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DESIGNED SYNTHESIS AND BIOEVOLUTION OF A NOVEL ANALOGOUS OF THIADIAZOLO [3, 2-A] PYRIMIDINE-6-CARBOXYLATE PROMOTED BY TRANSITION METAL ACETATES

S. TirumalaJagadeesh✉ and N.V.S.Venugopal
Department of Chemistry, GITAM School of Science, GITAM (Deemed to be a university), Visakhapatnam-590045, A.P., India
✉Corresponding author: sangamjagadeesh@gmail.com

ABSTRACT

In a novel series of [1, 3, 4] thiadiazol-2-amine, a simple new pathway and biological approach, the analogues of Imidazole [3, 2-a] pyrimidine-6-carboxylate **(5a-5q)**. These analogous were obtained by the reaction of intermediate (3) with ethylacetoacetate and substituted aryl aldehydes in the presence of transition metal acetates, while the reaction between thiosemicarbazide and indole-3-carboxylic acid occurs in the presence of protic acid scaffold compound (3). The newly derived compounds are characterised by advanced spectral analysis, including ^{1}H NMR, ^{13}C NMR, and LC-MS. When compared to a reference medication, the biological potency was excellent, and the results were in line with expectations.

Keywords: Indole-3-carboxylic Acid, Thiosemicarbazide, 1,3,4-thiadiazole, Ethylacatoacetate, Aryl Aldehyde, $Pd(OAc)_2$.

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INTRODUCTION

Heterocyclic chemistry is an essential component of the chemical sciences and accounts for a sizable portion of the current global research. Both theoretically and practically, the study of heterocyclic systems is quite interesting and is crucial in the development and identification of novel physiologically and pharmacologically active substances. The sulphur and nitrogen-containing heterocyclic moieties are powerful emergents not only in organic synthesis but also in medicinal chemistry with numerous biological benefits. Among the sulphur and nitrogen heterocycles, Thiadiazoles Fig.-1 are most important as they attract innate affinity for biological receptors. The most significant hetero cyclic compound in the "azole" family that contains five and six-membered ring nuclei, such as dithiazole and pyrimidine thiadiazolo [3, 2-a] pyrimidine-6-carboxylate. This moiety comprises both dithiazole and pyrimidine, which is shown by a broad range of emergent, significantly bioactive properties. The combination of these two heterocyclic systems with a bridgehead nitrogen atom is drawing interest from medicinal chemists all around the world who want to investigate the framework for its potential. Additionally, various characteristics of a wide range of pharmacology and bioactivity have been documented.

