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AN EFFICIENT SYNTHESIS OF NOVEL BIOACTIVE AZETIDINONES AND THIAZOLIDINONES OF 1, 5-DIMETHYL-2-PHENYL-1H-PYRAZOL-3(2H)-ONE

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ABSTRACT

A novel series of azetidinones, 3-chloro-4-(2-hydroxyphenyl)-1-(4-(4-(arylphenyl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,7,7a-tetrahydrodipyrazolo[3,4-b:4',3'-e]pyridin-8 (4H, 6H, 8a H)-yl)phenyl)azetidin-2-one **(3a-3e)** and thaizolidinones; 2-(aryl phenyl)-3-(4-(4-(2-hydroxyphenyl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,7,7a-tetrahydro-dipyrazol o[3,4-b:4',3'-e]pyridin-8(4H,6H,8a H)yl)phenyl) thiazolidin-4-one **(4a-4e)** were synthesized using new Schiff bases, 2-(8-(4-(arylbenzylideneamino)phenyl)-2,3,5,6-tetramethyl-1,7-diphen -yl-1,2,4,6,7,7a,8,8a-octahydrodipyrazolo[3,4-b:4',3'-e] pyridin-4-yl)phenol(2) **(2a-2e)**. The Schiff bases were synthesized by the reaction of aromatic aldehydes, and 2-(8-(4-aminophenyl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,4,6,7, 7a, 8, 8a-octahydrodipyrazolo[3,4-b:4',3'-e]pyridin-4-yl)phenol (**1**) under microwave and conventional methods. Our results shows that the synthesis of Schiff base under solvent free microwave condition is the most efficient method of synthesis having highest yield than both conventional method and microwave with solvent. The newly synthesized compounds were characterized on the basis of different spectroscopic (IR, ^{1}H-NMR, Mass) and elemental (CHN) analysis techniques. Compounds **(3a-3e and 4a-4e)** were screened for their biological activities against the panel of nine bacterial strains.

KEYWORDS

Schiff Base, Azetidinones, Thiazolidinones, Microwave Assisted Synthesis, Biological Activity

INTRODUCTION

Pyrazoles belong among the most representative five-membered heterocyclic systems. Despite the fact that the pyrazole ring is rarely a constituent of natural products, numerous synthetic compounds containing the pyrazole moiety have been the focus of medicinal chemists for the last 100 years because of their outstanding pharmacological, agrochemical, photographic, catalytic, liquid crystals, antitumor drugs and other applications.[1] This gave a great impetus to the search for potential pharmacologically active drugs carrying pyrazole substituents. These findings prompted this work to introduce several pharmacophores such as azetidinones and thiazolidinone moieties into a pyrazole system hoping to obtain compounds with enhanced potency.

An interesting group of β-lactams are the monocyclic β-lactams, which are molecules that do not contain another ring fused to the β-lactam. 2-Azetidinones, commonly known as β-lactams, are well-known heterocyclic compounds among the organic and medicinal chemists.[2, 3] A large number of 3-chloro monocyclic β-lactams possess powerful antibacterial, antimicrobial, anti-inflammatory, anticonvulsant and antitubercular activity.[4] They also function as enzyme inhibitors and are effective on the central nervous system.[5]

Thiazolidinone is one of the very important pharmacores. 4-thiazolidinone derivatives exhibit a broad spectrum of biological activity.[6] In recent years, 4-thiazolidinones are the most extensively investigated class of compounds, and its derivatives have been found to have potentially chemotherapic activities such as anticonvulsant[7], antibacterial, antifungal[8], anti-inflammatory[9], anticancer[10], and antipsychotic[11] properties. Some of the reported 4-thiazolidinones have showed envelope or half-chair conformation with different configurations. Their structural and conformational features are essential to correlate to the biological activity. [11]

Hence, in continuation to our efforts to synthesize some novel heterocyclic compounds[12-15] and with a view to further assess the pharmacological profile of this class of compounds containing nitrogen and sulphur, it was thought worthwhile to synthesize some new congeners of azetidinones and thiazolidinones moieties in a single molecular framework.

The synthetic route using conventional methodology is depicted for the synthesis of compound **(1)**. Compound (1) was prepared by the reaction of 1, 5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one, *p*-phenylenediamine and salicylaldehyde in ethanol. Condensation of compound **(1)** with various aromatic aldehydes in ethanol gave corresponding Schiff bases (**2**). Compound (**2**) was prepared by both conventional and microwave procedures. Cyclization of Schiff bases (**2**) with chloroacetic acid, $POCl_3$ in presence of triethylamine and with thioglycolic acid in dichloromethane afforded azetidinones and thiazolidinones respectively. The homogeneity of the compounds was checked by TLC. All the synthesized compounds were characterized by elemental analysis, IR, ^{1}H-NMR and mass spectrometric techniques. The antibacterial activities of the title compounds were evaluated against the different bacterial strains.

MATERIALS AND METHODS

General: All the chemicals and solvents were obtained from E-Merck, India (AR grade) and were used without further purification. Melting points were taken in an open capillary tube. The microwave assisted synthesis of Schiff base compounds were carried out in a CEM –

908010, bench mate model, 300watts laboratory microwave reactor. IR spectra were recorded on a Shimadzu Dr-8031 instrument. Elemental analyses were carried out using a Perkin-Elmer, CHN elemental analyzer model 2400. ^{1}H NMR spectra of the synthesized compounds were recorded on a Bruker-Avance (300 MHz) and Varian-Gemini (200 MHz) spectrophotometer using $CDCl_3$ solvent and TMS as an the internal standard. EI-MS spectra were determined on a LCQ ion trap mass spectrometer (Thermo Fisher, San Jose, CA, USA), equipped with an EI source.

