3 (1 equiv.), and an alkylating agent (1 equiv.) (propyl iodide, benzyl chloride or bromide, ethyl 2-chloroacetate, benzyl 4-trifluoro methyl bromide or methyl 4-bromomethyl benzoate) were added successively. The mixture was stirred at room temperature for 15-90 min. After the complete disappearance of the starting thiouracil (**4a-e**), crushed ice and a few drops of HCl (1M) were added to the reaction mixture until pH ≈ 2 was reached. The precipitate formed was filtered under a vacuum and washed several times with water. The resulting product was washed either with ethyl acetate or methanol or purified by column chromatography.

2-Ethyl-(5-cyano-4-oxo-6-phenyl-1,4-dihydropyrimidin-2-ylthio) acetate (**5a)** 90 min, washed with ethyl acetate, white powder, yield 90%, M.p. 240-242°C. IR $\bar{\nu}$ (cm^{-1}): 3205.89 (NH), 2229.40 (CN), 1663.60 (CO), 1733.63 (CO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.06−1.10 (t, *J* = 7.1 Hz, 3H, CH_3CH_2−O), 4.03−4.08 (q, *J* = 7.1 Hz, 2H, CH_3CH_2−O), 4.12 (s, 2H, CH_2–S), 7.54−7.63 (m, 3H, Ar−H), 7.88−7.90 (m, 2H, Ar−H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 13.9 (CH_3CH_2−O), 33.0 (CH_2−S), 61.4 (CH_3CH_2−O), 93.2 (−C−C≡N, pyrimidine), 115.8 (−C≡N), 128.6 (2x−CH−), 128.7 (2x−CH−), 132.0 (−CH−), 135.1 (−C−, Ar), 161.2 (−C=N, pyrimidine), 165.2 (−C=O), 167.0 (−C=O), 168.1 (−C=C−, pyrimidine). HRMS (ESI) for $C_{15}H_{14}N_3O_3S$ $[M+H]^+$: calcd 316.0678, found 316.0678.

Methyl 4-methyl-(5-cyano-4-oxo-6-phenyl-1,4-dihydropyrimidin-2-ylthio) benzoate (**5b**) 30min, washed with ethyl acetate, white powder, yield 70%, M.p. 265-267°C. IR $\bar{\nu}$ (cm^{-1}): 3246.16 (NH), 2226.60 (CN), 1694.41 (CO), 1646.80 (CO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.82 (s, 3H, CH_3−O), 4.59 (s, 2H, CH_2−S), 7.53−7.61 (m, 5H, Ar−H), 7.87−7.90 (m, 4H, Ar−H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 33.8 (CH_2−S), 52.1 (CH_3−O), 93.3 (−C−C≡N, pyrimidine), 115.8 (−C≡N), 128.6 (2x−CH−), 128.7 (3x−CH−), 129.3 (4x−CH−),131.8 (−C−, Ar), 135.1 (−C−, Ar), 142.4 (−C−, Ar), 161.1 (−C=N, pyrimidine), 165.4 (−C=O), 165.9 (−C=O), 167.3 (−C=C−, pyrimidine). HRMS (ESI) for $C_{20}H_{16}N_3O_3S$ $[M+H]^+$: calcd 378.0834, found 378.0834.

2-(4-(Trifluoromethyl)benzylthio)-4-oxo-6-phenyl-1,4-dihydropyrimidine-5-carbonitrile (**5c**) 45 min, purified by chromatography on silica gel (Ep / AcOEt 8:2), white powder, yield 89%, M.p. 235-237°C. IR $\bar{\nu}$ (cm^{-1}): 3229.36 (NH), 2229.40 (CN), 1691.61 (CO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.60 (s, 2H, CH_2−S), 7.53−7.68 (m, 7H, Ar−H), 7.86−7.87 (d, J = 7.0 Hz, 2H, Ar−H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 33.9 (CH_2−S), 93.5 (−C−C≡N, pyrimidine), 116.5 (−C≡N), 123.3 (−CH−), 125.7 (−CF_3−), 126.0 (−CH−, Ar), 128.2 (−C−, Ar), 128.9 (2x−CH−), 129.1 (2x−CH−), 130.2 (2x−CH−), 132.1 (−CH−), 135.8 (−C−, Ar), 142.5 (−C−, Ar), 162.3 (−C=N, pyrimidine), 166.3 (−C=O), 167.7 (−C=C−, pyrimidine). HRMS (ESI) for $C_{19}H_{13}F_3N_3OS$ $[M+H]^+$: calcd 388.0653, found 388.0723.

