Novel CAL-B catalyzed synthetic protocols for pyridodipyrimidines and mercapto oxadiazoles

REGULAR ARTICLE Published: 06 December 2022

Volume 134, article number 120, (2022) Cite this article

Journal of Chemical Sciences

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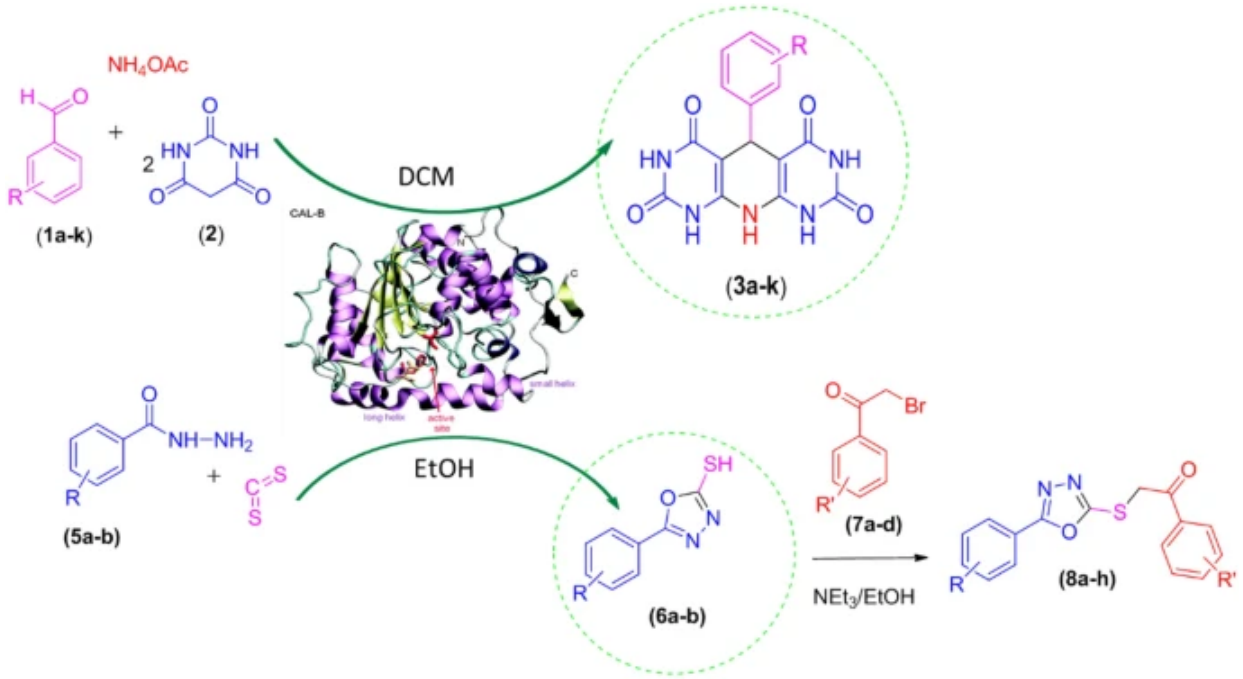
Abstract

CAL-B catalyzed novel synthetic routes have been developed for getting better to excellent yields of the pyridodipyrimidines and mercapto oxadiazoles. Here, for the first time, one pot cyclo condensation of barbituric acid, aromatic aldehydes, and ammonium acetate has been carried at room temperature in dichloromethane in the presence of biocatalyst, CAL-B and obtained 5-aryl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraones (**3a-k**). CAL-B catalyzed cyclo condensation of arylhydrazides and carbon disulphide has also been carried in ethanol for getting 5-(p-substituted phenyl)-1,3,4-oxadiazole-2-thiol (**6a-b**). Mercapto oxadiazoles (**6a-b**) are also separately allowed to react with substituted phenacyl bromides in the presence of trimethylamine and obtained 1-aryl-2-((5-substitutedphenyl-1,3,4-oxadiazol-2-yl)thio)ethanones (**8a-h**). The developed routes are efficient, clean, and cost-effective. Synthesized compounds; (**3a-k**), (**6a-b**), and (**8a-h**) are thoroughly

characterized by their spectral data.

Graphical abstract

CAL-B, catalyzed efficient one pot synthetic routes have been first time developed for getting better to excellent yields of the 5-aryl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraones (**3a-k**) and 5-(p-substituted phenyl)-1,3,4-oxadiazole-2-thiol (**6a-b**).



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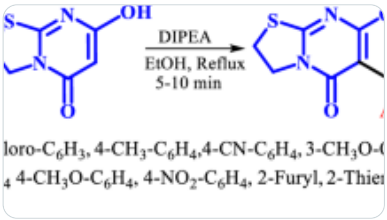

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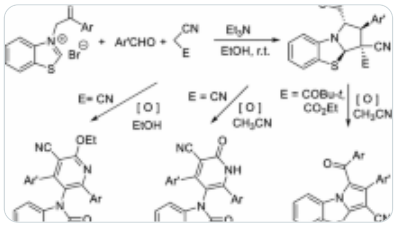

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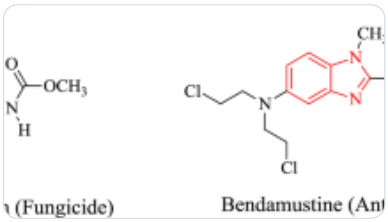