Synthesis of 2-(8-(4-aminophenyl)-2,3 ,5, 6-tetramethyl-1,7-diphenyl1,2,4,6,7,7a,8, 8a-octahydrodipyrazolo[3,4-b:4' ,3'-e]pyri din-4-yl)phenol (1): A mixture of phenazone (0.2 mol), salicylaldehyde (0.1 mol) and *p*-phenylenediamine (0.1mole) in ethanol (10 mL) was refluxed for about 3-4 h. After cooling, the reaction mixture was poured in ice cold water, the solid precipitate was obtained and then filtered, dried and crystallized from chloroform to give light yellow solid.

Synthesis of 2-(8-(4-(arylbenzylidenea mino) phenyl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,4,6,7, 7a, 8, 8a-octahydrod ipyrazolo[3,4-b:4',3'-e]pyridin-4-yl)phenoll(2a-e).

Microwave method with solvent: Equimolar amount of 2-(8-(4-aminophenyl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,4,6, 7,7a,8,8a-octahydrodipyrazolo[3,4-b:4',3'-e]pyridin-4-yl)phenol (compound 1), (0.01 mol) and aromatic aldehyde (0.01 mol) and ethanol were taken in a glass tube which was loosely closed and irradiated in MW oven for 2 min . The completion of the reaction was monitored by TLC. The reaction mixture was allowed to attain room temperature. The solvent was removed, and the crude product was recrystallized with chloroform.

Classical Method: Equimolar amount of 2-(8-(4-aminophenyl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,4,6,7,7a,8, 8a-octahydrodipyr-azolo[3,4-b:4',3'-e]pyridin-4-yl)phenol (compound 1), (0.01 mol) and aromatic aldehyde (0.01 mol) and 2-3 drops of glacial acetic acid in ethanol (10 ml) was refluxed for 5 hr. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was set on one side to cool. Then the reaction mixture was poured in ice cold water and the solid precipitate was separated out. Collect the solid deposit by filtration and the crude product was recrystallized from chloroform.

2-(8-(4-(benzylideneamino)phenyl)-2,3,5, 6-tetramethyl-1,7-diphenyl-1,2,4,6,7,7a,8, 8a-octahydrodipyrazolo[3,4-b:4',3'-e] pyridin-4-yl)phenol (2a): *m.p. : 170 ^{o}C, IR (KBr): 760 (1, 2* disubtituted benzene ring), 1280 (C-N), 1570 (C=C), 1620 (-C=N-), 2918 (Ar-CH), 2997 cm^{-1} (Ar-OH); ^{1}H NMR: δ = 2.20 (m, 6H, Ar-CH); 3.10 (s, 6H, $(N\text{-}CH_3)_2$); 4.10 (s, 1H, Ar-CH); 4.44 (d, J = 8.4 Hz, 2H, Ar-CH); 6.70-6.90 (m, 6H, Ar-CH); 7.10 (m, 6H, Ar-CH); 7.30-7.40 (m, 6H, Ar-CH); 7.50 (t, J = 7.1 Hz, 3H, Ar-CH); 7.80 (d, J = 8.2 Hz, 2H, Ar-CH); 8.30 (s, 1H, N=CH); 9.60 (s, 1H, Ar-OH); Anal. Calcd. For $C_{42}H_{40}N_6O$: C, 78.23; H, 6.25; N, 13.03; Found: C, 77.80; H, 5.20; N, 12.60 ; Mass spectra, m/z = 641 (100%).

2-(8-(4-(2-hydroxybenzylideneamino) phenyl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,4,6,7,7a,8,8a-octahydrodipyra - zolo[3,4-b:4',3'-e]pyridin-4-yl)phenol(2b).
m. p. : 190 ^{o}C, IR (KBr):733 (1, 2 disubtituted benzene ring), 1209 (C-N), 1550 (C=C), 1600 (-C=N-), 2849 (Ar-CH), 3010 cm^{-1} (Ar-OH); ^{1}H NMR: δ = 2.60 (m, 6H, Ar-CH); 3.30 (s, 6H, $(N\text{-}CH_3)_2$); 4.20 (s, 1H, Ar-CH); 4.60 (d, J = 8.1 Hz, 2H, Ar-CH); 6.80-7.20 (m, 6H, Ar-CH); 7.40 (m, 8H, Ar-CH); 7.45-7.60 (m, 7H, Ar-CH); 7.70 (s, 1H, Ar-CH); 8.40 (s, 1H, N=CH); 9.70 (s, 1H, Ar-OH); 11.20 (s, 1H, Ar-OH); Anal. Calcd. For $C_{42}H_{40}N_6O_2$: C, 76.34; H, 6.10; N, 12.72; Found: C, 75.60; H, 5.70; N, 12.10 ; Mass spectra, m/z = 658 (100%).

2-(8-(4-(4-hydroxybenzylideneamino) phenyl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,4,6,7,7a,8,8a-octahydrodipyra - zolo[3,4-b:4',3'-e]pyridin-4-yl)phenol (2c).
m. p. : 140 ^{o}C, IR (KBr):775(1, 2 disubtituted

benzene ring), 1290 (C-N), 1520 (C=C), 1630 (-C=N-), 2940 (Ar-CH), 3030 cm^{-1} (Ar-OH); ^1H NMR: δ = 1.90 (m, 6H, Ar-CH); 3.20 (s, 6H, (N-$CH_3)_2$); 3.90 (s, 1H, Ar-CH); 4.30 (d, J = 8.3 Hz, 2H, Ar-CH); 6.50-7.10 (m, 8H, Ar-CH); 7.20-7.40 (m, 6H, Ar-CH); 7.50-7.70 (m, 6H, Ar-CH); 7.80 (d, J = 8.1 Hz, 2H, Ar-CH); 8.60 (s, 1H, N=CH); 9.50 (s, 1H, Ar-OH); 9.90 (s, 1H, Ar-OH); Anal. Calcd. For $C_{42}H_{40}N_6O_2$: C, 76.34; H, 6.10; N, 12.72; Found: C, 75.80; H, 5.90; N, 12.40 ; Mass spectra, m/z = 657 (100%).

