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SYNTHESIS, CHARACTERIZATION AND MICROBIAL EVALUATION OF P-CHLORO-BENZO-PYROLLO- BIS- BENZODIAZEPINE

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Abstract:

In this synthetic protocol P-Chloro phenyl succinamide **5** converted in to bis-heterocyclic chalcone **8a-e** by reactions with substituted benzaldehyde. The chalcone then reacted with OPD ortho phenylene diamine with effect of microwave irradiation afforded to benzodiazepine **9a-e.**

The structure of all synthesized compound have been determined by FT IR and ^{1}H NMR Spectral techniques. The antimicrobial assay were carried out by disc diffusion method against photogenic bacterial and fungal strain. The synthesized compound showing promising antibacterial and antifungal activities.

Keywords: *phenyl succinamide, bis-heterocyclic chalcone, ortho phenylene diamine, benzodiazepine.*

1. INTRODUCTION

The benzodiazepine derivatives seven member heterocyclic compounds these are also useful for removal of alcohol addiction the chlorodiazepoxide used in detoxification and motivate to stop drinking alcohol [1]. Some of its derivatives used for CNS disorder treatment [2-3]. The benzodiazepine acts central nervous system and it is available since 1963 as a drug Valium it is derivative of benzodiazepine diazepam. The most widely used sedative and hypnotics are barbiturates but they causes many side effects to overcome these disadvantage the benzodiazepine is introduced and it is safer for treatment of muscle spam and anxiety[4]. On other hand the benzodiazepine derivatives found to possess Endothelia receptor antagonist [5], G-Protein coupled receptor [6], Peptide Antagonist and Cholecystokinin receptor Antagonist [7], Vasopressin receptor antagonist [8] properties and also act as Calcium Channel blocker [9] and used in the treatment of cardiovascular disorder [10]. The molecule incorporated benzodiazepine moiety serve as Peptidomimetics [11-12], Analgesic [13], Antipyretic [14], Anti-proliferative [15-16], Antioxidant [17], Anti-ulcerative **[18]** and Anti-inflammatory activities [19]**.** The benzodiazepine has broad spectrum Antimicrobial activity[20] and act as antifungal[21] Some other Pharmacological activities shown by benzodiazepine derivatives such as Antitumor[22] and Anti-cancer property[23-24]in addition to that it

shows Antiviral effect[25] the benzodizepine nucleoside used for viral disease like AIDS [26] and act as HIV-1 inhibitor [27] including such medicinal applications it is also used as dye for Acrylic fiber [28] by considering such huge application of benzodiazepine in this study made an attempt to synthesized p-chloro-pyrollo- bis-benzodiazepine derivatives by greener approach.

2. EXPERIMENTAL

2.1 Material and method

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 7a-e and 8a-e were synthesized by using microwave assisted solid phase synthetic method. 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 phenylene diamine was an analytical grade and of high purity. The important synthon chalcone have been synthesized from N-Chlorophenyl substituted succinamide with help of our previously reported synthetic protocol [29]

3. SYNTHESIS OF P-CHLORO-BENZO-PYROLLO- BIS- BENZODIAZEPINE

3.1 General procedure for synthesis of 6-(p-chloro)-12,13,13a,13b,14,15-hexahydro6H-benzo[b]benzo[6',7']azepino[3',4':4,5]pyrrolo[2,3-e]bis[1,4]diazepine: 9a-e:

The 5 milimole of chalcone **7a-e** and 10 milimole of Ortho phenylenediamine **8** and 3 gm of neutral alumina added then homogenized this mixture in morter then taken in 100 ml borosilicate glass beaker covered with glass petridish then reaction mixture was irradiated in microwave oven at 450 watt power for 4-6 min in solvent free condition thus fused solid derivatives of p-chloro -pyrrolo - bis – diazepine derivatives obtained and recrystallized it from ethyl alcohol.

3.2) 2,2'-(6-(p-chloro)-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 (9a):

M.F:$C_{36}H_{28}ClN_5O_2$, Physical appearance: Brown solid. M.P: 177-179 ^{0}C, M.W: 598.09, Yield: 72.42 % C H N Analysis: Cal.: C, 72.29; H, 4.72; N, 11.71 Obs.: C, 72.89; H, 4.72; N, 11.81 FTIR (KBr): 3328.71 (-NH) , 1518.66 (C=N), 3428.53 (–OH), 768.44 (Ar-Cl),^{1}H NMR (500 MHz ; DMSO d_6 ; δ ppm): 2.77 (d, 1H, -CH), 3.36 (d, 1H, -CH), 8.07 (s, 1H, -NH), 7.57-7.02 (m, 10H, ArH), 10.26 (s, 1H, -OH).