4-Oxo-2-(propylthio)-6-(pyridin-2-yl)-1,4-dihydropyrimidine-5-carbonitrile (**5d)** 45 min, washed with methanol, beige powder, yield 64%, M.p. 168-170°C. IR $\bar{\nu}$ (cm^{-1}): 3302.18 (NH), 2221.00 (CN), 1663.60 (CO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.98−1.02 (t, *J* = 7.3 Hz, 3H, CH_3), 1.72−1.77 (m, 2H, CH_2), 3.25−3.29 (t, *J* = 7.1 Hz, 2H, CH_2−S), 7.61−7.64 (m, 1H, pyridine), 8.04−8.08 (t, *J* = 7.8 Hz, 1H, pyridine),

8.18−8.20 (d, *J* = 7.9 Hz, 1H, pyridine)), 8.75−8.76 (d, *J* = 4.5 Hz, 1H, pyridine), 13.79 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO-d_6) δ 13.1 (CH_3), 22.0 (CH_2), 32.2 (**C**H_2−S), 93.1 (−C−C≡N, pyrimidine), 114.9 (−C≡N), 123.5 (−CH−), 128.6 (−CH−), 137.6 (−CH−), 148.9 (−CH−), 152.1 (−C−, pyridine), 161.4 (−C=N, pyrimidine), 163.7 (−C=O), 165.9 (−C=C−, pyrimidine). HRMS (ESI) for $C_{13}H_{13}N_4OS$ $[M+H]^+$: calcd 273.0732, found 273.0806.

2-Ethyl-(5-cyano-4-oxo-6-(pyridin-2-yl)-1,4-dihydropyrimidin-2-ylthio) acetate(**5e**) 15 min, washed with ethyl acetate, beige powder, yield 87%, M.p. 208-210°C. IR $\bar{\nu}$ (cm^{-1}): 3397.41 (NH), 2218.20 (CN), 1733.63 (CO), 1652.40 (CO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.11−1.14 (t, *J* = 7.0 Hz, 3H, CH_3CH_2−O), 4.06-4.11(q, *J* = 7.0 Hz, 2H, CH_3CH_2−O), 4.19 (s, 2H, CH_2−S), 7.62−7.65 (m, 1H, pyridine), 8.04−8.08 (t, *J* = 7.4 Hz, 1H, pyridine), 8.14−8.16 (d, *J* = 7.7 Hz, 1H, pyridine), 8.75−8.76 (d, *J* = 3.7 Hz, 1H, pyridine), 13.99 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO-d_6) δ 13.9 (CH_3CH_2−O), 32.2 (CH_2−S), 61.3 (CH_3CH_2−O), 93.3 (−C−C≡N, pyrimidine), 114.7 (−C≡N), 123.5 (−CH−), 126.8 (−CH−), 137.4 (−CH−), 148.9 (−CH−), 151.8 (−C−, pyridine), 161.5 (−C=N, pyrimidine), 163.5 (−C=O), 165.0 (−C=O), 168.0 (−C=C−, pyrimidine). HRMS (ESI) for $C_{14}H_{13}N_4O_3S$ $[M+H]^+$: calcd 317.0630, found 317.0703.

2-(Benzylthio)-4-oxo-6-(pyridin-yl)-1,4-dihydropyrimidine-5-carbonitrile (**5f**). 30 min, washed with ethyl acetate, beige powder, yield 45%, M.p. 210-212°C. IR $\bar{\nu}$ (cm^{-1}): 3400.00 (NH), 2223.80 (CN), 1658.00 (CO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.61 (s, 2H, CH_2−S), 7.25−7.34 (dt, *J* = 23.2, 7.1 Hz, 3H, Ar−H), 7.44−7.46 (d, *J* = 7.3 Hz, 2H, Ar−H), 7.62−7.65 (m, 1H, pyridine)), 8.03−8.07 (t, *J* = 7.3 Hz, 1H, pyridine), 8.23−8.25 (d, *J* = 7.9 Hz, 1H, pyridine), 8.76−8.77 (d, *J* = 4.2 Hz, 1H, pyridine). ^{13}C NMR (101 MHz, DMSO-d_6) δ 34.3 (CH_2−S), 93.4 (−C−C≡N, pyrimidine), 114.9 (−C≡N), 123.8 (−CH−), 126.7 (−CH−), 127.5 (−CH−), 128.6 (2x−CH−), 129.0 (2x−CH−), 136.4 (−C−, Ar), 137.6 (−CH−), 148.9 (−CH−), 152.0 (−C−, pyridine), 161.5 (−C=N, pyrimidine), 163.8 (−C=O), 165.4 (−C=C−, pyrimidine). HRMS (ESI) for $C_{17}H_{12}N_4OSNa$ $[M+Na]^+$: calcd 343.0630, found 343.0641.

4-methyl-((5-cyano)-4-oxo-6-(pyridin-2-yl)-1,4-(dihydropyrimidin-2-yl)thiobenzoate (**5g**) 30 min, washed with methanol, beige powder, yield 80%, M.p. 241-243°C. IR $\bar{\nu}$ (cm^{-1}): 3159.33 (NH), 2223.00 (CN), 1708.42 (CO), 1663.60 (CO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.82 (s, 3H, CH_3−O), 4.67 (s, 2H, CH_2−S), 7.60−7.64 (t, *J* = 9.0 Hz, 3H), 7.89−7.91 (d, *J* = 7.9 Hz, 2H), 8.02−8.06 (t, *J* = 7.5 Hz, 1H, pyridine), 8.17−8.19 (d, *J* = 7.8 Hz, 1H, pyridine), 8.75−8.76 (d, *J* = 3.6 Hz, 1H, pyridine). ^{13}C NMR (101 MHz, DMSO-d_6) δ 33.8 (CH_2−S), 52.1 (CH_3−O), 93.4 (−C−C≡N, pyrimidine), 114.8 (−C≡N), 123.8 (−CH−), 126.6 (−CH−), 128.6 (−CH−), 129.2 (2x−CH−), 129.3 (2x−CH−), 137.5 (−CH−), 142.4 (−C−, Ar), 148.9 (−CH−), 151.9 (−C−, pyridine), 161.6 (−C=N, pyrimidine), 163.6 (−C=O), 165.2 (−C=O), 165.8 (−C=C−, pyrimidine). HRMS (ESI) for $C_{19}H_{15}N_4O_3S$ $[M+H]^+$: calcd 379.0787, found 379.0857.