2-(8-(4-(4-methoxybenzylideneamino) phenyl)-2,3,5, 6-tetramethyl-1,7-diphenyl-1,2,4,6,7,7a,8,8a-octahydrodipyra -zolo [3,4-b:4',3'-e] pyridin-4-yl)phenol (2d). m. p. : 180 ^oC, IR (KBr):760(1, 2 disubtituted benzene ring), 1250 (C-N), 1510 (C=C), 1650 (-C=N-), 2910 (Ar-CH), 3060 cm^{-1} (Ar-OH); ^1H NMR: δ = 2.30 (m, 6H, Ar-CH); 3.40 (s, 6H, (N-$CH_3)_2$); 3.80 (s, 3H, Ar-OCH_3); 4.20 (s, 1H, Ar-CH); 4.50 (d, J = 8.5 Hz, 2H, Ar-CH); 6.30-6.90 (m, 6H, Ar-CH); 7.00-7.20 (m, 8H, Ar-CH); 7.30-7.40 (m, 6H, Ar-CH); 7.90 (d, J = 8.2 Hz, 2H, Ar-CH); 8.50 (s, 1H, N=CH); 9.70 (s, 1H, Ar-OH); Anal. Calcd. For $C_{43}H_{42}N_6O_2$: C, 76.53; H, 6.27; N, 12.45; Found: C, 75.60; H, 5.80; N, 1210 ; Mass spectra, m/z = 673.10 (100%).

2-(8-(4-(3-nitrobenzylideneamino)phenyl)-2,3,5,6-tetrameth yl-1,7-diphenyl-1,2,4,6,7,7a,8,8a-octahydrodipyrazolo[3,4-b:4',3'-e]pyridin-4-yl)phenol (2e). m. p. : 150 ^oC, IR (KBr):750(1, 2 disubtituted benzene ring), 1270 (C-N), 1580 (C=C), 1610 (-C=N-), 2910 (Ar-CH), 3051 cm^{-1} (Ar-OH); ^1H NMR: δ = 2.40 (m, 6H, Ar-CH); 3.30 (s, 6H, (N-$CH_3)_2$); 3.80 (s, 1H, Ar-CH); 4.20 (d, J = 8.4 Hz, 2H, Ar-CH); 6.60-7.00 (m, 6H, Ar-CH); 7.10-7.20 (m, 6H, Ar-CH); 7.40-7.60 (m, 7H, Ar-CH); 7.70 (s, 1H, Ar-CH); 8.10 (d, J = 8.1 Hz, 2H, Ar-CH); 8.60 (s, 1H, N=CH); 8.80 (s, 1H, Ar-CH); 9.30 (s, 1H, Ar-OH); Anal. Calcd. For $C_{42}H_{39}N_7O_3$: C, 73.13; H, 5.70; N, 14.21; Found: C, 72.60; H, 5.10; N, 13.80 ; Mass spectra, m/z = 688 (100%).

Synthesis of 3-chloro-4-(aryl)-1-(4-(4-(2-hydroxyphenyl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,7,7a-tetrahydrodipyra -zolo[3,4-b:4',3'-e]pyridin8(4H,6H ,8aH)-yl)phenyl)azetidin-2-one (3a-e).

A mixture of Schiff base (0.002 mols) and chloroacetic acid (0.002 mols) was dissolved in dichloromethane (10 ml) in stoppered conical flask, cooled and stirred. In cold condition of the reaction mixture, triethylamine [TEA] (0.002 mols) was added in it, followed by dropwise addition of $POCl_3$ in dichloromethane (0.002 mols) with vigorous stirring. The reaction mixture was then stirred for additional 16 hrs. The completion of the reaction was monitored by TLC. The reaction mixture was washed with water and dried over sodium sulphate. The products that were obtained after removing the solvent were purified from chloroform.

3-chloro-1-(4-(4-(2-hydroxyphenyl)-2,3,5, 6-tetramethyl-1,7-diphenyl-1,2,7,7a-tetra hydrodipyrazolo[3,4-b:4',3'-e]pyridin-8 (4H,6H,8aH)-yl)phenyl)-4-phenylazetid -in-2-one (3a). Yield: 60 %; m. p.: 190 ^oC, IR (KBr):760 (1, 2 disubtituted benzene ring), 1280 (C-N), 1320 (C-N, *β*-lactam ring), 1570 (C=C), 1740 (C=O *β*-lactam), 2918 (Ar-CH), 2997cm^{-1} (Ar-OH); ^1H NMR: δ = 2.20 (m, 6H, Ar-CH); 3.10 (s, 6H, (N-$CH_3)_2$); 4.10 (s, 1H, Ar-CH); 4.44 (d, J = 8.4 Hz, 2H, Ar-CH); 5.10 (s, 1H, Ar-CH); 5.40 (s, 1H, CH-Cl); 6.50 (d, J = 8.3 Hz, 2H, Ar-CH); 6.70-6.90 (m, 6H, Ar-CH); 7.00-7.20 (m, 6H, Ar-CH); 7.25-7.40 (m, 9H, Ar-CH); 9.60 (s, 1H, Ar-OH); Anal. Calcd. For $C_{44}H_{41}N_6O_2Cl$: C, 73.27; H, 5.73; N, 11.65; Found: C, 72.90; H, 5.20; N, 10.95 ; Mass spectra, m/z = 715 (100%).