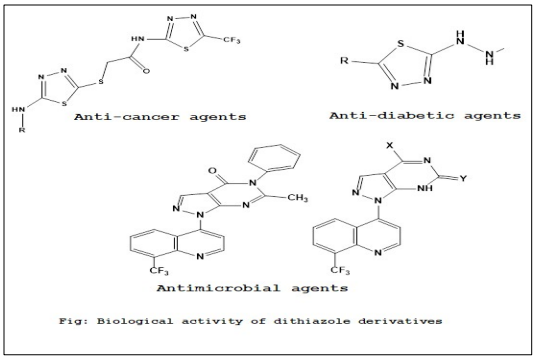

Fig-1: Biological Activity of Dithiazole Derivatives

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The various type of pyrimidine carboxylate and their outgrowth from the parent moiety have attracted numerous challenges of observation because of their advantageous pharmacological properties. Because of their industrial use and biological significance, heterocycles containing nitrogen atoms continue to be of interest in terms of chemistry1-5.5 The 1,3,4-Thiadiazolo[3,2-a]pyrimidine moiety is a member of a significant and well-known class of fused heterocycles that are found in many natural products of biological activities, such as antimicrobial Activity[3-4], Anticancer Agents[8-12], antiviral activity, Anti-Cholinesterase Activity[13], Vitro Antitumor[14], insecticidal against[15], HIV-1 RT inhibitors[16], antioxidant activity[17], antidepressant and anxiolytic[18], anti-tuberculosis activity[19], analgesic and anti-inflammatory agents[20], anti-leishmanial agents[21], anti-diabetic agent[22], carboxylic derivatives of functionalized titled compounds have been employed as essential building blocks in the synthesis of numerous new bioactive substances. However, the existing modular synthetic approaches for the synthetic routes are straightforward, and they involve multiple phases. Although a comparable two-step method, the desired title is analogous when an ethyl acetoacetate is combined with substituted aryl aldehydes, and followed by reaction takes place to scaffold the fused ring of thiadiazole [3, 2-a] pyrimidines in $Pd(OAc)_2$ to produce pyrimidine-6-carboxylate. Most of these are multi-step processes that produce better yields, fewer byproducts, and the use of catalysts that contain transition metal acetate. Hence, it is crucial to alter the straight, efficient, and excellent methods to obtain the thiadiazole [3,2-a] pyrimidine carboxylic analogue from the standpoint of conventional methods. Here, we would like to introduce a new, simpler process that uses a multi-step condensation reaction of substituted aldehydes, 2-aminothiadiazole, and acetoacetate to quickly, easily, and efficiently synthesise our titled derivatives in excellent yield. The traditional multistage methods for thiazolo derivative preparation entail a significant synthetic operation, including extraction and purification procedures for every step. This results in an efficient synthetic process and the creation of a good procedure for the synthesis of novel analogous compounds. Even while there are traditional synthetic methods for creating titles, they have drawbacks such as limited reactivity, slow reaction rates, and less-than-ideal outcomes, particularly for arylthiol syntheses. Recently, the Pd(OAc)2 catalyst system has been utilised to create pyrimidine-6-carboxylate-containing aromatic compounds through the catalytic 1,3,4-dithiazole derivatives of different. Consequently, we further simplified the reaction process in this study by employing a catalyst system and the analogy of ethyl 2-(5-bromo-1H-indol-3-yl). [1, 3, 4] -7-methyl-5-phenyl-5H- [3, 2-a] thiadiazolo 2-aminothiadiazole is added with ethyl acetoacetate and substituted aryl aldehydes in two steps to produce pyrimidine-6-carboxylate. The moiety combined with thiadiazole [3, 2-a] with pyrimidines in promoted by $Pd(OAc)_2$, is then obtained by cyclisation.

EXPERIMENTAL

Materials and Methods

Sigma-Aldrich provided all of the necessary starting materials, including chemicals, reagents, and solvents for the reactions, which were used without additional purification. By using an Agrawal thermal apparatus, the uncorrected melting points of all freshly prepared comparable substances were determined. The exact analysis of titled analogous title was estimated by a Broker for 400 ^1H NMR spectra, as well as 100 MHz for ^{13}C NMR spectra, in $CDCl_3$ as a solvent. Thin layer chromatography was used to monitor the reaction, employing ethyl acetate-hexane in various ratios as the eluent and silica gel as the adsorbent. LC-MS is used to determine the molecular weight of all produced molecules.

General Procedures

Synthesis of 5-(5-bromo-1H-indol-3-yl)-1, 3, 4-thiadiazol-2-amine (2)

Four RBF necks should be cleaned and dried. At room temperature, the combination of 1 mol of indole-3-carboxylic acid and 1 mol of semithiocarbazide soluble in 25 mL of ethanol and a few drops of phosphoric acid (H_3PO_4) in RBF, which was also attached to a magnetic stirrer with a hot plate? For five hours at 600 °C, the reaction was continuously carried out on the reaction mixture. The TLC monitored the reaction's progress (EtOAc: n-hexane = 4:6). After all of the reactants had been consumed, the reaction mixture was allowed to cool to room temperature. Ethyl acetate was used to dissolve the crude, and then a saturated sodium bicarbonate solution was used to wash away the ethyl acetate layer. Additionally, the organic layer was washed with water to separate it. Distillation can be used to remove the organic layer under vacuum, producing a solid substance. Pale red solid; yield-94%, m.p-154-156^{0}C: ^{1}HNMR (400 MHz, $CDCl_3$) δppm:

11.748 (N-H, Pyrrole,s), 8.457 (pyrole,s), 7.784 (1H,s), 7.407-7.358 (Ar,m,2H), 7.125(2H, NH_2,s).^{13}CNMR (400MHz, $CDCl_3$) δppm: 172.35, 160.33, 140.58, 135.75, 129.87, 127.02, 123.54, 120.94, 113.02, 110.40; Weight of the moiety (m/z): 496.27(M+2); Formulae of moiety: $C_{10}H_7BrN_4S$.

