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MICROWAVE ASSISTED SYNTHESIS OF P-TOLYL-BENZOAZEPINO-PYRROLO-BIS [1,4] DIAZEPINE AND THEIR MICROBIAL EVALUATION

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Abstract:
A greener and efficient method using microwave assistance has been created for making innovative bis-benzodiazepine derivatives, which are a type of seven-membered heterocyclic compounds that hold significant interest in the pharmaceutical world. The process began with N-phenyl-substituted succinimide chalcone as the main precursor, resulting in a variety of p-tolyl-benzoazepino-pyrrolo-bis [1,4] diazepine (3a–e). This microwave-assisted technique has several advantages over conventional methods, such as shorter reaction times, improved yields, and better ease of operation. The structures of the compounds we synthesized were clearly confirmed through detailed spectral analysis, including FT-IR, ^{1}HNMR, ^{13}CNMR, and mass spectrometry. This innovative and quick approach highlights the power of microwave irradiation in creating complex heterocyclic systems and offers a hopeful pathway for emergent biologically significant benzodiazepine derivatives. Synthesized compounds were tested against pathogenic bacterial strains the compound 3a showed potent antibacterial activity than standard antibacterial drug

Key words: *Succinimides, Bis-chalcone derivatives,1,4 azepine derivatives*

1 INTRODUCTION

It is Benzos and class of psychoactive drugs containing benzene and diazepine ring system. It is belongs to seven metered heterocyclic compounds containing two nitrogen atoms in their chemical structure. It was accidently discovered [1] in year 1955 by the scientist Leo Steinbach and the first synthesis of benzodiazepine derivative was carried by the scientist Hoffmann-LaRoche. Several Biologically active agents have been derived from benzodiazepine such as Clobazam [2], Arfendazam [3], Lofendazam [4] particularly used in Pharmaco psychiatry.

The benzodiazepine derivatives commonly known as tranquillizer. It increases the effect of neurotransmitter gamma amino butyric acid GABA at GABA receptor [5] results in the Sedative, hypnotics [6] anti-depressant [7], Anxiolytic [8-9]. Benzodiazepine derivatives have diverse application in the field of medicine. The compound containing benzodiazepine moiety used for treatment of GAD Generalized anxiety disorder the most popular drug is diazepam. It is also used in treatment of Insomnia sleep related disorder produced by prolong period of anxiety and mental agitational behavior it also has muscle relaxant properties [10] and effect on neurotransmitter and used for treatment of auditory hallucinations [11]

2. EXPERIMENTAL SECTION

2.1 Material and method

For synthesis of seven member heterocyclic compounds benzodiazepine N-phenyl substituted bis-chalcone condensed with orthophenylene diamine contain two nucleophilic amino groups able to react with α-β unsaturated carbonyl compounds. The different benzodiazepine derivatives have been prepared from chalcone **1a-e** reacted with OPD (Ortho phenylenediamine) in presence of neutral alumina as a solid support and irradiated it in microwave oven converted in to [1,4]diazepine derivatives **3a-e.**

The melting points were taken in to open capillaries and are uncorrected. The I.R spectra were recorded on FTIR shimazdu spectrophotometer using KBr disc method. The succinimide chalcone **1a-e** was synthesized by using microwave assisted solid phase synthesis of our reported method [12]. The reaction was monitored by thin layer chromatography by using pre-coated silica gel aluminum plates and mixture of n-hexane: ethyl acetate 5:5 proportion was used as mobile phase. The identification of spots was done by visualizing plate in U.V chamber. The chemicals used Ortho phenylenediamine was an analytical grade and of high purity.

3. PREPARATION OF P-TOLYL-BENZOAZEPINO-PYRROLO-BIS [1,4] DIAZEPINE:

3.1) General procedure for synthesis of p-tolyl-12,13,13a,13b,14,15-hexahydro-6H -benzo [b]benzo[6',7']azepino[3',4':4,5] pyrrolo[2,3-e] bis[1,4]diazepine: 31a-e:

The 5 milimole of chalcone **1a-e** and 10 milimole of Ortho phenylenediamine and 4 gm of neutral alumina added as solid support for reactant taken in 100 ml borosilicate glass beaker after carefully mixing of reaction mixture and covered with glass petridish then irradiated in microwave oven at 450 watt power for 4-6 min as solvent free condition thus fused solid derivatives of p-tolyl-benzoazepino-pyrrolo-bis [1,4] diazepine (3a–e) obtained and recrystalized it by ethyl alcohol.