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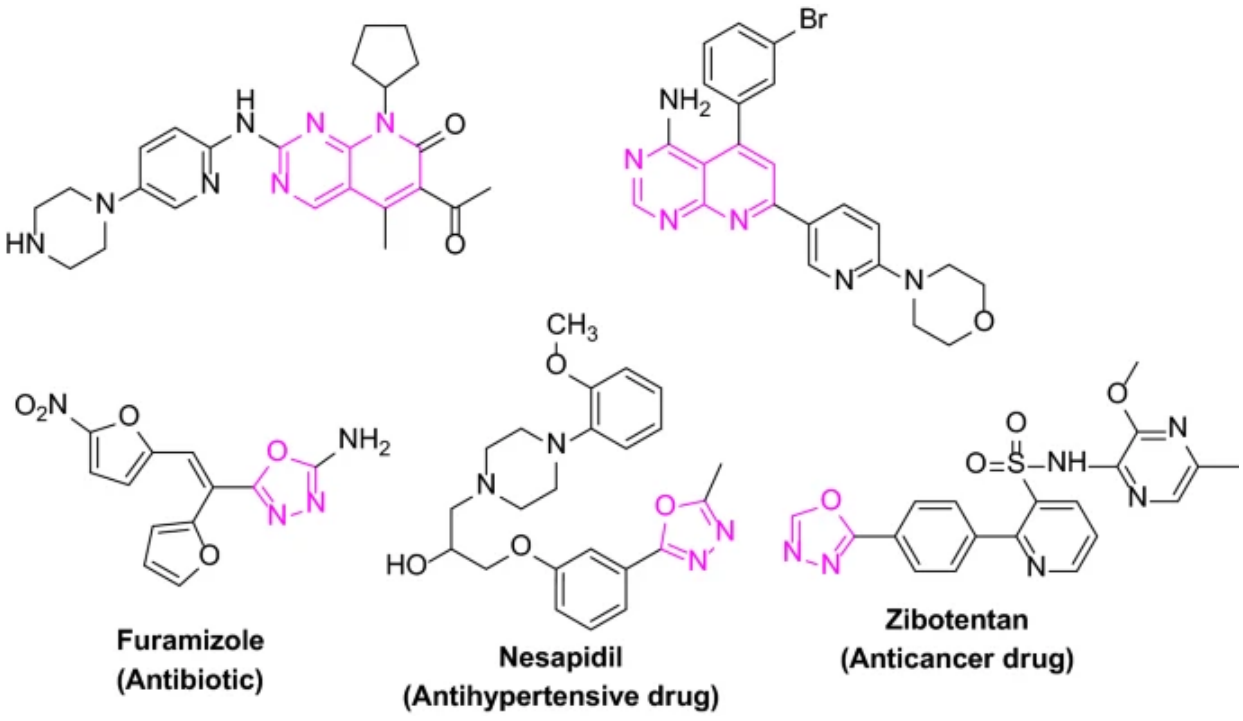
1 Introduction

Nitrogen-containing heterocycles, *viz.* pyridopyrimidines and 1,3,4-oxadiazoles, have diverse biological activities and are found to be interesting area of research in heteroaromatic chemistry.[1] Literature survey reveals that pyrimidine ring-bearing molecules are found to display a vital role in the various biological processes. The pyridopyrimidine scaffold has widely occurred in many bioactive heterocycles of natural and synthetic origins, and this also plays a significant role in different drug discovery programs. Heterocycles with pyridopyrimidine moiety are found to have a broad range of biological, medicinal, and pharmacological properties, like antitumor,[2] antibacterial,[3,4] antifungal,[4] antiviral,[5] anti-oxidant,[6] dihydrofolate reductase inhibitory,[7] tyrosine kinase inhibitory,[8] calcium channel antagonist,[9] and fibroblast growth factor receptor 3 inhibitory[10] (Figure 1).

Figure 1



Drugs having pyrido[2,3-d]pyrimidine and 1,3,4-oxadiazole scaffolds in their skeleton.

Mercapto oxadiazoles and 1,3,4-oxadiazoles are also nitrogen-containing heterocycles, generally utilized as pharmacophoric systems, due to their metabolic profile and ability to engage in hydrogen bonding interaction with receptors. Therefore mercapto oxadiazole and 1,3,4-oxadiazole scaffolds are well explored in agricultural, pharmaceutical, and industrial fields. Various substituted mercapto oxadiazoles possess significant anti-inflammatory, antibiotic, analgesic, anticonvulsant, hypoglycemic, and antitubercular activities.[11,12,13] The literature survey reveals that mercapto oxadiazoles, 1,3,4-oxadiazoles, and their amino derivatives are prominent antimicrobial agents.[14,15,16] These compounds are said to be more potent antibiotics compared to the standard antibiotics, penicillin G,[17] gentamicin, and ampicillin.[18] 1,3,4-Oxadiazole skeleton in association with various other heterocycles are displaying broad spectrum of biological activities like anti-inflammatory, antidiabetic, antitumor,[19] antifungal,[20] hypotensive,[21] antitubercular,[22] corrosion inhibiting and tyrosinase inhibitory[23] (Figure 1).

Due to this wide range of pharmacological properties and biological activities, pyridodipyrimidines and mercapto oxadiazoles occupy a noteworthy place in the subject of medical research. These applications of pyridodipyrimidines and mercapto oxadiazoles have insisted that researchers synthesize therapeutically important newer pyridodipyrimidines and mercapto oxadiazoles. Researchers have reported one pot cyclocondensation of barbituric acid, aldehydes and ammonium acetate separately incorporating ultrasound irradiation,[24] catalyst-free condition,[25] SBA-15-supported sulfonic acid nanocatalyst,[26] ionic liquid [H-NMP]$^+$ [HSO_4]$^-$ under ultrasonic irradiation,[27] and β-cyclodextrin-ultrasonication,[28] for obtaining pyridodipyrimidines.