Synthesis of ethyl **2-(5-bromo-1H-indol-3-yl)-7-methyl-5-phenyl-5H-[1,3,4]thiadiazolo[3,2-a] pyrimidine-6-carboxylate derivatives (5a-5s)**

Take a dry and clean 50mL RBF and a mixture of aromatic aldehyde (1.125 mole), compound (2) (1.015 mol) and β-diketone (1.0m) appropriate amount of catalytic, such as palladium acetate, was added in ethanol was taken in a 50mL flask and it was continued at reflux for 5hrs. The continuous reaction was identified by TLC (3:7, Ethylacetate: n-hexane). After the completion of the reaction, after neutralising the reaction's crude with an aqueous solution of diluted HCl and extracting the result with ethyl acetate, the mixed ethyl acetate layer was cleaned with a brine solution. To obtain the solid product, the solvent in the crude was extracted using a vacuum pump at a lower pressure. From ethanol, every synthetic chemical was recrystallised.

RESULTS AND DISCUSSION

The structures of the disclosed compounds (5a-5q) were characterised by ^{1}H and 13C NMR, mass analysis. ^{1}H NMR spectrum of the desired derivatives exhibited signals at various regions like indole protons at δ 8.314 to 7.721 ppm, NH_2 protons at δ 7.214 ppm, quaternary protons at δ 4.610-4.174 ppm, hydroxyl protons appear at δ 9.023 to 9.275 ppm, methoxy protons at δ 3.528 to 3.712 ppm, methyl protons at δ 0.889 to 1.124, methylene protons at δ 3.913 to 4.088 ppm in ethycarboxylate and the protons appear at δ 11.067 to 11.974 ppm. ^{13}C NMR is displayed at various values. The keto group appeared at 163-169. The mass spectrum of all the derivatives exhibited molecular ion peaks at (m/z)(M+2).

Derivative (5a)

Paleredsolid; yield-86%, m.p-212-214^{0}C: ^{1}HNMR (400 MHz, $CDCl_3$) δppm: 11.152 (s, 1H, N-H, Pyrrole), 7.810 (s, 1H, pyrrole), 7.542 (s, 1H, pyrrole), 7.412-7.271 (Ar, 7H, m), 4.312 (s,1H,-CH-),4.0291 – 3.847(q,2H,), 2.842(s,3H), 0.967 (t, J=8.0Hz,3H),^{13}CNMR (400MHz, $CDCl_3$) δppm:165.25, 161.02, 153.74, 142.25, 140.12, 135.09, 131.07, 129.14, 128.75, 128.43, 127.28, 124.32, 120.25, 119.39, 117.46, 113.02, 110.40, 64.24, 60.52, 20.62, 13.28; weight of the derivative (m/z): 496.27(M+2); Molecular formulae of the derivatives: $C_{23}H_{19}BrN_4O_2S$.

Derivative (5b)

White compound; yield-91%, m.p-224-226^{0}C: ^{1}HNMR (400 MHz, $CDCl_3$) δppm: 11.210 (s, 1H, N-H, Pyrrole), 9.275(s,1H,-OH),7.772 (s, 1H, pyrrole), 7.548 (s, 1H, pyrrole), 7.422 (Ar,d, J=6.8Hz,2H), 7.328 (Ar, d, J=8.0Hz, 2H), 7.082-6.849(Ar,m,4H),4.208(s,1H,-CH-), 4.025 – 3.815(q,2H), 2.894(s,3H), 1.123 (t,3H, CH_3), ^{13}CNMR (400MHz, $CDCl_3$) δppm: 164.74, 158.04, 151.45, 149.02, 144.52, 135.25, 130.49, 128.84, 128.26, 127.67, 127.02, 125.36, 123.66, 121.96, 120.62, 119.65, 114.02, 66.02, 58.72,20.32,12.62; weight of the derivative (m/z): 512.37(M+2); Molecular formulae of the derivatives: $C_{23}H_{19}BrN_4O_3S$.

Derivative (5c)

Pale yellow solid; yield-92%, m.p-232-234^{0}C: ^{1}HNMR (400 MHz, $CDCl_3$)δppm: 11.067 (s, Ar,1H),7.757(s,1H, Ar),7.523(d, J=8.8Hz, Ar-H,1H),7.393(1H, J=7.8Hz,dH),7.297(d, J=9.2Hz, 1H),7.297-6.658(2H,m),.315(s,1H,-CH-),4.053-3.854(m,2H),3.712(3H, CH_3),3.598(3H, CH_3), 2.895(s,3H), 1.967 (t,3H), ^{13}CNMR (400MHz, $CDCl_3$) δppm: 166.62,158.74, 153.65, 150.62,144.75, 137.27, 135.23, 129.62, 128.63, 123.15, 122.86, 120.02, 119.65, 114.62, 110.84, 108.69, 65.67, 60.49, 57.29, 53.35, 20.62, 13.78; weight of the derivative (m/z): 586.49(M+2); Molecular formulae of the derivatives: $C_{26}H_{25}BrN_4O_5S$.