3-chloro-4-(2-hydroxyphenyl)-1-(4-(4-(2-hydroxyphenyl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,7,7a-tetrahydrodipyrazolo [3,4-b:4',3'-e]pyridin-8(4H,6H,8aH)-yl)phenyl) azetidin-2-one (3b). *Yield: 57 %; m. p.: 210 ^oC, IR (KBr):733 (1, 2 disubtituted benzene ring), 1209 (C-N), 1340* (C-N, *β*-lactam ring),1550 (C=C), 1720 (C=O *β*-lactam), 2849 (Ar-CH), 3010 cm^{-1} (Ar-OH); ^1H NMR: δ = 2.30 (m, 6H, Ar-CH); 2.90 (s, 6H, (N-$CH_3)_2$); 3.80 (s, 1H, Ar-CH); 4.40 (d, J = 8.1 Hz, 2H, Ar-CH); 5.20 (s, 1H, Ar-CH); 5.50 (s, 1H, CH-Cl); 6.60 (d, J = 8.5 Hz, 2H, Ar-

CH); 6.60-6.70 (m, 8H, Ar-CH); 7.00-7.20(m, 8H, Ar-CH); 7.50 (m, 4H, Ar-CH); 9.60(d, J = 8.6 Hz, 2H, Ar-OH); Anal. Calcd. For $C_{44}H_{41}N_6O_3Cl$: C, 71.68; H, 5.61; N, 11.40; Found: C, 71.10; H, 5.00; N, 10.80 ; Mass spectra, m/z = 732 (100%).

3-chloro-4-(4-hydroxyphenyl)-1-(4-(4-(2-hydroxyphenyl)-2, 3,5,6-tetramethyl-1,7-diphenyl-1,2,7,7a-tetrahydrodipyrazo lo[3,4-b:4',3'-e]pyridin-8(4H,6H,8aH)-yl)phenyl) azetidin-2-one (3c). Yield: 65 %; m. p.: 180 ^oC, IR (KBr):775 (1, 2 disubtituted benzene ring), 1290 (C-N), 1330 (C-N, *β*-lactam ring), 1520 (C=C), 1730 (C=O *β*-lactam), 2940 (Ar-CH), 3030 cm^{-1} (Ar-OH); ^1H NMR: δ = 2.00 (m, 6H, Ar-CH); 3.10 (s, 6H, $(N\text{-}CH_3)_2$); 4.00 (s, 1H, Ar-CH); 4.20 (d, J = 8.1 Hz, 2H, Ar-CH); 5.10 (s, 1H, Ar-CH); 5.50 (s, 1H, CH-Cl); 6.50 (d, J = 8.6 Hz, 2H, Ar-CH); 6.70 (d, J = 8.0 Hz, 2H, Ar-CH); 6.80-6.90 (m, 6H, Ar-CH); 7.10 (m, 8H, Ar-CH); 7.30 (m, 4H, Ar-CH); 9.40 (s, 1H, Ar-OH); 9.70 (s, 1H, Ar-OH); Anal. Calcd. For $C_{44}H_{41}N_6O_3Cl$: C, 71.68; H, 5.61; N, 11.40; Found: C, 71.00; H, 5.10; N, 11.10 ; Mass spectra, m/z = 733 (100%).

3-chloro-1-(4-(4-(2-hydroxyphenyl)-2,3,5, 6-tetramethyl-1,7-diphenyl-1,2,7,7a-tetrahydrodipyrazolo[3,4-b:4',3'-e]pyridi -ne-8(4H,6H,8aH)-yl)phenyl)-4-(4-methoxyphenyl)azetidin-2-one (3d). Yield: 72 %; m. p.: 250 ^oC, IR (KBr):760 (1, 2 disubtituted benzene ring), 1250 (C-N), 1360 (C-N, *β*-lactam ring), 1510 (C=C), 1750 (C=O *β*-lactam), 2910 (Ar-CH), 3060 cm^{-1} (Ar-OH); ^1H NMR: δ = 2.30 (m, 6H, Ar-CH); 3.20 (s, 6H, $(N\text{-}CH_3)_2$); 3.90 (s, 3H, Ar-OCH_3); 4.30 (s, 1H, Ar-CH); 4.45 (d, J = 8.3 Hz, 2H, Ar-CH); 5.20 (s, 1H, Ar-CH); 5.30 (s, 1H, CH-Cl); 6.40 (d, J = 8.6 Hz, 2H, Ar-CH); 6.70-6.90 (m, 8H, Ar-CH); 7.00-7.20 (m, 8H, Ar-CH); 7.40 (m, 4H, Ar-CH); 9.20 (s, 1H, Ar-OH); Anal. Calcd. For $C_{45}H_{43}N_6O_3Cl$: C, 71.94; H, 5.77; N, 11.19; Found: C, 71.20; H, 4.90; N, 10.80 ; Mass spectra, m/z = 745 (100%).