Classical methods for the preparation of the 1,3,4-oxadiazole-2(3*H*)-thiones include the cyclo condensation of acylhydrazides and carbon disulphide in ethanol in the presence of potassium hydroxide,[29] under the microwave.[30] It is also reported that the conversion of aromatic acyl hydrazides into 1,3,4-oxadiazoles is more convenient than aliphatic hydrazides, assisted separately by microwave,[31] DMF,[32] sodium dodecyl sulfate (SDS),[33] polymer-supported reagents/resin-bound reagents,[34] polymer-supported reagents separately under thermal and microwave condition,[35] tosylchloride and pyridine,[36] under microwave irradiation using $POCl_3$, and Al_2O_3,[37] and resin-bound acylhydrazines.[38]

These above-reported protocols are found to have certain limitations, such as tedious workup procedures, non-readily available catalysts, and require high energy. It seems from the above reports that there is no attention paid to the use of enzymes as catalysts while carrying the syntheses of pyridodipyrimidines and mercapto oxadiazoles.

Recently, biocatalysts/enzymes have been used to accelerate various organic transformations leading to biodynamic compounds, and they are functional proteins used currently as innocuous and cost-effective catalysts. Lipases are ubiquitous, naturally endowed catalysts with the ability to perform reactions in aqueous and organic solvents. They are well-explored as biocatalysts to catalyze the hydrolysis of water-soluble carboxylic esters, particularly triglycerides and phospholipids.[39] Among the lipases, Candida antartica lipase B (CAL-B) has been used as a biocatalyst in its pure form as well as immobilized CAL-B form to accelerate various organic reactions and biotransformations.[40,41,42,43] Recently, CAL-B has been well characterized and is structurally similar to several other lipases and has Serine, Histidine, and Aspartic catalytical triads with secondary alcoholic binding pocket. Usually, these active sites *viz.,* Serine, Histidine, Aspartic residues participate to display catalytic behaviors to accelerate the rates of organic/biotranformations.[44,45] Our group has used biocatalysts, Baker's yeast as a whole cell source of enzymes and lipase as an isolated pure enzyme for conducting various organic transformations.[46,47,48,49]

To overcome the limitations in the above-mentioned synthetic protocols, and considering the eco-friendly nature of biocatalysts, and in continuation of our earlier interest in developing greener protocols for the synthesis of different therapeutically important heterocycles, here we have decided to use a biocatalyst, CAL-B for the synthesis of pyridodipyrimidines and mercapto oxadiazoles.

2 Experimental

2.1 General

All the chemicals used were of laboratory grade. Lipase B Candida Antarctica immobilized on immobead 150 recombinant from yeast is procured from Sigma Aldrich. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded with a BrukerAvance 300 spectrometer operating at 400 MHz using DMSO-d_6 solvent and tetramethylsilane (TMS) as the internal standard, and chemical shift in δ ppm.^{13}C NMR spectra were recorded on BrukerAvance 75 MHz on Jeol. The purity of each compound was checked by Thin Layer Chromatography using silica-gel, 60F_{254} aluminum sheets as adsorbent, and visualization was accomplished by iodine/ultraviolet light.

2.2 General procedure for the synthesis of 5-(substituted phenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraones (3a-k)

A mixture of substituted aldehydes (0.94 mmol), barbituric acid (1.88 mmol), and ammonium acetate

(1.2 mmol) was stirred in DCM (10 mL). CAL-B (200 mg) was added to this reaction mass, and the reaction mixture was further stirred at room temperature for 18 h. After completion of reaction, the reaction content was then stirred with ethanol (50 mL) + DMF (5 mL) and then filtered. The residue, CAL-B was then reused. The crude pyridodipyrimidines were obtained by removing the solvent from the filtrate by a rotatory evaporator. The crude products have been crystalized using ethanol. All the synthesized compounds are known, and their ^{1}H NMR, ^{13}C NMR, and HRMS spectral data and melting points are found to be in good agreement with those reported in the literature[28].

Scan copies of spectra of **3a** are provided as a representative of the series (**3a-k**).

2.2.1 Spectral data of the compounds

5-Phenyl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraone (3a): Yield: 77%; M.p.: 284-286 °C

^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 5.95 (s, 1H, -CH), 6.98-7.16 (m, 5H, Ar-H), 7.95 (s, 2H, -2NH) and 9.96 (s, 3H, -3NH). ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm): 35.79, 91.01, 124.36, 126.70, 127.38, 144.83, 150.73, 162.34 and 163.96. HRMS: (ESI^{+}) Mode: Calculated 326.0889, Observed 326.3425.

5-(4-Hydroxyphenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraone (3b): Yield: 65%; M.p.: >300 °C

^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 5.87 (s, 1H, -CH), 6.95-7.64 (m, 4H, Ar-H), 7.98 (s, 2H, 2NH) and 10.04 (s, 3H, 3NH). ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm): 35.89, 91.45, 124.67, 126.53, 127.47, 144.74, 150.65, 162.38 and 164.86. HRMS (ESI^{+}): (M+H)$^{+}$ Calculated 342.0838, Observed 342.0414.

5-(4-*N*,*N*-Dimethylaminophenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraone (3c): Yield: 61%; M.p.: 288-289 °C

^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 3.19 (s, 6H, -2CH_3), 5.67 (s, 1H, -CH), 6.22-6.96 (m, 4H, Ar-H), 7.93 (s, 2H, 2NH) and 9.26 (s, 3H, 3NH). ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm): 35.88, 42.97, 91.27, 124.87, 126.94, 127.54, 144.92, 150.81, 162.54 and 164.33. HRMS (ESI^{+}): (M+H)$^{+}$ Calculated 369.1311, Observed 369.1345.