Derivative (5d)

Redcompoud; yield-91%, m.p-226-228^{0}C: ^{1}HNMR (400 MHz, $CDCl_3$) δppm: 11.567 (s, C_6H_5,1H), 7.810 (s, C_6H_5,1H), 7.528 (s, 1H, Ar), 7.471-7.270 (6H, Ar, m), 4.413 (s,1H),4.012-3.940 (2H,m),2.786(s,3H), 1.028 (t,3H), ^{13}CNMR (400MHz, $CDCl_3$) δppm: 168.09, 161.74, 157.33, 153.03, 144.19, 137.94, 135.02, 131.32, 128.71, 128.24, 127.46, 123.44, 121.62, 120.24, 119.32, 114.64, 112.92, 64.45, 58.74, 20.45, 13.74; weight of the derivative (m/z): 514.74(M+2); Molecular formulae of the derivatives: $C_{23}H_{18}BrFN_4O_2S$.

Derivative (5e)
Paleredsolid; yield-89%, m.p-219-221^{0}C: ^{1}HNMR (400 MHz, $CDCl_3$) δppm: 11.675 (1H,s), 7.513 (1H,s), 7.542 (1H,s), 7.393(1H, J=9.2Hz,1H), 7.331(J=6.8Hz,1H,d),7.328-7.280 (4H, m), 4.516 (1H,-CH-), 4.018(s,2H), 2.667(s,3H,), 1.114 (t, J=4.6Hz), ^{13}CNMR (400MHz, $CDCl_3$) δppm: 166.69, 159.74, 152.44, 145.74, 140.63, 135.73, 130.44, 129.66, 128.54, 128.02, 127.37, 123.33, 122.04, 120.34, 118.74, 113.32, 110.62, 66.43, 60.37, 21.42, 13.33; weight of the derivative (m/z): 529.39(M+2); Molecular formulae of the derivatives: $C_{23}H_{18}BrClN_4O_2S$.

Derivative (5f)
Yellow compound; yield-86%, m.p-236-238^{0}C: ^{1}HNMR (400 MHz, $CDCl_3$) δppm: 11.746 (s, 1H), 7.814 (s, 1H), 7.542 (s, 1H), 7.410(C_5H_5,d, J=8.0Hz,1H), 7.328(d, J=140.2Hz,1H), 7.317(dd, J=9.2Hz,2.4Hz,2H), 6.943(d, J=4.8Hz,1H), 4.418 (s,1H,-),4.028-3.815(q,2H), 2.984(s, CH_3,3H), 0.948 (t, J=12.4Hz,3H), ^{13}CNMR (400MHz, $CDCl_3$) δppm: 168.92, 161.11, 155.75, 142.62, 139.56, 136.62, 134.19, 130.07, 128.44, 128.22, 127.74, 124.69, 121.62, 120.04, 118.34, 112.62, 111.34, 66.02, 59.74, 20.32, 12.94; weight of the derivative (m/z): 621.09(M+2); Molecular formulae of the derivatives: $C_{23}H_{18}BrIN_4O_2S$.

Derivative (5g)
Colourless compound; yield-88%, m.p-245-247^{0}C: ^{1}HNMR (400 MHz, $CDCl_3$) δppm: 11.974 (s,1H),7.829(s,1H),7.773(dd, J=9.6Hz, 1.4Hz, 2H), 7.768(2H, dd, J=5.2Hz,2.8Hz),7.561(C_6H_5,1H,s),7.415(C_6H_5d, J=8.0),7.362(Ar,d, J=7.2Hz),4.413(1H,s),4.088-3.913(2H,m),3.015(3H,s),1.086 (J=8.4Hz, 3H,t);^{13}CNMR(400MHz, $CDCl_3$) δppm: 169.75, 165.62, 161.66, 155.39, 140.02, 138.15, 135.05,130.02, 129.15, 128.38, 126.71, 124.06, 123.05, 121.84, 120.62, 113.19, 111.67, 66.94, 58.85, 22.04, 13.66; weight of the derivative (m/z): 540.31(M+H); Molecular formulae of the derivatives: $C_{24}H_{19}BrN_4O_4S$.