2-(4-(Trifluoromethyl)benzylthio)-4-oxo-6-(pyridin-2-yl)-1,4-dihydropyrimidine-5-carbonitrile (**5h**) 30 min, washed with methanol, beige powder, yield 50%, M.p. 220-222°C. IR $\bar{\nu}$ (cm^{-1}): 3272.43 (NH), 2221.50 (CN), 1662.35 (CO). ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.69 (s, 2H, CH_2−S), 7.60−7.65 (m, 1H, pyridine), 7.68 (s, 4H, Ar−H), 7.99−8.06 (td, *J* = 7.8, 1.7 Hz, 1H, pyridine), 8.15−8.18 (d, *J* = 7.9 Hz, 1H, pyridine), 8.74−8.76 (d, *J* = 4.1 Hz, 1H, pyridine). ^{13}C NMR (63 MHz, DMSO-d_6) δ 33.5 (CH_2−S), 93.5 (−C−C≡N, pyrimidine), 114.9 (−C≡N), 122.0 (−CH−), 123.8 (−CH−, Ar), 125.7 (−CF_3−), 126.3 (−CH−), 126.7 (−CH−), 128.0 (−C−, Ar), 129.7 (2x−CH−), 137.6 (−CH−), 141.9 (−C−, Ar), 148.9 (−CH−), 151.9 (−C−, pyridine), 161.7 (−C=N, pyrimidine), 163.9 (−C=O), 165.2 (−C=C−, pyrimidine). HRMS (ESI) for $C_{18}H_{12}F_3N_4OS$ $[M+H]^+$: calcd 389.0606, found 389.0674.

6-(4-Methoxyphenyl)-4-oxo-2-propylthio-1,4-dihydropyrimidine-5-carbonitrile **(5i)** 30 min, purified by silica gel column chromatography (AcOEt: MeOH; 8:2), beige powder, yield 43%, M.p. 251-253°C. IR $\bar{\nu}$ (cm^{-1}): 3439.43 (NH), 2206.99 (CN), 1664.80 (CO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.94−0.98 (t, *J* = 7.3 Hz, 3H, CH_3), 1.64−1.73 (m, 2H, CH_2), 3.10−3.14 (t, *J* = 7.1 Hz, 2H, CH_2−S), 3.84 (s, 3H, CH_3−O), 7.07−7.09 (d, *J* = 8.7 Hz, 2H, Ar−H), 7.92−7.94 (d, *J* = 8.7 Hz, 2H, Ar−H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 13.2 (CH_3), 22.4 (CH_2), 32.0 (CH_2−S), 55.5 (CH_3−O), 90.1 (−C−C≡N, pyrimidine), 113.9 (2x−CH−), 117.8 −C≡N), 128.2 (−C−, Ar), 130.4 (2x−CH−), 161.7 (−C−OCH_3), (164.6 (−C=N, pyrimidine), 166.2 (−C=O), 167.8 (−C=C−, pyrimidine). HRMS (ESI) for $C_{15}H_{16}N_3O_2S$ $[M+H]^+$: calcd 302.0885, found 302.0885.

Methyl 4-methyl–(5-cyano-6-(methoxyphenyl)-4-oxo-1,4-dihydropyrimidin-2-ylthio)benzoate (**5j**) 30 min, washed with methanol, white powder, yield 66%, M.p. 246-248°C. IR $\bar{\nu}$ (cm^{-1}): 3355.40 (NH), 2215.40 (CN), 1660.80 (CO), 1562.50 (CO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.83−3.85 (d, *J* = 11 Hz, 6H, CH_3−O), 4.61 (s, 2H, CH_2−S), 7.10−7.12 (d, *J* = 8.4 Hz, 2H, Ar−H), 7.56−7.58 (d, *J* = 7.7 Hz, 2H, Ar−H), 7.89−7.98 (dd, *J* = 28.1, 8.0 Hz, 4H, Ar−H), 13.76 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO-d_6) δ 33.7 (CH_2−S), 52.1 (CH_3−O), 55.5 (CH_3−O), 91.6 (−C−C≡N, pyrimidine), 114.0 (2x−CH−), 116.2 (−C≡N−), 127.1 (−C−, Ar), 128.6 (−C−, Ar), 129.3 (4x−CH−), 130.8 (2x−CH−), 142.4 (−C−, Ar), 161.2 (−C−OCH_3), 162.3 (−C=N, pyrimidine), 164.7 (−C=O), 165.9 (−C=O), 166.3 (−C=C−, pyrimidine). HRMS (ESI) for $C_{21}H_{18}N_3O_4S$ $[M+H]^+$: calcd 408.0940, found 408.1010.