3.2) *2,2'-(6-(p-tolyl)-12,13,13a,13b,14,15-hexahydro-6H-benzo[b]benzo[6',7'] azepino [3',4':4,5]pyrrolo[2,3-e]bis[1,4]diazepine-13,14-diyl)diphenol (31a):*

M.F: $C_{37}H_{31}N_5O_2$, M.W: 577.67, Yield: 70.32 %, M.P (^{0}C): 93-95 ^{0}C, Colour: Reddish Brown Solid. C, H, N Analysis: Cal.: C, 76.93; H, 5.41; N, 12.12 Obs.: C, 76.43; H, 5.71; N, 12.62 FTIR (KBr, Cm^{-1}) (Spectrum No.- 01): 3400.05 (-OH), 3228.84 (-NH), 2972.94 (CH_3), 1514.12 (C=N), 1598.99 (Ar, C=C). ^{1}H NMR (500 MH_Z ; DMSO d_6 ; δ ppm): (Spectrum No.- 02): 2.35 (s, 3H, CH_3), 2.77 (d, 1H, -CH), 3.39(d, 1H, -CH), 8.09 (s, 1H, -NH), 10.0 (s, 1H, -OH), 7.48-6.38 (m, 10H, Ar-H).

3.3) ***13,14-bis(3-nitrophenyl)-6-(p-tolyl)-12,13,13a,13b,14,15-hexahydro-6H-benzo [b] benzo [6',7'] azepino[3',4':4,5]pyrrolo[2,3-e]bis[1,4]diazepine (31b)***

M.F: $C_{37}H_{29}N_7O_4$, M.W: 635.67, Yield: 73.42 % , M.P (^{0}C): 155- 157 ^{0}C, Colour: black solid C H N Analysis: Cal.: C, 69.91; H, 4.60; N, 15.42 Obs.: C, 69.61; H, 4.80; N, 15.82 FTIR (KBr, Cm^{-1}): 3340.82 (-NH), 1591.33 (C=N), 1388.79 (Ar-NO_2), 1629.90 (Ar, C=C). ^{1}H NMR (500 MH_Z ; DMSO d_6; δ ppm): 2.41 (s, 3H, -CH_3), 2.77 (d, 1H, -CH), 3.39 (d, 1H, -CH), 8.19 (s, 1H, -NH), 7.78-7.13 (m, 10H, Ar-H).

3.4) ***13,14-bis(2-chlorophenyl)-6-(p-tolyl)-12,13,13a,13b,14,15-hexahydro-6H-benzo [b] benzo [6',7']azepino[3',4':4,5]pyrrolo[2,3-e]bis[1,4]diazepine (31c):***