Derivative (5h)
Paleredsolid;yield-90%,m.p-224-226^{0}C:);^{1}HNMR(400MHz, $CDCl_3$)δppm:11.402(s,1H),7.802(s,1H),7.754(dd, J=9.8Hz,1.6Hz,2H),7.561(s.1H),7.415(dd, J=5.2Hz,,2.8Hz,2H),7.395(d, J=10.8Hz,1H),7.352(d, J=7.6Hz,1H),4.312(s,1H),4.021-3.854(s,2H),2.941(s,3H,-CH_3),0.924(t, J=4.6Hz,3H), ^{13}CNMR (400MHz, $CDCl_3$) δppm: 163.29, 156.63, 152.11, 145.04, 141.36, 134.78, 130.09, 129.38, 128.44, 128.15, 127.05, 124.22, 122.46, 121.05, 120.02, 115.26, 112.75, 64.44, 60.23, 40.27, 20.75, 13.48; weight of the derivative (m/z): 539.22(M+2); Molecular formulae of the derivatives: $C_{25}H_{24}BrN_5O_2S$.

Derivative (5i)
Paleredsolid; yield-84%, m.p-245-247^{0}C:^{1}HNMR (400 MHz, $CDCl_3$) δppm: 11.538 (s, 1H), 7.814 (1H,s, C_6H_5), 7.532 (1H,s), 7.373-7.345 (Ar, 2H, m), 6.762(1H,s),6.634(1H,s), 4.416 (1H,s), 4.027-3.846(2H,s),3.726(6H,s), 2.942(s,3H,-CH3), 1.065 (3H, J=5.4Hz,t),13CNMR (400MHz, CDCl3) δppm: 168.25, 160.04, 154.75, 152.02, 149.75, 142.64, 134.22, 129.38, 128.92, 125.09, 122.04, 120.66, 119.63, 114.48, 112.05, 108.78, 104.62, 92.39, 66.06, 60.72, 54.45, 20.38, 12.69; weight of the derivative (m/z): 681.32(M+2); Molecular formulae of the derivatives: $C_{25}H_{24}BrIN_4O_4S$.

Derivative (5j)
Red brown compound; yield-86%, m.p-274-276^{0}C: ^{1}HNMR (400 MHz, $CDCl_3$)δppm:11.667(s, Ar-H,1H),7.824(s, 1H, Ar), 7.542(Ar,s,1H), 7.362-7.315(2H,m), 7.126-7.044(m,2H),4.156(s,1H),4.038-3.852(q,2H),3.772(s,3H),3.694(s,3H),2.740(s,3H),1.064(3H, J=7.6Hz,t);^{13}CNMR (400MHz, $CDCl_3$) δppm: 169.28, 158.09, 151.38, 150.26, 146.08, 142.67, 138.26, 134.28, 130.05, 128.66, 127.42, 127.08, 124.28, 122.04, 120.64, 119.33, 114.06, 112.22, 110.36, 66.62, 60.25, 58.24, 56.15, 20.18, 12.65; weight of the derivative (m/z): 633.54(M+2); Molecular formulae of the derivatives: $C_{25}H_{22}BrN_4O_4S$.

Derivative (5k)
Paleredsolid; yield-84%, m.p-249-251^{0}C: ^{1}HNMR (400 MHz, $CDCl_3$) δppm: 11.436(s, py,1H), 10.024(s,1H, py),7.810(s, Ar-H,1H),7.746-7.615(Ar,2H,m),7.534(s,1H, C_6H_5),7.452-7.365(q,4H),4.364(s, C_4-H),4.026-3.841(q,2H,),2.627(s, CH_3),1.124(t, J=7.2Hz,3H), ^{13}CNMR (400MHz, $CDCl_3$) δppm: 165.25, 161.02, 153.74, 142.25, 140.12, 135.09, 131.07, 129.14, 128.75, 128.43, 127.28, 124.32, 120.25, 119.39,

117.46, 113.02, 110.40, 64.24, 60.52, 20.62, 13.28; weight of the derivative (m/z): 524.28(M+2); Molecular formulae of the derivatives: $C_{24}H_{19}BrN_4O_3S$.