2-(4-Trifluoromethyl)benzylthio)-6-(4-methoxypheny)-4-oxo-1,4-dihydropyrimidine-5-carbonitrile (**5k)** 30 min, washed with methanol, white powder, yield 62%, M.p. 273-275°C. IR $\bar{\nu}$ (cm^{-1}): 3363.80 (NH), 2218.20 (CN), 1658.00 (CO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.86 (s, 1H, CH_3−O), 4.63 (s, 2H, CH_2−S), 7.10−7.12 (d, *J* = 8.8 Hz, 2H, Ar−H), 7.64−7.70 (m, 4H, Ar−H), 7.94−7.96 (d, *J* = 8.7 Hz, 2H, Ar−H), 13.73 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO-d_6) δ 33.5 (CH_2−S), 55.5 (CH_3−O), 91.6 (−C−C≡N, pyrimidine), 114.0 (2x−**C**H−), 116.3 (−C≡N), 122.8 (−CH−), 125.3 (−CF_3), 125.5 (−CH−), 127.1 (−C−, Ar), 127.9 (−C−, Ar), 129.7 (2x−CH−), 130.8 (2x−CH−), 141.9 (−C−, Ar), 161.2 (−C−OCH_3), 162.3 (−C=N, pyrimidine), 166.2 (−C=C−, pyrimidine), 164.6 (−C=O). HRMS (ESI) for $C_{20}H_{15}F_3N_3O_2S$ $[M+H]^+$: calcd 418.0759, found 418.0828.

*6-(3-Benzyloxyphenyl)-4-oxo-2-propylthio-1,4-dihydropyrimidine-5-carbonitrile (**5l**)* 30 min, washed with methanol, white powder, yield 62%, M.p. 160-162°C. IR $\bar{\nu}$ (cm^{-1}): 3380.61 (NH), 2221.00 (CN), 1669.20 (CO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.94−0.98 (t, *J* = 7.3 Hz, 3H, CH_3), 1.68−1.74 (m, 2H, CH_2), 3.17−3.21 (t, *J* = 7.1 Hz, 2H, CH_2−S), 5.18 (s, 2H, CH_2−O), 7.26−7.55 (m, 9H, Ar−H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 13.1 (CH_3), 22.1 (CH_2), 32.2 (CH_2−S), 69.5 (CH_2−O), 93.1 (−C−C≡N, pyrimidine), 114.9 (−CH−), 115.8 (−CH−), 118.3 (−C≡N), 121.1 (−CH−), 127.6 (−CH−), 127.9 (2x−CH−), 128.5 (2x−CH−), 129.8 (−CH−), 136.6 (−C−, Ar), 136.7 (−C−, Ar), 158.2 (−C−OCH_2), 160.9 (−C=N, pyrimidine), 166.1 (−C=O), 166.8 (−C=C−, pyrimidine). HRMS (ESI) for $C_{21}H_{20}N3O_2S$ $[M+H]^+$: calcd 378.1198, found 378.1268.

Ethyl 2-((6-(3-(benzyloxy)phenyl)-5-cyano-4-oxo-1,4-dihydropyrimidin-2-yl)thio)acetate (**5m)** 30 min, washed with methanol, white powder, yield 70%, M.p. 202-204°C. IR $\bar{\nu}$ (cm^{-1}): 3405.82 (NH), 2223.80 (CN), 1658.00 (CO), 1744.83 (CO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.03−1.06 (t, *J* = 7.1 Hz, 3H, CH_3CH_2−O), 4.02−4.08 (q, *J* = 7.1 Hz, 2H, CH_3CH_2−O), 4.13 (s, 2H, CH_2−S), 5.17 (s, 2H, CH_2−O), 7.27−7.53 (m, 9H, Ar−H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 13.8 (CH_3CH_2−O), 32.9 (CH_2−S), 61.3 (CH_3CH_2−O), 69.6 (CH_2−O), 93.2 (−C−C≡N, pyrimidine), 115.3 (−CH−), 115.6 (−CH−), 118.1 (−C≡N), 121.1 (−CH−), 127.8 (2x−CH−), 129.0 (−CH−), 128.5 (2x−CH−), 129.7 (−CH−), 136.3 (−C−, Ar), 136.6 (−C−, Ar), 158.3 (−C−OCH_2), 161.0 (−C=N, pyrimidine), 165.1 (−C=O), 166.5 (−C=O), 168.0 (−C=C−, pyrimidine). HRMS (ESI) for $C_{22}H_{20}N_3O_4S$ $[M+H]^+$: calcd 422.1096, found 422.1165.