5-(4-Chlorophenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraone (3d): Yield: 73%; M.p.: >300 °C

^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 5.87 (s, 1H, -CH), 7.02-7.36 (m, 4H, Ar-H), 7.92 (s, 2H, 2NH) and 9.98 (s, 3H, 3NH). ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm): 35.97, 91.52, 124.54, 126.93, 127.56, 145.14, 150.93, 162.87 and 164.62. HRMS (ESI$^+$): $(M+H)^+$ Calculated 360.0499, Observed 360.0443.

5-(3-Bromophenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraone (3e): Yield: 59%; M.p.: >300 °C

^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 5.91 (s, 1H, -CH), 7.32-7.56 (m, 4H, Ar-H), 8.09 (s, 2H, 2NH) and 10.26 (s, 3H, 3NH). ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm): 35.66, 91.23, 124.41, 126.83, 127.49, 144.90, 150.87, 162.49 and 164.26. HRMS (ESI$^+$): $(M+H)^+$ Calculated 403.9994, Observed 403.9456.

5-(4-Nitrophenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraone (3f): Yield: 67%; M.p.: >300 °C

^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 5.85 (s, 1H, -CH), 7.38-7.76 (m, 4H, Ar-H), 8.15 (s, 2H, 2NH) and 10.31 (s, 3H, 3NH). ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm): 36.19, 91.14, 124.37, 126.76, 127.67, 144.88, 150.89, 162.55 and 164.18. HRMS (ESI$^+$): $(M+H)^+$ Calculated 371.0740, Observed 371.0625.

5-(4-Methoxyphenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraone (3g): Yield: 64%; M.p.: >300 °C

^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 3.92 (s, 3H, -OCH_3), 5.89 (s, 1H, -CH), 6.32-6 96 (m, 4H, Ar-H), 7.12 (s, 2H, 2NH) and 9.34 (s, 3H, 3NH). ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm): 36.04, 59.09, 91.43, 124.49, 126.86, 127.49, 144.95, 150.84, 162.87 and 164.26. HRMS (ESI$^+$): $(M+H)^+$ Calculated 356.0995, Observed 356.0425.

5-(4-Tolyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraone (3h):

Yield: 72%; M.p.: >300 °C

^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 2.43 (s, 3H, -CH_3), 5.87 (s, 1H, -CH), 6.38-7.02 (m, 4H, Ar-H), 7.65 (s, 2H, 2NH) and 9.45 (s, 3H, 3NH). ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm): 23.67, 35.88, 91.28, 124.48, 126.89, 127.49, 144.98, 150.96, 162.74 and 163.78. HRMS (ESI$^+$): $(M+H)^+$ Calculated 340.1046, Observed 340.0854.

5-(4-Trifluromethyl-phenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraone (3i): Yield: 71%; M.p.: >300 °C

^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 5.91 (s, 1H, -CH), 7.18-7.36 (m, 4H, Ar-H), 8.09 (s, 2H, 2NH) and 10.26 (s, 3H, 3NH). ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm): 36.22, 91.31, 124.36, 124.57, 126.82, 127.45, 144.92, 150.86, 162.57 and 164.22. HRMS (ESI$^+$): $(M+H)^+$ Calculated 394.0763, Observed 394.0531.

5-(4-Fluorophenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraone (3j): Yield: 68%; M.p.: >300 °C

^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 5.96 (s, 1H, -CH), 7.18-7.31 (m, 4H, Ar-H), 8.15 (s, 2H, 2NH) and 10.19 (s, 3H, 3NH). ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm): 36.32, 91.21, 124.49, 126.88, 127.51, 145.09, 151.17, 162.74 and 164.36. HRMS (ESI$^+$): $(M+H)^+$ Calculated 344.0795, Observed 344.0642.

5-(4-Trifluromethoxyphenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraone (3k): Yield: 73%; M.p.: >300 °C

^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 5.94 (s, 1H, -CH), 7.18-7.44 (m, 4H, Ar-H), 7.95 (s, 2H, 2NH) and 9.96 (s, 3H, 3NH). ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm): 36.89, 91.45, 124.36, 126.98, 127.65, 130.46, 144.98, 150.78, 162.45 and 164.22. HRMS (ESI$^+$): $(M+H)^+$ Calculated 410.0712, Observed 410.0425.

2.3 General procedure

2.3.1 Synthesis of 5-aryl-1,3,4-oxadiazole-2-thiols (6a-b)

P-Substituted phenyl hydrazides (**4a-b**, 3.4 mmole) was dissolved in ethanol (10 mL). Then CAL-B (50 mg) and carbon disulphide (1.7 mmole) were added to the reaction mass. It was then stirred at room

temperature. The reaction was monitored by thin layer chromatography. After 11 h of stirring at room temperature, the reaction mass was dissolved in ethyl acetate (25 mL) and filtered. The residue CAL-B was then reused. The solvent ethyl acetate was removed using rotatory evaporator, and the residual solid was crystallized using ethanol. All the synthesized compounds are known, and their ^{1}H NMR, ^{13}C NMR and HRMS spectral data and melting points are found to be in good agreement with those reported in the literature.[30]