Derivative (5l)
Colorlesssolid; yield-88%, m.p-251-254^{0}C: ^{1}HNMR (400 MHz, $CDCl_3$) δppm: 11.125 (s, 1H, Ar-H), 9.023(s,1H,-OH), 7.804 (s, Ar-H, 1H), 7.512 (s, 1H, Ar), 7.392-7.315 (Ar-H, 2H, m), 6.946-6.854 (Ar, 2H, m), 4.126 (s,1H,-CH-), 4.051- 3.746 (2H, m), 3.612(s,6H), 2.674(s,3H), 0.874 (t, J=6.4Hz,3H), ^{13}CNMR (400MHz, $CDCl_3$) δppm: 164.78, 168.79, 161.66, 155.76, 148.42, 142.65, 135.41,133.35,130.09,129.62, 128.38, 127.06, 125.26, 123.02, 121.88, 119.36, 114.06, 112.36, 64.74, 60.74, 60.09, 20.45, 13.38; weight of the derivative (m/z): 572.41(M+2); Molecular formulae of the derivatives: $C_{25}H_{23}BrN_4O_5S$.

Derivative (5m)
Paleredsolid; yield-91%, m.p-241-243^{0}C: ^{1}HNMR (400 MHz, $CDCl_3$) δppm: 11.493 (Ar,1H,s), 9.567 (-OH,1H,s), 7.513 (Ar,s,1H), 7.394-312 (Ar,2H, m), 6.923-6.724(Ar-H,2H,m),4.325(s,1H,-CH-),4.042-3.912(q,3H),3.714(s, CH_3),2.811(s, CH_3),1.123(t, J=3.4Hz,3H),^{13}CNMR (400MHz, $CDCl_3$) δppm: 163.73, 158.17, 152.27, 146.19, 144.72, 141.68, 135.79, 133.03, 129.71, 128.66, 125.09, 123.15, 121.60, 119.49, 118.02, 114.26, 112.55, 110.06, 108.35, 64.74, 59.35, 20.36, 13.56; weight of the derivative (m/z): 524.13(M+2); Molecular formulae of the derivatives: $C_{24}H_{21}BrN_4O_4S$.

Derivative (5n)
Paleredsolid; yield-84%, m.p-203-205^{0}C: ^{1}HNMR (400 MHz, $CDCl_3$)δppm: 11.284 (1H,s, C_6H_5), 8.266(1H, J=8.0Hz,d, C_6H_5),7.762(1H,s, Ar),7.584(J=6.4Hz, Ar,2H,t),7.512(1H, Ar-H,s),7.422 (1H,d, Ar-H),7.362(d, Ar-H, J=12.4Hz1H),7.312(J=9.6Hz,1H,d, Ar-H),7.280(C_6H_5, J=8.0Hz,2H,t),4.296(1H,-CH-,s),4.021-3.862(q,3H),2.621(3H,-CH_3,s),0.842(J=6.4Hz,3H,t); ^{13}CNMR(400MHz, $CDCl_3$) δppm: 164.70, 158.85, 154.74, 151.11, 146.79, 142.02, 135.71, 134.44, 128.94, 12832, 127.41, 126.62, 123.33, 121.11, 119.85, 112.07, 110.62, 60.24, 55.71, 20.28, 13.48.Weight of the derivative (m/z): 497.45(M+2); Molecular formulae of the derivatives: $C_{22}H_{18}BrN_5O_2S$.

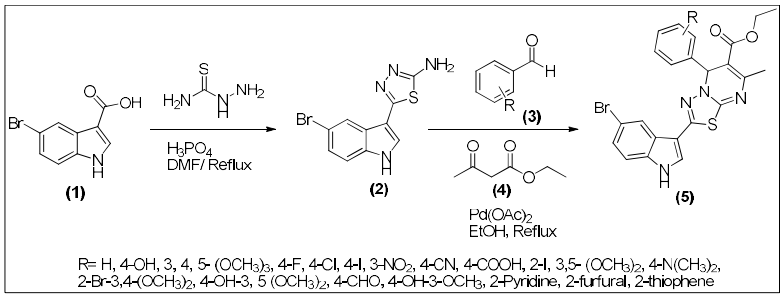
Derivative (5o)
Paleredsolid; yield-83%, m.p-206-208^{0}C: ^{1}HNMR (400 MHz, $CDCl_3$) δppm: 11.325 (py,1H,s), 8.341(1H,s, py),8.124(1H, Ar,s),7.805(J=8.8Hz,d,1H, Ar-H),7.524(1H,s, Ar),7.403(J=6.4Hz, Ar,1H,d),7.356-7.253(2H,m),4.432(1H,s),4.032-3.836(2H,s),2.884(3H,s,-CH_3),1.066(J=6.4Hz,3H,t);^{13}CNMR (400 MHz, $CDCl_3$) δppm: 166.72, 159.01, 152.28, 148.15, 145.11, 134.22, 130.15, 129.68, 128.58, 128.02, 127.74, 124.66, 121.95, 118.89, 113.33, 110.65,64.75, 60.06, 20.08, 12.77; weight of the derivative (m/z): 497.27(M+2); Molecular formulae of the derivatives: $C_{22}H_{18}BrN_5O_2S$.