3-chloro-1-(4-(4-(2-hydroxyphenyl)-2,3,5, 6-tetramethyl-1,7-diphenyl-1,2,7,7a-tetrahydrodipyrazolo[3,4-b:4',3'-e]pyrid -ine-8(4H,6H,8aH)-yl)phenyl)-4-(3-nitrophenyl) azetidin-2-one (3e). Yield: 75 %; m. p.: 230 ^oC, IR (KBr):750 (1, 2 disubtituted benzene ring), 1270 (C-N), 1360 (C-N, *β*-lactam ring), 1580 (C=C), 1770 (C=O *β*-lactam), 2910 (Ar-CH), 3051 cm^{-1} (Ar-OH); ^1H NMR: δ = 2.10 (m, 6H, Ar-CH); 3.00 (s, 6H, $(N\text{-}CH_3)_2$); 3.90 (s, 1H, Ar-CH); 4.20 (d, J = 8.5 Hz, 2H, Ar-CH); 4.90 (s, 1H, Ar-CH); 5.10 (s, 1H, CH-Cl); 6.20 (d, J = 8.3 Hz, 2H, Ar-CH); 6.40-6.90 (m, 6H, Ar-CH); 7.10-7.20 (m, 6H, Ar-CH); 7.50 (m, 4H, Ar-CH); 7.70 (d, J = 8.1 Hz, 2H, Ar-CH); 8.00 (s, 1H, Ar-CH); 8.20 (s, 1H, Ar-CH); 9.50 (s, 1H, Ar-OH); Anal. Calcd. For $C_{44}H_{40}N_7O_4Cl$: C, 68.97; H, 5.26; N, 12.80; Found: C, 68.00; H, 4.90; N, 12.10 ; Mass spectra, m/z = 764 (100%).

Synthesis of 2-(arylphenyl)-3-(4-(4-(2-hydroxyphenyl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,7,7a-tetrahydrodipyraz -olo[3,4-b:4',3'-e]pyridin-8(4H,6H,8aH)-yl)phenyl)thiazo- lidin-4-one (4a-e). A mixture of Schiff base (0.002 mols) and thioglycolic acid (0.002 mols) was dissolved in ethanol (10ml) and the reaction mixture was refluxed for 14-16 hrs. The completion of the reaction was monitored by TLC. After the completion of reaction, it was poured in ice cold water and the solid precipitate was separated out. Collect the solid deposit by filtration and the crude product was recrystallized from chloroform.

3-(4-(4-(2-hydroxyphenyl)-2,3,5,6-tetra methyl-1,7-diphenyl-1,2,7,7a-tetrahydro di\pyrazolo[3,4-b:4',3'-e]pyridin-8(4H,6H, 8aH)-yl)phenyl)-2-phenylthiazolidin-4-one (4a). Yield: 60 %; m. p.: 210 ^oC, IR (KBr):617 (C-S-C, 4-thiazolidinone), 760 (1, 2 disubtituted benzene ring), 1280 (C-N), 1570 (C=C), 1610 (C=O, thiazolidinone), 2918 (Ar-CH), 2997 cm^{-1} (Ar-OH); ^1H NMR: δ = 2.20 (m, 6H, Ar-CH); 3.10 (s, 6H, $(N\text{-}CH_3)_2$); 3.90-4.00 (d, J = 8.6 Hz, 2H, Ar-CH, thiazolidinone); 4.10 (s, 1H, Ar-CH); 4.44 (d, J = 8.1 Hz, 2H, Ar-CH); 6.40 (s, 1H, Ar-CH, thiazolidinone); 6.60 (d, J = 8.5 Hz, 2H, Ar-CH); 6.80-6.90 (m, 6H, Ar-CH); 7.10-7.30 (m, 6H, Ar-CH); 7.40-7.70 (m, 9H, Ar-CH); 9.60

(s, 1H, Ar-OH); Anal. Calcd. For $C_{44}H_{42}N_6O_2S$: C, 73.51; H, 5.89; N, 11.69; S, 4.46; Found: C, 72.90; H, 5.20; N, 11.20 ; S, 4.00; Mass spectra, m/z = 715 (100%).

2-(2-hydroxyphenyl)-3-(4-(4-(2-hydro xyphenyl)-2,3,5,6-tetramethyl-1,7-diphe nyl-1,2,7,7a-tetrahydrodipyrazolo[3,4-b: 4',3'-e]pyridin-8(4H,6H,8aH)-yl)phenyl) thia zolidin-4-one (4b). Yield: 55 %; m. p.: 260 ^oC, IR (KBr): 630 (C-S-C,4-thiazolidinone), 733 (1, 2 disubtituted benzene ring), 1209 (C-N), 1550 (C=C), 1640 (C=O, thiazolidinone), 2849 (Ar-CH), 3010 cm^{-1} (Ar-OH); ^1H NMR: δ = 2.58-2.59 (m, 6H, Ar-CH); 3.10 (s, 6H, $(N\text{-}CH_3)_2$); 4.00 (s, 2H, Ar-CH, thiazolidinone); 4.18-4,20 (d, J = 8.3 Hz, 2H, Ar-CH); 4.40 (d, J = 8.0 Hz, 2H, Ar-CH); 6.40 (s, 1H, Ar-CH, thiazolidinone); 6.90-7.60 (m, 21H, Ar-CH); 9.90 (s, 1H, Ar-OH); 10.88 (s, 1H, Ar-OH); Anal. Calcd. For $C_{44}H_{42}N_6O_3S$: C, 71.91; H, 5.76; N, 11.44; S, 4.36; Found: C, 71.10; H, 5.30; N, 11.10 ; S, 3.95; Mass spectra, m/z = 730 (100%).