2.4 Synthesis of 1-aryl-2-((5-substitutedphenyl-1,3,4-oxadiazol-2-yl)thio)ethanones (8a-h)

5-Aryl-1,3,4-oxadiazole-2-thiols (0.8 mmol) was dissolved in ethanol (10 mL), and then trimethylamine (1 mmol) was added to the reaction solution. The reaction mass was stirred for 15 min, and then 2-bromo-1-phenylethanones (0.8 mmol) were added to the reaction mass and refluxed at 80 °C. The reaction was monitored by thin-layer chromatography. After 6 h of reflux, the reaction mass was then poured on ice, neutralized with glacial acetic acid and filtered. The obtained solid was then crystalized using ethanol. All the synthesized compounds are known, and their ^{1}H NMR, ^{13}C NMR, and HRMS spectral data and melting points are found to be in good agreement with those reported in the literature.[50,51]

Scan copies of spectra of **6a** and **8b** are submitted as a representative of the series (**6a-b** and **8a-h**).

2.5 Spectral data of compounds

5-(*P*-Tolyl)-1,3,4-oxadiazole-2-thiol (6a) Yield: 81%; M.p.: 171-173 °C

^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 2.50 (s, 3H, CH_3), 7.37-7.39 (d, 2H, Ar-H), 7.82-8.84 (d, 2H, Ar-H) and no signal up to 12 for SH. ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm): 21.50, 21.61, 120.47, 126.38, 129.47, 129.91, 130.41, 142.59, 142.69, 161.11, and 177.95. HRMS (ESI^{+}): $(M+H)^{+}$ Calculated 193.0435, Observed 193.0441.

5-(*p*-Chlorophenyl)-1,3,4-oxadiazole-2-thiol (6b) Yield: 78%; M.p.: 211-213 °C

^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 7.46-7.48 (d, 2H, Ar-H), 7.93-8.97 (d, 2H, Ar-H) and no signal up to 12 for SH. ^{13}C NMR (DMSO-d_6, 75 MHz, δ ppm): 21.61, 120.47, 126.38, 129.47, 129.91, 130.41, 142.59, 142.69, 161.11, and 177.95. HRMS (ESI^{+}): $(M+H)^{+}$ Calculated 211.9811, Observed 211.9715.

1-(4-Methoxyphenyl)-2-((5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)thio)ethanone (8b) Yield: 78%; M.p.:

155–157 °C

^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 2.42 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.95 (s, 2H, -CO-CH_2-S), 7.10 (d, 2H, Ar–H) 7.31 (d, 2H, Ar–H) 7.82 (d, 2H, Ar–H) and 8.05 (d, 2H, Ar–H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 21.65, 41.61, 55.61, 114.15, 118.74, 120.77, 126.69, 127.95, 129.75, 130.97, 142.27, 163.57, 164.39, 166.11 and 190.67. HRMS (ESI^+): $(M+H)^+$ Calculated 341.0960, Observed 341.0965.

1-(4-Phenyl)-2-((5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)thio)ethanone (8a) Yield: 85%; M.p.: 135–137 °C

^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 2.39 (s, 3H, CH_3), 4.93 (s, 2H, -CO-CH_2-S), 7.23 (d, 2H, Ar–H), 7.39 (d, 2H, Ar–H), 7.78 (d, 3H, Ar–H) and 8.01 (d, 2H, Ar–H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 21.45, 57.68, 115.27, 119.82, 122.74, 126.93, 128.74, 129.69, 131.27, 143.31, 164.63, 165.39, 166.29 and 190.73. HRMS (ESI^+): $(M+H)^+$ Calculated 311.0854, Observed 311.0865.

4-(2-((5-(*p*-Tolyl)-1,3,4-oxadiazol-2-yl)thio)acetyl)benzonitrile (8c) Yield: 87%; M.p.: 165–167 °C

^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 2.48 (s, 3H, CH_3), 4.93 (s, 2H, -CO-CH_2-S), 7.24 (d, 2H, Ar–H), 7.40 (d, 2H, Ar–H) 7.89 (d, 2H, Ar–H) and 8.21 (d, 2H, Ar–H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm):21.61, 57.38, 115.34, 119.31, 121.37, 127.75, 128.04, 129.59, 131.98, 144.73, 165.62, 166.39, 167.11 and 191.62. HRMS (ESI^+): $(M+H)^+$ Calculated 335.0728, Observed 335.0774.

1-(3-Methoxyphenyl)-2-((5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)thio)ethanone (8d) Yield: 88%; M.p.: 145–147 °C

^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 2.44 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 5.05 (s, 2H, -CO-CH_2-S), 7.11 (d, 2H, Ar–H), 7.38 (d, 2H, Ar–H), 7.85 (d, 2H, Ar–H) and 8.17 (d, 2H, Ar–H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 21.57, 42.11, 56.17, 115.19, 119.24, 121.35, 126.69, 127.95, 129.75, 130.97, 142.27, 163.62, 165.39, 167.21 and 191.61. HRMS (ESI^+): $(M+H)^+$ Calculated 341.0960, Observed 341.0965.

2-((5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)-1-phenylethanone (8e) Yield: 78%; M.p.: 122–124 °C

^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 4.85 (s, 2H, -CO-CH_2-S), 7.11 (d, 2H, Ar–H), 7.38 (d, 2H, Ar–H), 7.77 (t, 1H, Ar–H), 7.85 (d, 2H, Ar–H) and 8.17 (d, 2H, Ar–H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 56.17, 115.19, 121.35, 126.69, 127.75, 129.85, 130.97, 142.27, 163.62, 165.39, 167.21 and 191.61. HRMS (ESI^+): $(M+H)^+$

Calculated 330.0230, Observed 330.0214.