Derivative (5p)
Paleredsolid; yield-86%, m.p-212-214^{0}C: ^{1}HNMR (400 MHz, $CDCl_3$) δppm: 11.765(1H, py,s), 7.815(1H,pyrimdine,s),7.516(Ar,1H,s),7.484-7.392(3H,m, Ar),7.362-7.274(Ar,3H,m),4.612(1H,s, Ar-H),4.024-3.924(2H,m), 2.714(3H,s),1.047 (J=9.4Hz,3H,t);^{13}CNMR (400MHz, $CDCl_3$) δppm: 163.74, 157.65, 153.76, 149.02, 141.11, 139.64, 135.27, 129.71, 128.49, 128.62, 122.88, 121.05, 120.16, 114.24, 111.02, 109.75, 60.74, 20.62, and 13.76; weight of the derivative (m/z): 486.21(M+H); Molecular formulae of the derivatives: $C_{21}H_{17}BrN_4O_3S$.

Derivative (5q)
Paleredsolid; yield-84%, m.p-195-197^{0}C: ^{1}HNMR (400 MHz, $CDCl_3$) δppm: 11.407 (pyrrole,1H,s), 7.763(1H,s, Ar),7.531(s, Ar-H,1H),7.395(C_6H_5,1H,d, J=8.0Hz),7.346(1H,s),7.312(1H, J=10Hz,d, Ar),6.956(1H, J=8.8Hz,d, Ar-H),6.784(1H, J=6.8, Ar-H,d),4.312(1H,s),4.021-3.956(3H,s),2.644 (3H,s),1.029(J=8.0Hz,3H,t);^{13}CNMR (400MHz, $CDCl_3$) δppm: 165.23, 158.04, 151.44, 144.09, 138.11, 135.02, 129.28, 128.74, 127.95, 126.84, 126.02, 124.19, 122.39, 120.05, 118.74, 114.33, 112.56, 60.07, 56.15, 20.03, 13.95; weight of the derivative (m/z): 502.38(M+2); Molecular formulae of the derivatives: $C_{21}H_{17}BrN_4O_2S_2$.

RESULTS AND DISCUSSION

The synthetic route of a novel compound (5a-5q) is shown in Scheme 1. Indole-3-carboxylic acid **(1)** was transformed into derivatives of the [1, 3, 4] thiadiazole derivatives **(2)** by using thiosemicarbazide in the presence of DMF at reflux temperature. The intermediate **(2)** is then converted to a novel series of thiadiazolo [3,2-a] pyrimidine-6-carboxylates by reacting with ethylacetoacetate and aryl aldehydes and using palladium acetate [$Pd(OAc)_2$] as catalyst in ethanol.



Scheme-1: Preparation of Compounds 5a-5q

Various catalysts like zinc acetate ($Zn(OAc)_2$), copper acetate ($Cu(OAc)_2$) and silver acetate (AgOAc) are employed for the job but found inferior to Palladium acetate ($Pd(OAc)_2$). The corresponding results are shown in Table-1.

Table-1: The Effect of the Catalyst on the Preparation of Derivatives (5)[a]

Entry	Catalyst	Time (min)	Yields (%)[b]
1	AgOAc	270	65
2	$Zn(OAc)_2$	240	60
3	$Cu(OAc)_2$	320	51
4	$Pd(OAc)_2$	150	94

[a] Compound (2) (1.0 mol), aromatic aldehyde (1.15 mol), Ethyalacetoacetae (1.25 mol), and $Pd(OAc)_2$ (4mol mol%) in ethanol; [b] Isolated yields.

As discussed above, the catalyst plays a crucial role in the progress of the reaction. However, the quantity of catalyst that has been loaded in the reaction also affects the reaction time and isolated yields in the preparation of desired derivatives (5a-5q), as shown in Table-2.