6-(3-(Benzyloxy)phenyl)-2-(benzylthio)-4-oxo-1,4-dihydropyrimidine-5-carbonitrile (5n) 30 min, washed with methanol, white powder, yield 85%, M.p. 198-200°C. IR $\bar{\nu}$ (cm^{-1}): 3252.72 (NH), 2204.02 (CN), 1550.61 (CO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.51 (s, 2H, CH_2−S), 5.15 (s, 2H, CH_2−O), 7.25−7.55 (m, 14H, Ar−H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 34.2 (CH_2−S), 69.5 (CH_2−O), 93.4 (−C−C≡N, pyrimidine), 114.9 (−CH−), 115.7 (−CH−), 118.4 (−C≡N), 121.2 (−CH−), 127.5 (−CH−), 127.7 (2x−CH−), 127.9 (−CH−), 128.5 (4x−CH−), 129.0 (2x−CH−), 129.8 (−CH−), 136.3 (−C−, Ar), 136.5 (−C−, Ar), 136.7 (−C−, Ar), 158.2 (−C−OCH_2), 161.1 (−C=N, pyrimidine), 165.7 (−C=O), 166.9 (−C=C−, pyrimidine). HRMS (ESI) for $C_{25}H_{20}N_3O_2S$ $[M+H]^+$: calcd 426.1198, found 426.1267.

Methyl 4-(((6-(3-(benzyloxy)phenyl)-5-cyano-4-oxo-1,4-dihydropyrimidin-2-yl)thio)methyl)benzoate (**5o)** 30min, washed with methanol, white powder, yield 82%, M.p. 280-282°C. IR $\bar{\nu}$ (cm^{-1}): 3156.53 (NH), 2215.40 (CN), 1725.22 (CO), 1652.40 (CO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.80 (s, 3H, CH_3−O), 4.57 (s, 2H, CH_2−S), 5.11 (s, 2H, CH_2−O), 7.25−7.56 (m, 11H, Ar−H), 7.87−7.89 (d, *J* = 8.0 Hz, 2H, Ar−H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 34.7 (CH_2−S), 52.1 (CH_3−O), 69.5 (CH_2−O), 93.4 (−C−C≡N, pyrimidine), 114.8 (−CH−), 115.7 (−CH−), 118.4 (−C≡N), 121 (−CH−), 127.6 (2x−CH−), 127.9 (−CH−), 128.5 (2x−CH−), 128.6 (−CH−), 129.3 (4x−CH−), 129.8 (−C−, Ar), 136.5 (−C−, Ar), 136.6 (−C−, Ar), 142.3 (−C−, Ar), 158.2 (−C−OCH_2), 161.1 (−C=N, pyrimidine), 165.4 (−C=O), 165.8 (−C=O), 166.9 (−C=C−, pyrimidine). HRMS (ESI) for $C_{27}H_{22}N_3O_4S$ $[M+H]^+$: calcd 484.1253, found 484.1321.

6-(3-(Benzyloxy)phenyl)-4-oxo-2-((4-(trifluoromethyl)benzyl)thio)-1,4-dihydropyrimidine-5-carbonitrile (**5p)** 15 min, washed with methanol, white powder, yield 72%, M.p. 228-230°C. IR $\bar{\nu}$ (cm^{-1}): 3335.79 (NH), 2226.85 (CN), 1661.15 (CO). ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.59 (s, 2H, CH_2−S), 5.14 (s, 2H, CH_2−O), 7.26−7.49 (m, 9H, Ar−H), 7.64 (s, 4H, Ar−H). ^{13}C NMR (63 MHz, DMSO-d_6) δ 33.5 (CH_2−S), 69.5 (CH_2−O), 93.5 (−C−C≡N, pyrimidine), 115.0 (−CH−), 115.7 (−CH−), 118.3 (−C≡N), 121.2 (−CH−), 121.9 (−CH−), 125.3 (−CF_3), 126.3 (−CH−), 127.6 (2x−CH−), 127.9 (−CH−), 128.0 (−CH−), 128.5 (2x−CH−), 129.8 (2x−CH−), 129.8 (−C−, Ar), 136.4 (−C−, Ar), 136.7 (−C−, Ar), 141.8 (−C−, Ar), 158.3 (−C−OCH_2), 161.1 (−C=N, pyrimidine), 165.4 (−C=O), 166.9 (−C=C−, pyrimidine). HRMS (ESI) for $C_{26}H_{19}F_3N_3O_2S$ $[M+H]^+$: calcd 494.1072, found 494.1140.

4-Oxo-6-(thiophen-2-yl)-2-((4-(trifluoromethyl)benzyl)thio)-1,4-dihydropyrimidine-5-carbonitrile (**5q)** 30 min, washed with ethyl acetate, beige powder, yield 93%, M.p. 250-252°C. IR $\bar{\nu}$ (cm^{-1}): 3341.39 (NH), 2229.40 (CN), 1652.40 (CO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.65 (s, 2H, CH_2−S), 7.34−7.36 (m, 1H, thiophene), 7.70 (s, 4H, Ar), 8.06−8.07 (d, J = 4.9 Hz, 1H, thiophene), 8.27−8.28 (d, J = 3.7 Hz, 1H, thiophene). ^{13}C NMR (101 MHz, DMSO-d_6) δ 33.2 (CH_2−S), 88.4 (−C−C≡N, pyrimidine), 116.1 (−C≡N), 122.8 (−CH−), 125.4 (−CF_3−), 128.1 (−CH−), 129.5 (−CH−), 129.6 (2x−CH−), 131.7 (−CH−), 135.1 (−C−, Ar), 139.3 (−CH−), 142.0 (−C−, thiophene), 158.6 (−C−, Ar), 160.9 (−C=N, pyrimidine), 164.8 (−C=O), 165.5 (−C=C−, pyrimidine), HRMS (ESI) for $C_{17}H_{11}F_3N_3OS_2$ $[M+H]^+$: calcd 394.0217, found 394.0217.