1-(4-Mecaptophenyl)-2-((5-(*p*-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)ethanone (8f) Yield: 82%; M.p.: 133-137 °C

^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 5.25 (s, 2H, -CO-CH_2-S), 7.11 (d, 2H, Ar-H), 7.38 (d, 2H, Ar-H), 7.85 (d, 2H, Ar-H) and 8.17 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 54.17, 117.18, 119.24, 121.35, 126.69, 127.95, 129.75, 130.97, 142.27, 163.62, 165.39, 167.21 and 191.61. HRMS (ESI$^+$): $(M+H)^+$ Calculated 355.0182, Observed 355.0845.

1-(4-Methoxyphenyl)-2-((5-(*p*-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)ethanone (8g) Yield: 80%; M.p.: 112-114 °C

^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 3.83 (s, 3H, OCH_3), 5.15 (s, 2H, -CO-CH_2-S), 7.14 (d, 2H, Ar-H), 7.39 (d, 2H, Ar-H), 7.76 (d, 2H, Ar-H) and 7.87 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 48.17, 58.12, 115.19, 119.24, 121.35, 126.69, 127.95, 130.97, 142.27, 163.62, 165.39, 167.21 and 191.61. HRMS (ESI$^+$): $(M+H)^+$ Calculated 360.0335, Observed 360.0235.

1-(3-Methoxyphenyl)-2-((5-(*p*-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)ethanone (8h) Yield: 71%; M.p.: 129-131 °C

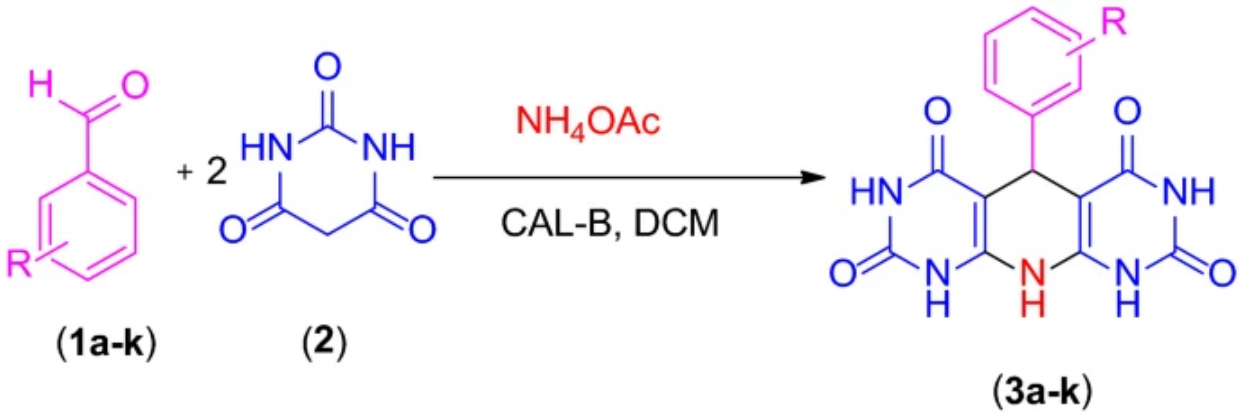
^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 3.91 (s, 3H, OCH_3), 5.09 (s, 2H, -CO-CH_2-S), 7.11 (d, 1H, Ar-H), 7.36 (s, 1H, Ar-H), 7.76 (d, 1H, Ar-H), 7.78 (m, 1H, Ar-H) 7.82 (d, 2H, Ar-H), and 7.91 (d, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 42.11, 55.27, 116.18, 117.23, 121.45, 125.29, 127.55, 129.64, 130.87, 142.57, 163.74, 165.48, 167.41 and 191.97. HRMS (ESI$^+$): $(M+H)^+$ Calculated 360.0335, Observed 360.0325.

3 Results and Discussion

The advantageous pharmacological properties of molecules containing pyridodipyrimidines and mercapto oxadiazoles prompted us to develop CAL-B-assisted efficient, environmentally benign methods for synthesizing pyridodipyrimidines and mercapto oxadiazoles. To optimize the reaction conditions, we initiated our studies by conducting one-pot cyclo condensation of benzaldehyde (**1**) (0.94 mmol), barbituric acid (**2**) (1.88 mmol), and ammonium acetate (1.2 mmol) as a model reaction in the presence of a biocatalyst, CAL-B by varying solvents, amount of catalyst and temperature (Scheme 1). It has been observed that when the reaction was performed in dichloromethane gave product (**3a**)

with better yield (77%) as compared to other solvents (Table 1). Keeping dichloromethane as a solvent, we varied the amount of CAL-B, then we noticed that when 200 mg CAL-B was used under similar conditions, the yield of **3a** was better (Table 1, entry 4). To check the influence of temperature, we performed the model reaction under various temperatures (RT, 40. 45, and 50 °C) and noticed no considerable rise in the yield of **3a**. It was noticed that the reaction was efficiently catalyzed by CAL-B in dichloromethane at room temperature using 200 mg of CAL-B, leading to a better product yield (**3a**) within 18 h.