Table-2: Effect of the Amount of Catalyst on the Preparation of Derivatives (5) [a]

Entry	Amount of Catalyst	Time (min)	Yields (%)[b]
1	1.0 mole	180	65
2	2.0 mole	150	70
3	3.0 mole	60	94
4	4.0 mole	90	94

[a] Compound (2) (1.0 mol), aromatic aldehyde (1.15 mol), Ethyalacetoacetae (1.25 mol), in ethanol; [b] Isolated yields

Further, solvents also impacted the reaction progress considerably, and the observed results are shown in Table-3.

Table-3: Impact of the Solvent on the Preparation of Derivatives (5)[a]

Entry	Solvent	Time (min)	Yields (%)[b]
1	Water	150	25
2	Dimethylformamide	150	41
3	Toluene	150	59
4	Dichloromethane	150	52
5	Ethanol	150	94

[a] Compound (2) (1.0 mol), aromatic aldehyde (1.15 mol), Ethyalacetoacetae (1.25 mol), and $Pd(OAc)_2$ (4mol mol%); [b] Isolated yields.

Antimicrobial Activity

The micro broth dilution method was used to assess the identified compounds' antibacterial and antifungal properties in vitro. Gram-positive (Bacillus subtilis and Staphylococcus aureus) and gram-negative

(Escherichia coli and P. aeruginosa) microorganisms were used to investigate the ***in vitro*** antibacterial activity. The antifungal activity was tested in vitro using the bacteria Aspergillum niger and Candida albicans. Streptomycin served as the standard for bacterial screening in this study. An antifungal ketoconazole screening was carried out. The Culture Collection and Genebank (MTCC), located in Chandigarh, India, provided the standard strains that were utilised to screen for antibacterial and antifungal activities. The fungi were grown in Sabouraud dextrose broth, whereas the bacteria were fed Mueller-Hinton broth. By comparing the turbidity, the inoculum size of the test strain was adjusted to 108 CFU/mL. The results of the main and secondary analyses were documented. The compounds under investigation and popular medications were diluted twice in quick succession to create a stock solution (2000 µg/mL).

Table-4: Screening of Antimicrobial Activity for Synthesised Derivatives (5a-5p)

Entry	Zone of Inhibition in (mm)					
	Antibacterial strains				Antifungal strains	
	B. subtilis	*S. aureus*	*P. aeruginosa*	*E. coli*	*A. Niger*	*C. Albicans*
5a	07	06	07	08	04	05
5b	18	17	16	17	12	14
5c	18	16	18	14	13	14
5d	22	21	20	21	16	17
5e	21	20	19	18	16	18
5f	20	18	18	17	17	16
5g	08	07	10	09	08	06
5h	12	15	17	15	15	18
5i	15	12	18	20	15	16
5j	16	15	14	15	14	15
5k	20	21	21	22	15	17
5l	18	20	22	20	13	16
5m	21	22	20	21	09	12
5n	20	20	22	19	05	08
5o	17	17	19	12	11	13
5p	15	10	08	12	07	06
Streptomycin	25	25	25	25	-	-
Ketonozole	-	-	-	-	22	22
DMSO	-	-	-	-	-	-

In the first analysis, the substances were utilised at doses of 500, 250, and 100 µg/mL. Further study was performed on the compounds that were found to be active during this initial screening. For secondary screening, concentrations of 200, 100, 50, and 25 µg/mL were used. The inoculation wells were maintained at 37°C in a humid environment for the duration of the night. The minimum inhibitory concentration, or MIC, was the highest dilution at which total inhibition was seen. The produced compounds exhibited moderate to good inhibition, according to the MIC values. Table IV lists the compounds' antibacterial activity (5a–5p).

CONCLUSION

In conclusion, we have been asked to follow the procedure for synthesising compounds with the above names (5a-5p) in a high yield and assessing their antibacterial activity in vitro using the corresponding bacterial strains. Enhancing the yield of this multistep synthesis was the primary focus of our observations. The catalyst's straightforward experimental setup process is one of its advantages, which makes it a practical technique for the synthesis of derivatives with the same name. Furthermore, the antibacterial potent activity against both bacterial and fungal strains was satisfactorily evaluated by us.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

S. Tirumala Jagadeesh https://orcid.org/0009-0005-4008-6974
N. V. S. Venugopal https://orcid.org/0000-0003-0552-1377

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