Antibacterial Assay

Antimicrobial tests of synthesized compounds 4a-d and 5a-p were evaluated against *P. aeruginosa* and *E. coli* (Gram-negative bacteria) and then against *S. aureus* and *E. faecalis* (Gram-positive bacteria). The microdilution method used was performed in a 96-well plate**.**[19] Compounds were dissolved in sterile DMSO so that their concentration in the wells of column 12 was 256 µg/mL followed by a dilution range of order 2 in DMSO to obtain a concentration series of the sample solution (from 256 to 0.063 µg/mL). After this dilution, 225 µL of Mueller-Hinton culture medium (previously prepared according to the supplier's data) and 20 µL of the different inocula were added to 5 µL of the sample solution at different concentrations. Then the microplates were incubated at 37°C for 24 hours. Absorbance measurements were performed at 600 nm with a plate reader. Bacterial growth results in opacity in the well (Absorbance greater than 0.1) indicating that the tested compound did not allow its inhibition (the compound has no antibacterial activity) at the corresponding concentration. In the opposite case, if there is an absence of this disorder (Absorbance lower than 0.1), the tested compound has inhibited the growth of bacteria at the corresponding concentration (the compound has an antibacterial activity).

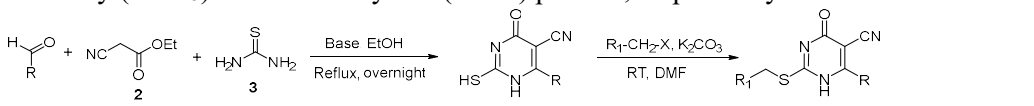
RESULTS AND DISCUSSION

Chemistry

Multicomponent reactions are useful synthetic routes for the preparation of polyfunctionalized heterocyclic compounds which are important for drug discovery in medicinal chemistry. The desired compounds were prepared following the standard methods summarized in Scheme-1.

Briefly, the starting materials 6-aryl-5-cyano-2-thiouracils 4a-e were prepared by condensing the appropriate aldehyde with ethyl cyanoacetate and thiourea in the presence of potassium carbonate (K_2CO_3)[20] or piperidine.[21] The reaction includes both Knoevenagel condensation and Michael addition mechanisms. First, various aryl aldehydes react with ethyl cyanoacetate in ethanolic solution in the presence of a base to generate intermediates *via* Knoevenagel condensation reaction. Then, these condensation products react with thiourea by Michael's addition to give the corresponding pyrimidine derivatives. The synthesis of final compounds 5a-q was achieved by *S*-benzylation/alkylation in absolute ethanol and in the presence of potassium carbonate. The formation of the 6-aryl-4-oxo-1,4-dihydropyrimidine-5-carbonitrile derivatives 5a-q was confirmed by ^{1}H NMR, ^{13}C NMR, mass spectrometry, and IR. As an example, ^{1}H

NMR analysis of compound 5k indicates two singlets at 3.86 ppm and 4.63 ppm which are characteristic signals of methoxy (OCH_3) and thiomethylene (SCH_2) protons, respectively.



1a. R= C_6H_5
1b. R= 2-C_5H_4N
1c. R= 4-$MeOC_6H_4$
1d. R= 3-C_6H_4-CH_2O-C_6H_5
1e. R= 2-C_4H_3S

4a. R= C_6H_5
4b. R= 2-C_5H_4N
4c. R= 4-$MeOC_6H_4$
4d. R= 3-C_6H_4-CH_2O-C_6H_5
4e. R= 2-C_4H_3S

5a R=C_6H_5	R_1= EtOOC
5b. R=C_6H_5,	R_1= 4-MeOOC-C_6H_4
5c. R=C_6H_5	R_1= 4-CF_3-C_6H_4
5d. R=2-C_5H_4N	R_1= CH_3CH_2
5e R=2-C_5H_4N,	R_1= EtOOC
5f. R=2-C_5H_4N	R_1= C_6H_5
5g. R= 2-C_5H_4N	R_1= 4-MeOOC-C_6H_4
5h. R=2-C_5H_4N	R_1= 4-CF_3-C_6H_4
5i. R=4-$MeOC_6H_4$	R_1= CH_3CH_2
5j. R= 4-$MeOC_6H_4$	R_1= 4-MeOOC-C_6H_4
5k. R=4-$MeOC_6H_4$	R_1= 4-CF_3-C_6H_4
5l. R= 3-C_6H_4-CH_2O-C_6H_5	R_1= CH_3CH_2
5m R= 3-C_6H_4-CH_2O-C_6H_5	R_1= EtOOC
5n. R= 3-C_6H_4-CH_2O-C_6H_5	R_1= C_6H_5
5o. R= 3-C_6H_4-CH_2O-C_6H_5	R_1= 4-MeOOC-C_6H_4
5p. R= 3-C_6H_4-CH_2O-C_6H_5	R_1= 4-CF_3-C_6H_4
5q. R= 2-C_4H_3S	R_1= 4-CF_3-C_6H_4