2-(4-hydroxyphenyl)-3-(4-(4-(2-hydroxy phenyl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,7,7a-tetrahydrodipyrazolo-[3,4-b:4',3'-e]pyridin-8(4H,6H,8aH)-yl)phenyl)thiazo lidin-4-one (4c). Yield: 65 %; m. p.: 240 ^oC, IR (KBr): 620 (C-S-C, 4-thiazolidinone),775 (1, 2 disubtituted benzene ring), 1290 (C-N), 1520 (C=C), 1620 (C=O, thiazolidinone), 2940 (Ar-CH), 3030 cm^{-1} (Ar-OH); ^1H NMR: δ = 2.10 (m, 6H, Ar-CH); 2.90 (s, 6H, $(N\text{-}CH_3)_2$); 3.90 (s, 1H, Ar-CH, thiazolidinone); 4.10 (s, 1H, Ar-CH); 4.20 (d, J = 8.4 Hz, 2H, Ar-CH); 6.30 (s, 1H, Ar-CH, thiazolidinone); 6.50-6.60 (m, 5H, Ar-CH); 6.70-7.10 (m, 6H, Ar-CH); 7.20-7.40 (m, 6H, Ar-CH); 7.50 (m, 4H, Ar-CH); 7.70 (d, J = 8.1 Hz, 2H, Ar-CH); 9.40 (s, 1H, Ar-OH); 9.60 (s, 1H, Ar-OH); Anal. Calcd. For $C_{44}H_{42}N_6O_3S$: C, 71.91; H, 5.76; N, 11.44; S, 4.36; Found: C, 71.20; H, 5.40; N, 11.00 ; S, 3.95; Mass spectra, m/z = 730 (100%).

3-(4-(4-(2-hydroxyphenyl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,7,7a-tetrahydrodipyrazolo[3,4-b:4',3'-e]pyridin-8(4H, 6H,8aH)-yl)phenyl)-2-(4-methoxyphenyl) thiazolidin-4-one (4d). *Yield:* 68 %; m. p.: 270 ^oC, IR (KBr): 610 (C-S-C, 4-thiazolidinone), 760 (1, 2 disubtituted benzene ring), 1250 (C-N), 1510 (C=C), 1650 (C=O, thiazolidinone), 2910 (Ar-CH), 3060 cm^{-1} (Ar-OH); ^1H NMR: δ = 2.30 (m, 6H, Ar-CH); 3.20 (s, 6H, $(N\text{-}CH_3)_2$); 3.80 (s, 3H, Ar-OCH_3); 4.10 (s, 1H, Ar-CH, thiazolidinone); 4.20 (s, 1H, Ar-CH); 4.50 (d, J = 8.5 Hz, 2H, Ar-CH); 6.30 (s, 1H, Ar-CH, thiazolidinone); 6.50 (d, J = 8.0 Hz, 2H, Ar-CH); 6.80-6.90 (m, 7H, Ar-CH); 7.10-7.20 (m, 8H, Ar-CH); 7.30-7.40 (m, 4H, Ar-CH); 7.80 (d, J = 8.3 Hz, 2H, Ar-CH); 9.70 (s, 1H, Ar-OH); Anal. Calcd. For $C_{45}H_{44}N_6O_3S$: C, 72.17; H, 5.92; N, 11.22; S, 4.28; Found: C, 71.70; H, 5.15; N, 11.10 ; S, 4.15; Mass spectra, m/z = 745 (100%).

3-(4-(4-(2-hydroxyphenyl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,7,7a-tetrahydrodipyrazolo[3,4-b:4',3'-e]pyridine-8(4H,6H,8aH)-yl)phenyl)-2-(3-nitrophenyl)thiazo lidin-4-one(4e). Yield: 70 %; m. p.: 240 ^oC, IR (KBr): 650 (C-S-C, 4-thiazolidinone), 750 (1, 2 disubtituted benzene ring), 1270 (C-N), 1580 (C=C), 1650 (C=O, thiazolidinone), 2910 (Ar-CH), 3051 cm^{-1} (Ar-OH); ^1H NMR: δ = 2.40 (m, 6H, Ar-CH); 3.30 (s, 6H, $(N\text{-}CH_3)_2$); 4.10 (s, 1H, Ar-CH, thiazolidinone); 4.20 (s, 1H, Ar-CH); 4.50 (d, J = 8.1 Hz, 2H, Ar-CH); 6.20 (s, 1H, Ar-CH, thiazolidinone); 6.70 (d, J = 8.4 Hz, 2H, Ar-CH); 6.80-7.00 (m, 5H, Ar-CH); 7.20 (m, 4H, Ar-CH); 7.30-7.90 (m, 8H, Ar-CH); 8.00 (s, 1H, Ar-CH); 8.10 (s, 1H, Ar-CH); 8.10-8.20 (d, J = 8.0 Hz, 2H, Ar-CH); 9.80 (s, 1H, Ar-OH); Anal. Calcd. For $C_{44}H_{41}N_7O_4S$: C, 69.18; H, 5.41; N, 12.83; S, 4.20; Found: C, 68.50; H, 5.10; N, 12.30 ; S, 3.90; Mass spectra, m/z = 760 (100%).

RESULTS

2-(8-(4-aminophenyl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,4,6,7,7a,8, 8a-octa hydrodipyra zolo [3,4-b:4',3'-e]pyridin-4-yl)phenol (**1**) was prepared in quantitative yield. By the reaction of compound **1** with different aldehydes, we have synthesized 2-(8-(4-(arylbenzylideneamino)phenyl)-2,3,5,6-

tetramethyl-1,7-diphenyl-1,2,4,6,7,7a,8,8a-octahydrodipyrazolo [3,4-b:4',3'-e] pyridin-4-yl) phenol (**2a-2e**), in good yields by using neat conditions under microwave irradiation in presence of solvent as well as solvent free as compared to that of conventional reflux reactions in ethanol (**Figure 1**). The comparison of isolated yields and reaction time of the three conditions employed showed microwave-assisted reactions as the most efficient synthetic method in terms of energy and time consumption (**Table 1**). The comparison of the isolated yield by different methods has been depicted graphically as shown in **Figure 2**.