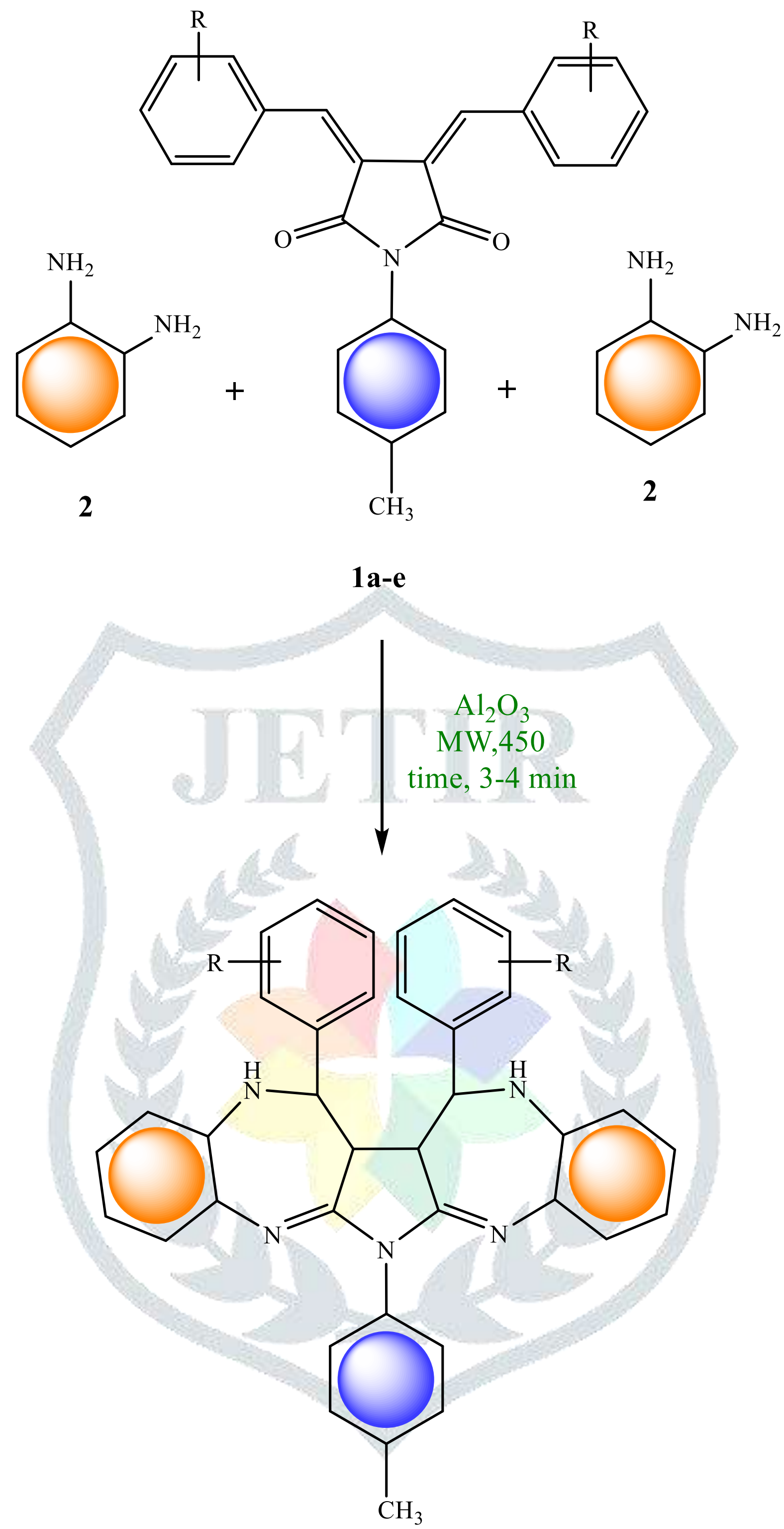
M.F: $C_{37}H_{29}Cl_2N_5$, M.W: 614.57, Yield: 72.51 %, M.P (^{0}C): 70-73 ^{0}C , Colour: brown Solid, C H N Analysis: Cal.: C, 72.31; H, 4.76; N, 11.40 Obs.: C, 72.61; H, 4.86; N, 11.80 FTIR (KBr, Cm^{-1}): 3385.18 (-NH), 2922.25 (Ar-CH_3), 1518.03 (C=N), 750.33 (Ar-Cl). ^{1}H NMR (500 MH_Z ; DMSO d_6 ; δ ppm): 2.34 (s, 3H, -CH_3), 2.50 (d, 1H, -CH), 2.76 (d, 1H, -CH), 7.27-6.39 (m, 10H, Ar-H), 8.90 (s, 1H,-NH). ^{13}C NMR (400 MH_Z ; DMSO d_6 ; δ ppm): (Spectrum No.-07): 20.68 (-CH_3), 40.10, 114.59, 117.34, 126.84, 129.23, 130.08,134.77, 137.55, 137.55, 176.97(C=N).

3.5) ***13,14-bis(4-methoxyphenyl)-6-(p-tolyl)-12,13,13a,13b,14,15-hexahydro-6H-benzo [b]benzo[6',7']azepino[3',4':4,5]pyrrolo[2,3-e]bis[1,4]diazepine (31d):***

M.F: $C_{39}H_{35}N5O_2$, M.W: 605.73, Yield:71.23 %, M.P (^{0}C): 98-100 ^{0}C , Colour: brown Solid, C H N Analysis: Cal.: C, 77.33; H, 5.82; N, 11.56 Obs.: C, 77.73; H, 5.62; N, 11.86 FTIR (KBr, Cm^{-1}): 3367.71 9-NH), 2981.95 (-CH_3, Ar-CH_3), 1502.55 (C=N), 1138.36 (O-CH_3).^{1}H NMR (500 MH_Z ; DMSO d_6 ; δ ppm): 2.76 (d, 1H, -CH), 2.34 (s, 3H, -CH3), 3.36 (d, 1H, -CH), 3.86 (s, 1H, -OCH_3), 8.12 (s, 1H, -NH), 7.297.08, (m, 8H, Ar-H).