Scheme-1: Synthesis of 6-aryl-4-oxo-1,4-dihydropyrimidine-5-carbonitrile Derivatives (5a-q)

The broad singlet at 13.73 ppm is attributed to the NH present in the pyrimidine ring while all aromatic protons gave peaks at the expected values. In the ^{13}C NMR spectrum, compound 5k showed three signals at 33.4, 116.2, and 162.2 ppm which are characteristic of thiomethylene, carbonitrile, and imine carbon peaks, respectively. The signal at 164.6 ppm indicates the presence of the carbonyl carbon while all further carbons gave peaks at the expected values. High-resolution mass spectrometry (HRMS) for compound 5k yielded a molecular ion peak at m/z = 418.0828. Similarly, the IR spectrum of compound 5k showed strong absorption bands features for C=O, C≡N, and NH at $\bar{\nu}$ = 1658, 2218, and 3363 cm^{-1}, respectively.

Antibacterial Activity

The *in vitro* antibacterial activity of synthetic compounds 4a-d and 5a-p was evaluated against the Gram-positive *S. aureus* and *E. faecalis* bacteria and Gram-negative *P. aeruginosa* and *E. coli* bacteria. MIC values were determined using the microdilution method performed on a 96-well plate. Ciprofloxacin was used as the reference antibacterial agent. All the biological results of the tested compounds are resumed in Table-1. The tested compounds were found to be not potent against the Gram-negative *P. aeruginosa* and *E. coli* bacteria. Compounds 4a-c and 5b-f, 5i, 5j, 5n, and 5o were also observed as inactive against all bacteria tested at the concentrations used. However, compounds 4d and 5g, 5h, 5k, 5l, 5m, and 5p, showed moderate to good bacterial inhibition against Gram-positive bacteria. In particular, compounds 4d, 5g, 5h, 5k, 5m, and 5p showed bacterial inhibition against *E. faecalis* while only 5l showed moderate activity against *S. aureus*. Antibacterial assay analysis showed that compound 4d with a MIC = 128 µg/mL against *E. faecalis* loses its activity when it is *S*-alkylated with the benzyl (5n) or methyl 4-methylene benzoate groups (5c). However, the use of ethyl acetate group 5m (MIC = 64 µg/mL against *E. faecalis*) increase its activity while the use of 4-trifluoromethyl benzyl 5p (MIC = 1 µg/mL against *E. faecalis*) was even better. Thus, 5p was as active as ciprofloxacin. *S*-alkylation of compound 4d with the propyl moiety to give compound 5l generated an activity against *S. aureus* with a MIC = 16 µg/mL.

In addition, *S*-alkylation of the inactive compound 4b with methyl 4-methylene benzoate groups or 4-trifluoromethyl benzyl led to the antibacterial activity of compounds 5h and 5g against *E. faecalis* with MICs of 256 µg/mL and 16µg/mL, respectively. Furthermore, compound 5k obtained by *S*-alkylation of the inactive compound 4c with the 4-trifluoromethyl benzyl group became potent against *E. faecalis* with a MIC= 8 µg/mL. It is clear from the results that *S*-alkylation is beneficial in improving the antibacterial activity of the thiouracil derivatives. The presence of the 4-trifluoromethyl benzyl group showed the best inhibitory effect. Likewise, the use of 3-phenoxybenzaldehyde could be promising for the generation of antibacterial activity in thiouracil derivatives.

CONCLUSION

We have synthesized a series of new 6-aryl-4-oxo-1,4-dihydropyrimidine-5-carbonitrile derivatives. Some of them (compounds 4d, 5g, 5h, 5k, 5l, 5m, 5n, and 5p) exhibited moderate to good antibacterial activity against the tested Gram-positive bacteria. Compound 5p was as active as ciprofloxacin against *E. faecalis*.

This last compound has the best result for antiproliferative bacterial activity such as the reference, suggesting that it could be a promising candidate for bacterial treatment.