3.3) 13,14-bis(3-nitrophenyl)-6-(p- chloro)-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 (9b):

M.F: $C_{36}H_{26}ClN_7O_4$, Physical appearance: Dark brown solid, M.P: 113-115 ^{0}C, M.W: 598.09, 656.09, Yield: 71.03% , C H N Analysis: Cal.: C, 65.90; H, 3.99; N, 14.94 Obs.: C, 65.70; H, 3.49; N, 14.34 FTIR (KBr, Cm^{-1}):1521.84 (C=N), 3437.75 (-NH), 1348.24 (Ar-NO_2), 742.69 (Ar-Cl).^{1}H NMR (500 MHz ; DMSO d_6 ; δ ppm): 2.77 (d, 1H, -CH), 3.35(d, 1H, -CH), 8.63-7.25 (m, 10H, Ar-H), 9.02 (s, 1H, -NH).

3.4) 13,14-bis(2-chlorophenyl)-6-(p-chloro)-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 (9c):

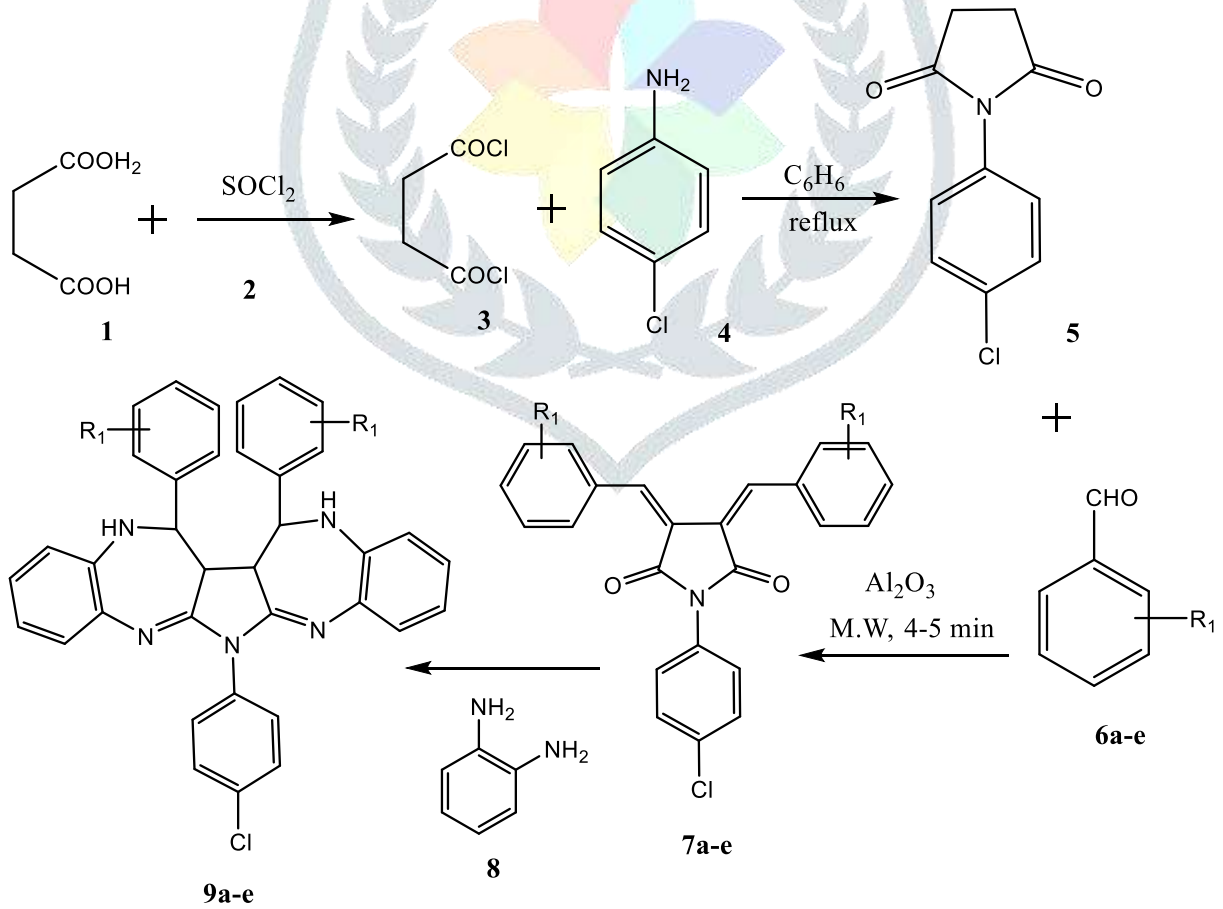
M.F: $C_{36}H_{26}Cl_3N_5$, Physical appearance: Gray Solid, M.P: 152-154 ^{0}C, M.W:634.98, Yield: 70.14 % C H N Analysis: Cal.: C, 68.09; H, 4.13; N, 11.03 Obs.: C, 68.39; H, 4.83; N, 11.73 FTIR (KBr, Cm^{-1}): 3288.63 (-NH), 1489.05 (C=N), 742.52 (Ar-Cl).^{1}H NMR (500 MHz ; DMSO d_6 ; δ ppm): 2.4 (d, 1H, -CH), 3.4 (d, 1H, -CH), 7.6-7.2 (m, 10H , Ar-H), 8.9 (s, 1H, -NH)