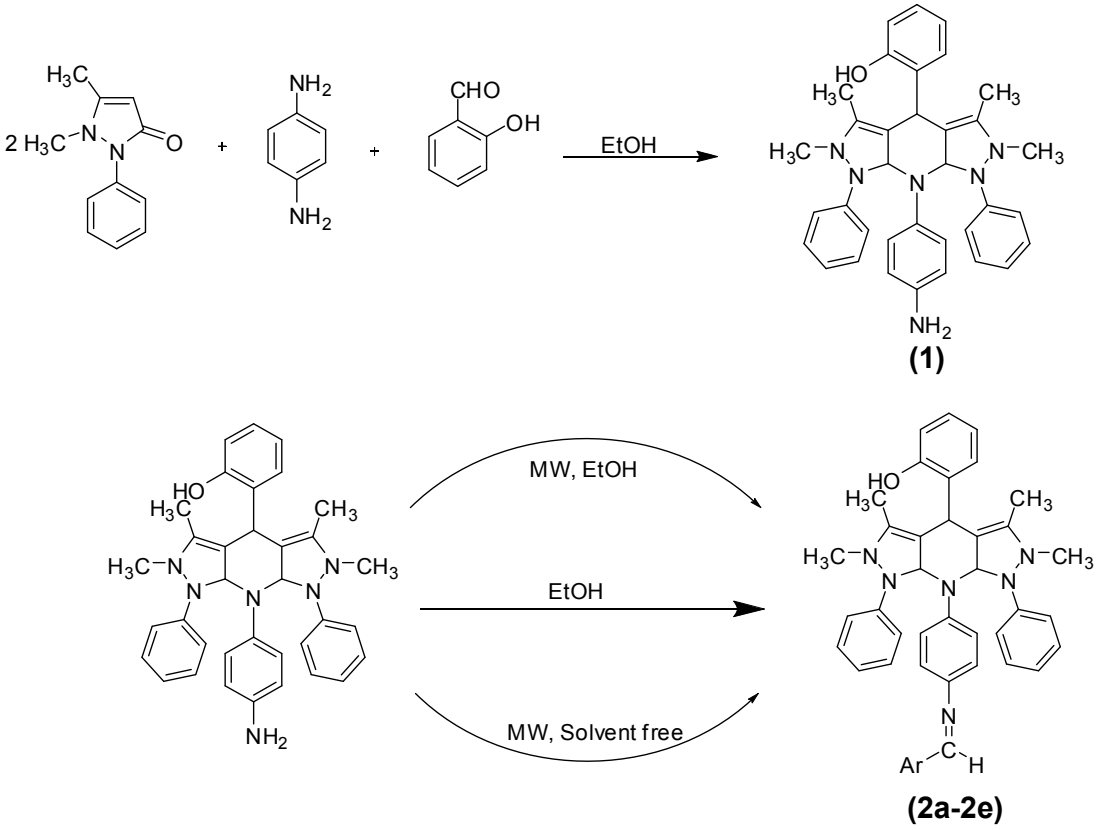

Figure 1
Synthesis of Schiff bases (2a-2e) by MW, MW Solvent free and Classical Technique.

Table 1
Time and yield comparison between classical and MW Irradiation.

Compound	Ar	Reaction time (min/sec)			Yield (%)[a]		
		MWI (Solvent) free)	MWI (EtOH)	Classical (EtOH)	MWI (Solvent) free)	MWI (EtOH)	Classical (EtOH)
2a	$-C_6H_5$	2 min	2 min	300 min	95	90	80
2b	$2\text{-}OHC_6H_4$	2 min	2 min	300 min	88	76	68
2c	$4\text{-}OHC_6H_4$	2 min	2 min	300 min	85	70	65
2d	$4\text{-}OCH_3C_6H_4$	2 min	2 min	300 min	90	80	75
2e	$3\text{-}NO_2C_6H_4$	2 min	2 min	300 min	82	75	67

[a]*Isolated Yield*

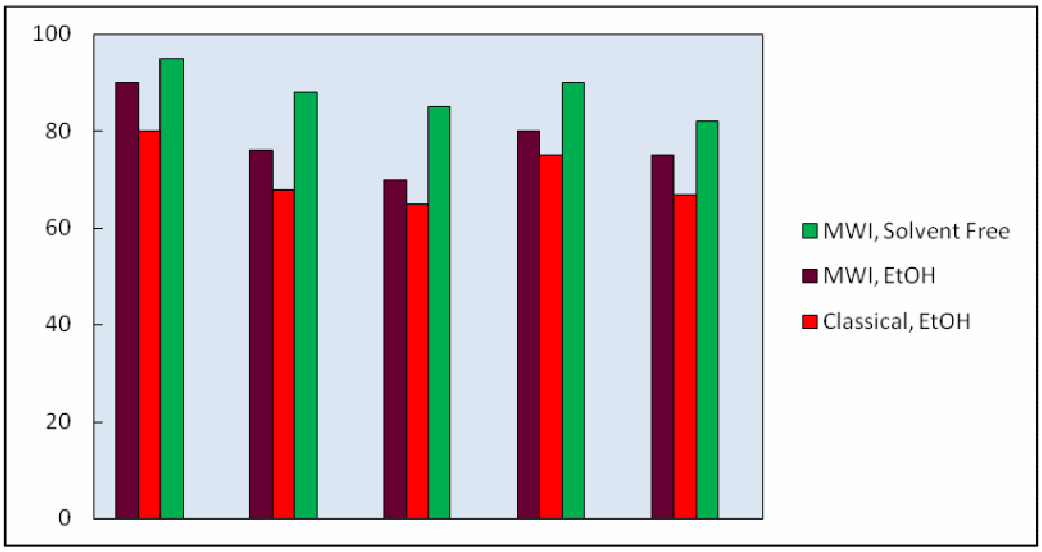

Figure 2
Comparison of the yields of compounds (2a-2e) using different method.