Table-1: In Vitro Antibacterial Activity of Compounds 4a-d and 5a-p

Compounds	MIC: Minimum Inhibition Concentration (µg/mL)			
	Gram-negative bacteria		Gram-positive bacteria	
	P. aeruginosa	*E. coli*	*S. aureus*	*E. faecalis*
4a	_	_	_	_
4b	_	_	_	_
4c	_	_	_	_
4d	_	_	_	128
5a	_	_	_	_
5b	_	_	_	_
5c	_	_	_	_
5d	_	_	_	-
5e	_	_	_	_
5f	_	_	_	_
5g	_	_	_	16
5h	_	_	_	256
5i	_	_	_	_
5j	_	_	_	_
5k	_	_	_	8
5l	_	_	16	_
5m	_	_	_	64
5n	_	_	_	_
5o	_	_	_	_
5p	_	_	_	1
Ciprofloxacine (Ctrl+)	1	0,125	8	1

- means no activity, Ctrl+ means control, Compounds 4e and 5q were not tested

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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REFERENCES

1. M. M. Heravi and V. Zadsirjan, *Royal Society of Chemistry Advances*, **10(72)**, 44247(2020), https://doi.org/10.1039/D0RA09198G
2. N. Kerru, L. Gummidi, S. Maddila, K. K. Gangu and S. B. Jonnalagadda, *Molecules*, **25(8)**, 1909(2020), https://doi.org/10.3390/molecules25081909
3. V. Sharma, N. Chitranshi and A. K. Agarwal, *International Journal of Medicinal Chemistry,* **2014**, 1(2014), https://doi.org/10.1155/2014/202784
4. K. Mikio and A. Masayuki, US Patent US5795497A (1998).
5. K. J. Chetan, S. N. Amol, V. C. Asha, D. S. Vishal, P. P. Anil and H. G. Charansingh, *ACS Omega*, **4(27)**, 22313(2019), https:/ /doi.org/10.1021/acsomega.9b02286
6. K. S. Jain, T. S. Chitre, P. B. Miniyar, M. K. Kathiravan, V. S. Bendre, V. S. Veer, S. R. Shahane and C. J. Shishoo, *Current Science*, **90(6),** 793(2006)
7. C. O. Kappe, *Tetrahedron*, **49(32)**, 6937(1993), https://doi.org/10.1016/S0040-4020(01)87971-0
8. P. A. Achi, C. Siomenan, D. Zon, T. Adéyolé, E. Bolou, T. Daouda, D. Sissouma and A. Adjou, *Open Journal of Medicinal Chemistry,* **11(3)**, 27(2021), https://doi.org/10.4236/ojmc.2021.113003
9. Z. Wang, Y. Gao, L. He, S. Sun, T. Xia, L. Hu, L. Yao, L. Wang, D. Li, H. Shi and X. Liao, *Journal of Medicinal Chemistry*, **64(11)**, 7507(2021), https://doi.org/10.1021/acs.jmedchem.1c00179
10. L. Chen, Y. Jin, W. Fu, S. Xiao, C. Feng, B. Fang, Y. Gu, C. Li, Y. Zhao, Z. Liu and G. Liang *ChemMedChem,* **12(13)**, 1022(2017), https://doi.org/10.1002/cmdc.201700175
11. A. M. Farghaly, O. M. AboulWafa, Y. A. Elshaier, W. A. Badawi, H. H. Haridy, and H. A. Mubarak, *Medicinal Chemistry Research,* **28**, 360(2019), https://doi.org/10.1007/s00044-019-02289-6
12. V. Virsodia, R. R. S. Pissurlenkar, D. Manvar, C. Dholakia, P. Adlakha, A. Shah and E. Coutinho, *European Journal of Medicinal Chemistry,* **43(10)**, 2103(2008), https://doi.org/10.1016/j.ejmech.2007.08.004
13. A. S. Chaudhary, J. Jin, Chen, P. C. Tai and B. Wang, *Bioorganic & Medicinal Chemistry,* **23(1)**, 105(2015), https://doi.org/10.1016/j.bmc.2014.11.017
14. F. Bamba, J. Jin, A. S. Chaudhary, P. C. Tai and B. Wang, *Medicinal Chemistry Research,* **30**, 1334(2021), https://doi.org/10.1007/s00044-021-02717-6
15. F. Bamba, J. Jin, P. C. Tai and B. Wang, *Heterocyclic Communications,* **26(1)**, 76(2020), https://doi.org/10.1515/hc-2020-0100
16. C. V. S. Rao, E. De Waelheyns, A. Economou and J. Anné, *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research,* **1843(8)**, 1762(2014), https://doi.org/10.1016/j.bbamcr.2014.02.004
17. A. S. Chaudhary, W. Chen, J. Jin, P. C. Tai and B. Wang, *Future Medicinal Chemistry,* **7(8)**, 989(2015), https://doi.org/10.4155/fmc.15.42
18. J. Jin, Y. H. Hsieh, A. S. Chaudhary, J. Cui, J. E. Houghton, S. F. Sui, B. Wang and P. C. Tai, *FEMS Microbiology Letters,* **365(15)**, fny145(2018), https://doi.org/10.1093/femsle/fny145
19. A. Thabaut and J. L. Durosoir, *Médecine et Maladies Infectieuses,* **9(9)**, 490(1979), https://doi.org/10.1016/S0399-077X(79)80006-2
20. W. Chen, Y. J. Huang, S. R. Gundala, H. Yang, M. Li, P. C. Tai and B. Wang, *Bioorganic & Medicinal Chemistry,* **18(4)**, 1617(2010), https://doi.org/10.1016/j.bmc.2009.12.074
21. M. B. Chetan, A. M. Irfan, B. Ramesh and G. Ramu, *Arabian Journal of Chemistry,* **7(6),** 986(2014), https://doi.org/10.1016/j.arabjc.2010.12.021

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