Scheme 1



(1a-k) (2) (3a-k)

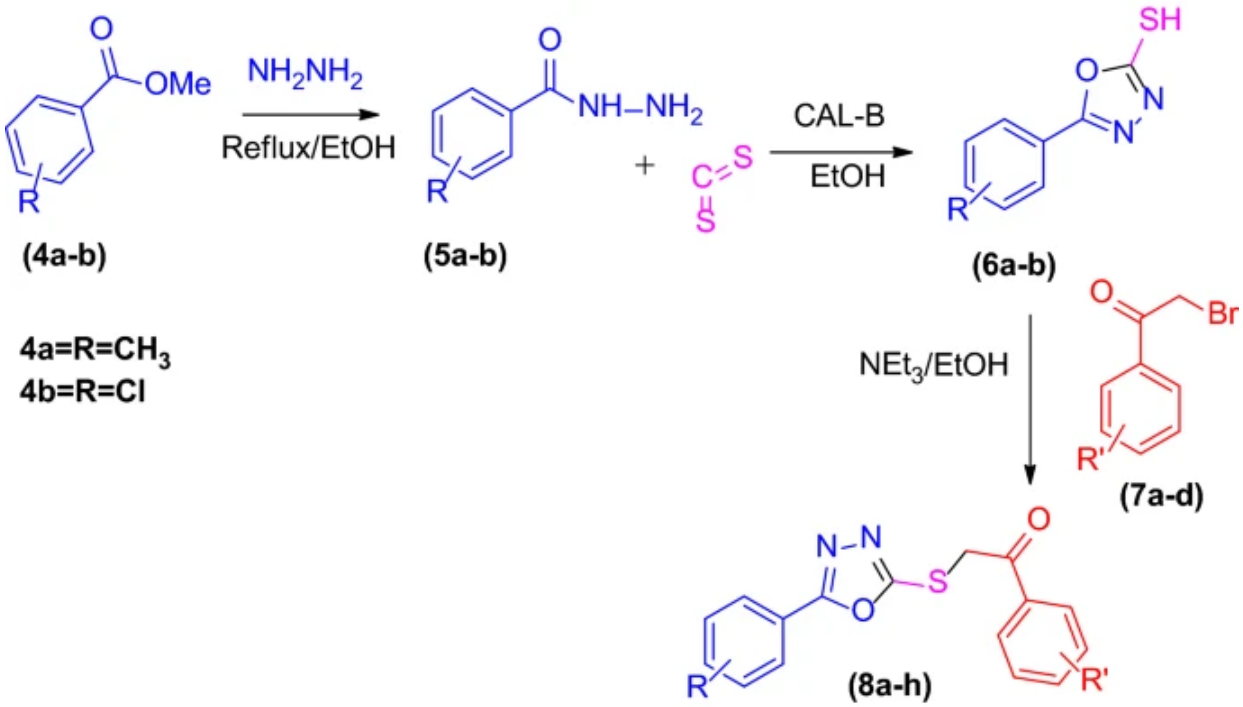
Synthesis of 5-(substituted phenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraones (**3a-k**).

Table 1 Screening of reaction media, amount of catalyst, and temperature for the synthesis of 5-phenyl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraone (3a).

Similarly, we have also carried the synthesis of 5-(*p*-tolyl)-1,3,4-oxadiazole-2-thiol (**6a**), allowing cyclo condensation of *p*-tolyl hydrazide (**5a**) and carbon disulphide as a model reaction, (Scheme 2) varying the amount of CAL-B. By changing the amount of CAL-B, it was noted that there was no proportionate rise in the product yield. (**6a**) (Table 2, entries 1-3) We observed that when the transformation conducted in ethanol (10 mL) using lipase (50 mg) at room temperature gave a better yield of **6a** within 11 h. The cyclocondensations under reference were not found to be run satisfactorily in the absence of CAL-B (Table 1 entry 6 and Table 2 entry 4), indicating that the CAL-B is necessary

for the cyclocondensations leading to substituted pyridodipyrimidines (**3a**) and substituted mercapto oxadiazoles (**6a**).

Scheme 2



Synthesis of 1-aryl-2-((5-substitutedphenyl-1,3,4-oxadiazol-2-yl)thio)ethanones (**8a-h**).

Table 2 Screening of amount of catalyst and temperature for the synthesis of 5-(*p*-Tolyl)-1,3,4-oxadiazole-2-thiol (6a).