Compounds **2** reacts with chloroacetic acid in presence of triethylamine, $POCl_3$ and mercaptoacetic acid to afford 3-chloro-4-(2-hydroxyphenyl)-1-(4-(4-(aryl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,7,7a-tetrahydrodipyrazolo[3,4-b:4',3'-e]pyrid ine-8(4H,6H,8a H)-yl)phenyl) azetidin-2-one and 2-(aryl)-3-(4-(4-(2-hydroxyphenyl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,7, 7a-tetrahydrodipyrazolo[3,4-b:4',3'e]pyridine-8(4H,6H,8aH)yl) phenyl)thiazolidin-4-one respectively (**Figure 3**).

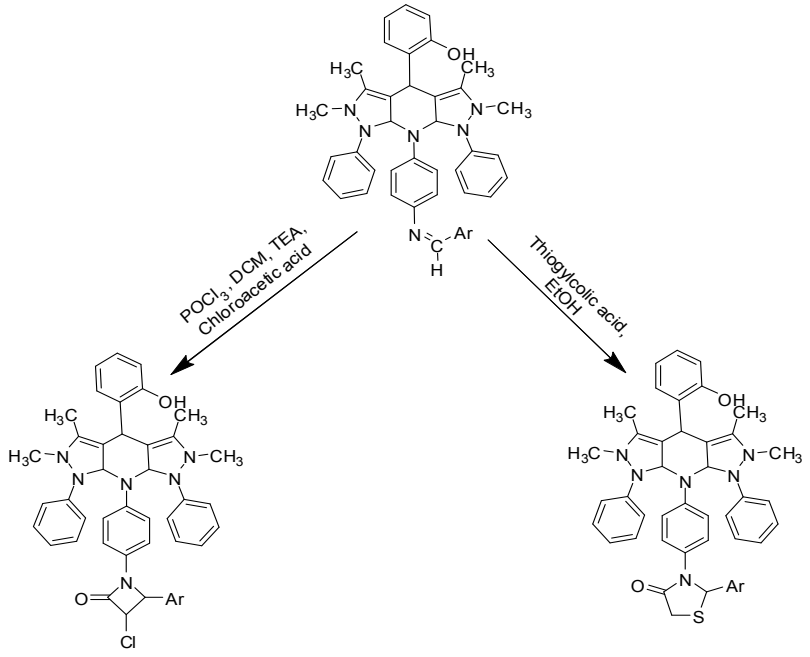

Figure 3
Synthesis of azetidinones (3a-3e) and thiazolodinones (4a-4e).

Antibacterial Activity

Antibacterial activities of all the compounds were studied against nine different bacterial strains (E. coil (mixed), B. subtilis, Pseudomonas sp., S.aureus, P.vulageris, Salmonella sp. , E. coil(+ve strain,), Rhodococci, B. stearothermopelus) by measuring the zone of inhibition on agar plates. The compounds possess moderate to good activity against all stains in comparison with standard drug (**Table 2**). It can be observed from these results that compounds **3a-e and 4a-e** have shown positive bacterial activity against different bacterial species, which are also known as human pathogenic bacteria. It was also observed that within the synthesized compound extracts, all compounds show good activity against all bacterial strains.

Table 2

Biological activities of azetidinones and thiazolidinones.

Bacterial strain	Zone of inhibition in mm along without well diameter (5mm)										
	Chemical compounds										
	3a	3b	3c	3d	3e	4a	4b	4c	4d	4e	Standard Nystatin
E. coil (mixed)	15	14	8	13.8	-	9	15	10	9	10	17
B. subtilis	4	3.5	5	-	4	4	5	3	10	6	6
Pseudomonas sp.	10	6	13	11.2	9	7	8	11	7	3.6	12
S. aureus	5	-	5.5	6.6	4	8.1	9	7.5	6	8.8	9
P. vulageris	12	15	10.6	14.5	16	12.9	7.4	12	16	9	17
Salmonella sp.	12	16	16.5	19	14	16	11	13	10	17	19.1
E. coil(+ve strain)	-	9	7.2	5.3	10	6.5	10	5	-	4	11
Rhodococci	3	-	-	3	4.5	4.8	5	3.8	4	2.6	6
B. stearothermopelus	4.5	4	5.1	6.4	3.7	6.4	4.8	3	11	5.8	7.2

"-" represent "not active"

CONCLUSION

Microwave irradiation technique is becoming an increasingly popular method of heating which replaces the classical chemical route, because of some of its features like clean, cheap & convenience. Often, it affords higher yields and results within short reaction times. In this paper we reported synthesis of imine **2a-2e** using microwave irradiation, offers significant improvements over existing procedures. In microwave synthesis the yield of all the products are more than good. The reaction time is drastically reduced to 2 minute instead of 5 hours in the classical way. From data of antimicrobial activity, it could be observed that compounds of the series, **3a-3e and 4a-4e** show good comparable activity against standard drugs

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