3.6)*13,14-tri-p-tolyl-12,13,13a,13b,14,15-hexahydro-6H-benzo[b]benzo[6',7'] azepino [3',4':4,5]pyrrolo[2,3-e]bis[1,4]diazepine (31e):*

M.F: $C_{39}H_{35}N_5$, M.W: 573.73, Yield: 69.12 % , M.P (^{0}C): 129-131 ^{0}C , Colour: brown Solid, C H N Analysis: Cal.: C, 81.64; H, 6.15; N, 12.21 Obs.: C, 81.84; H, 6.55; N, 12.41 FTIR (KBr, Cm^{-1}): 3367.71 (-NH) , 1510. M 26 (C=N), 2916.37 (CH3, Ar-CH_3).^{1}H NMR (500 MH_Z ; DMSO d6 ; δ ppm): 2.76 (d, 1H, -CH), 2.38 (s, 3H, CH3), 3.35 (d, 1H, -CH), 7.63-6.88 (m, 8H, Ar-H) 8.07 (s, 1H, -NH)



3a-e

SCHEME-1

4. RESULT AND DISCUSSION:

The synthesis of hexahydro-6H-benzo[b] benzo [6', 7'] azepino [3', 4':4, 5] pyrrolo [2,3-e] bis [1, 4] diazepine derivatives 3a -e were carried out from reaction of chalcone with OPD in presence of neutral alumina as solid support under microwave irradiation . IR spectra of compound 3a showed stretching frequency at 3400.05Cm^{-1}

indicated the presence of (-OH) group, 3228.84 Cm^{-1} corresponds to (-NH) group, 2972.94 Cm^{-1} for ($-CH_3$) group and 1514.12 Cm^{-1} indicated the presence of (C=N) group. The 1HNMR Spectrum compound 31ain DMSO d6 appeared a peak around 2.77 δ doublet for 1H of -CH of benzodiazepine , 3.39 δ doublet for 1H of -CH of benzodiazepine , 8.09 δ singlet for 1H of -NH benzodiazepine and 10.0 δ singlet for 1H of -OH group. The spectral analysis of this series of compounds were found to consistent with the considered structures of synthesized compounds.

4.1. Microbial Evaluation p-tolyl-benzoazepino-pyrrolo-bis [1,4] diazepine:

Antimicrobial evaluation of Bis-benzodiazepine (3a-e) were screened for antibacterial activity in vitro against Gram positive bacteria Staphylococcus auras (NCIM 2079) , Bacillus subtilis (NCIM 2250) and Gram negative bacteria Pseudomonas aeruginosa (NCIM 2036), Escherichia coli(NCIM 2109). The solution of all compounds 3a-e were prepared in DMSO solvent .The assay was carried by taking 100 µgm per disc by using disc diffusion method for this purpose nutrient agar media was employed. The results were obtained in the form of zone of inhibition and noted after period of incubation (at 37^0C for 24-28 hrs).The zone of inhibition was measured in mm and compared with standard drug Chloramphenicol (Chmpl) shown in table.

Sr.No	**Sample Code**	**Bacterial Strain**			
		Gram +ve		***Gram –ve***	
		S.Aureus	***B.Subtilis***	***E.coli***	***P.aeurginosa***
1	**3a**	18.21	10.08	--	--
2	**3b**	12.43	-	--	--
3	**3c**	7.64	11.56	--	--
4	**3d**	8.35	-	--	--
5	**3e**	13.97	13.34	--	--
std	**Chmpl**	18.17	20.91	22.23	14.18

Note: Zone of inhibition measured in mm; "--" means no activity

Figure: Compound **3a** shows antibacterial activity against S.Aureus

5. CONCLUSION

From spectral analysis we successfully synthesized a series of p-tolyl-benzoazepino-pyrrolo-bis [1,4] diazepine, starting with N-phenyl substituted succinimide chalcone. This fresh approach led to the development of compounds 3a-e, which we carefully characterized using Fourier Transform Infrared (FT IR) spectroscopy and Proton Nuclear Magnetic Resonance (^{1}H NMR) spectral analysis. The FT IR spectra revealed the functional groups involved, while the ^{1}H NMR spectra provided in-depth insights into the hydrogen environments within the molecular structure. This thorough characterization not only confirms that we synthesized the desired compounds. The microbial investigation reveals that synthesized compounds showed promising antibacterial activities particularly compound **3a** showed potent antibacterial activity against S.Aureus. This study will helpful in medicinal chemistry and pharmacology.

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