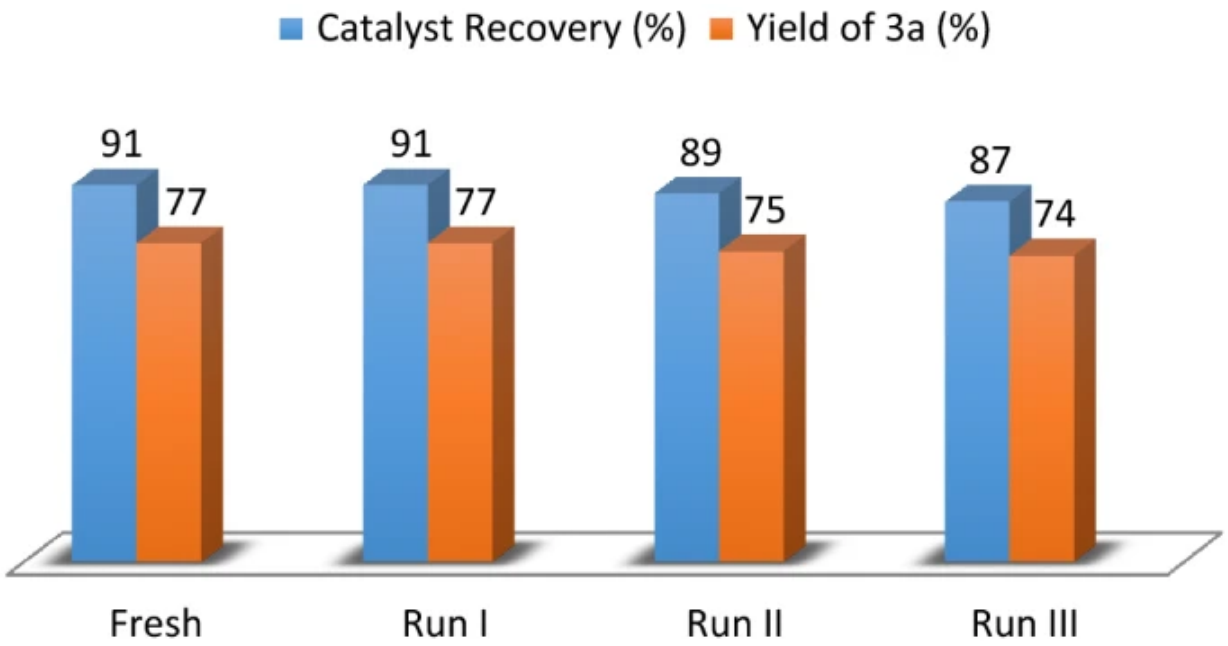
To evaluate the scope and applicability of these optimized catalytic protocols and in order to generalize the reaction conditions, we have performed separately i) cyclocondensation of different substituted benzaldehydes, barbituric acid, and ammonium acetate in DCM in the presence of CAL-B (Scheme 1) and ii) cyclo condensation of benzohydrazides, and carbon disulfide in ethanol (Scheme 2) and obtained titled substituted 5-aryl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraones (**3a-k**) and 5-phenyl-1,3,4-oxadiazole-2-thiols (**6a-b**), respectively with better to excellent yields. Encouraged by these results, an effort was also made to obtain 1-aryl-2-((5-substituted phenyl-1,3,4-oxadiazol-2-yl)thio)ethanones (**8a-h**) with better yield

by carrying condensation of 5-phenyl-1,3,4-oxadiazole-2-thiols (0.8 mol, **6a-b**) separately with substituted phenacyl bromides/2-bromo-1-phenylethanones (0.8 mol, **7a-d**) in the presence of triethylamine (1 mmol), in ethanol (10 mL).

3.1 Recycling study of catalyst CAL-B

The recycling study of the catalyst was done using the model reaction of benzaldehyde (**1**) (0.94 mmol), barbituric acid (**2**) (1.88 mmol), ammonium acetate (1.2 mmol), and CAL-B (200 mg) in DCM (10 mL) to afford **3a**. The reaction mixture was stirred at room temperature for 18 h. After completion of the reaction, the reaction content was then stirred with ethanol (50 mL) + DMF (5 mL) to dissolve the product. The reaction mass was filtered to separate the catalyst CAL-B which was then reused for the next three consecutive cycles for the synthesis of **3a**. The crude pyridodipyrimidines were obtained by removing the solvent from the filtrate. The catalyst was reused for subsequent cycles and was found to retain the catalytic activity up to the third cycle with over 74% conversion of the substrate to the product (Figure 2).

Figure 2



Recycling and reuse of CAL-B and its effect on yield of (**3a**).

The synthesized 5-aryl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraones (**3a-k**), 5-phenyl-1,3,4-oxadiazole-2-thiols (**6a-b**) and 1-aryl-2-((5-substituted phenyl-1,3,4-oxadiazol-2-yl)thio)ethanones (**8a-h**) are thoroughly characterized with the help of

their HRMS, ^{1}H NMR, and ^{13}C NMR. The melting points and spectral data are in good agreement with those reported in the literature.[28,30,50,51]

The enzymes having strong nucleophilic and electrophilic active amino residues and these may be interacting with carbonyl carbon of aldehydes, active methylene group of barbituric acid, acid hydrazide, and carbon disulphide, enhancing the electrophilic character of carbonyl carbon, carbon of carbon disulphide, and nucleophilic character of active methylene group of barbituric acid and the amino group of acid hydrazide, respectively. This fact might help accelerate the rates of reactions of these works. Our earlier reports have already elaborated on the details of these mechanistic pathways.[49]

4 Conclusions

For the first time, we have utilized CAL-B as an excellent biocatalyst for the synthesis of 5-aryl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraones while carrying cyclo condensation of barbituric acid, aromatic aldehydes, and ammonium acetate in DCM. The cyclo condensation of acid hydrazides and carbon bisulfide has also been performed in the presence of CAL-B for getting 5-aryl-1,3,4-oxadiazole 2-thiols. The additional features of these protocols are easy workup, rapid rate of reactions, moderate to excellent yields, and reusability of biocatalyst CAL-B. Here we have also reported the condensation of 5-aryl-1,3,4-oxadiazole 2-thiols and phenacyl bromides in the presence of trimethylamine, and obtained biodynamic 1-aryl-2-((5-substituted phenyl-1,3,4-oxadiazol-2-yl)thio)ethanones.

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Ethics declarations

Conflict of interest

The authors declare no conflict of interest.

Supplementary Information

Below is the link to the electronic supplementary material.

Supplementary file1 (PDF 778 KB)

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Cite this article

Chavan, A.S., Kharat, A.S., Bhosle, M.R. *et al.* Novel CAL-B catalyzed synthetic protocols for pyridodipyrimidines and mercapto oxadiazoles. *J Chem Sci* **134**, 120 (2022). https://doi.org/10.1007/s12039-022-02116-3

Received
06 May 2022

Revised
26 August 2022

Accepted
02 November 2022

Published
06 December 2022

DOI
https://doi.org/10.1007/s12039-022-02116-3

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Keywords

CAL-B pyridodipyrimidines mercapto oxadiazoles cyclocondensation