3.5) 13,14-bis(4-methoxyphenyl)-6-(p-chloro)-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 (9d):

M.F: $C_{38}H_{32}ClN_5O_2$, Physical appearance: Gray Solid , M.P: 134-136 ^{0}C, M.W: 626.15, Yield: 70.12 % , C H N Analysis: Cal.: C, 72.89; H, 5.15; N, 11.18 Obs.:C, 72.49; H, 5.55; N, 11.58 FTIR (KBr, Cm^{-1}): 1587.42 (C=N), 3095.75, 3464.15 (-NH), 1166.93(O-CH_3), 742.69 (C-Cl).^{1}H NMR (500 MHz ; DMSO d_6 ; δ ppm): 3.37 (s, 1H, -CH), 4.26 (d, 1H, -CH), 3.84 (s, 3H, -OCH_3), 7.73-7.29 (m, 8H, Ar-H), 8.11 (s, 1H, -NH)

3.6) 13,14-bis(4-methyl)-6-(p-chloro)-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 (9e):

M.F:$C_{39}H_{35}ClN_5$, Physical appearance: brown Solid, M.P:187-189 ^{0}C, M.W: 594.15, Yield: 68.32 % C H N Analysis: Cal.:C, 81.64; H, 6.15; N, 12.21 Obs.:C, 61.64; H, 6.75; N, 12.61 FTIR (KBr, Cm^{-1}): 3387.38 (-NH) , 1521.16 (C=N), 2928.21 (CH_3, Ar-CH_3), 762.19 (C-Cl).^{1}H NMR (500 MHZ ; DMSO d_6 ; δ ppm): 2.38 (s, 3H, -CH_3), 3.35 (d, 1H, -CH), 2.77 (d, 1H, -CH), 7.57-7.17 (m, 8H, Ar-H),8.05 (s,1H,-NH).



Scheme 1

4. RESULT AND DISCUSSION:

4.1 Microbial evaluation:

All the synthesized compounds (9a-e) were evaluated invitro for antibacterial action counter to gram +ve S.aureus, B. Subtilis and gram –ve Escherichia coli, P.aeruginosa bacterial strains with the dilution concentrations of 100µg/ml by using disc diffusion method DMSO solvent and nutrient agar. After 48 hrs of incubation at 37 ºC, the results were achieved by clear zone and noted after the completion of incubation. The inhibition zones were recorded in 'mm' evaluated invitro likewise for antifungal activity against Aspergillus Niger and Candida albicans fungal strains at the concentration 100µg/ml per disc by paper disc diffusion method using DMSO as solvent. The yeast Candida albicans cultured using a malt extract, glucose yeast extract peptone agar medium (MGYP medium) and for fungi Aspergillus Niger potato dextrose agar medium was used. After 3-7 days of incubation at 30ºC, the diameters of the zones of inhibition were measured. Similarly antifungal evaluation was also carried out in vitro against fungi Aspergillus niger (NCIM 545) and Candida albicans (NCIM 3471) in Hi-Media at conc. of 100 µgm per disc. The zone of inhibition was measured in mm and compared with standard drug Amphotericin-B. The anti-bacterial and anti-fungal results obtained are mentioned in table.

Sr.No	Sample Code	Bacterial Strain				Fungal strain	
		Gram +ve		*Gram –ve*			
		S.Aureus	***B.Subtilis***	***E.coli***	***P.aeurginosa***	***C. Albicans***	***A.niger***
1	**9a**	15.60	8.51	--	--	11.81	--
2	**9b**	7.63	-	--	--	6.79	--
3	**9c**	11.85	11.80	--	--	9.34	--
4	**9d**	8.54	-	--	--	10.9	--
5	**9e**	8.60	6.78	--	--	16.73	--
Std	**Chmpl**	18.17	20.91	22.23	14.18		--
Std	**Amp-B**	--	--	--	--	19.29	7.58

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

Fig:1-Antibacterial activity of compounds against S.Aureus

Fig:2- Antifungal activity of compounds against C.Albicans

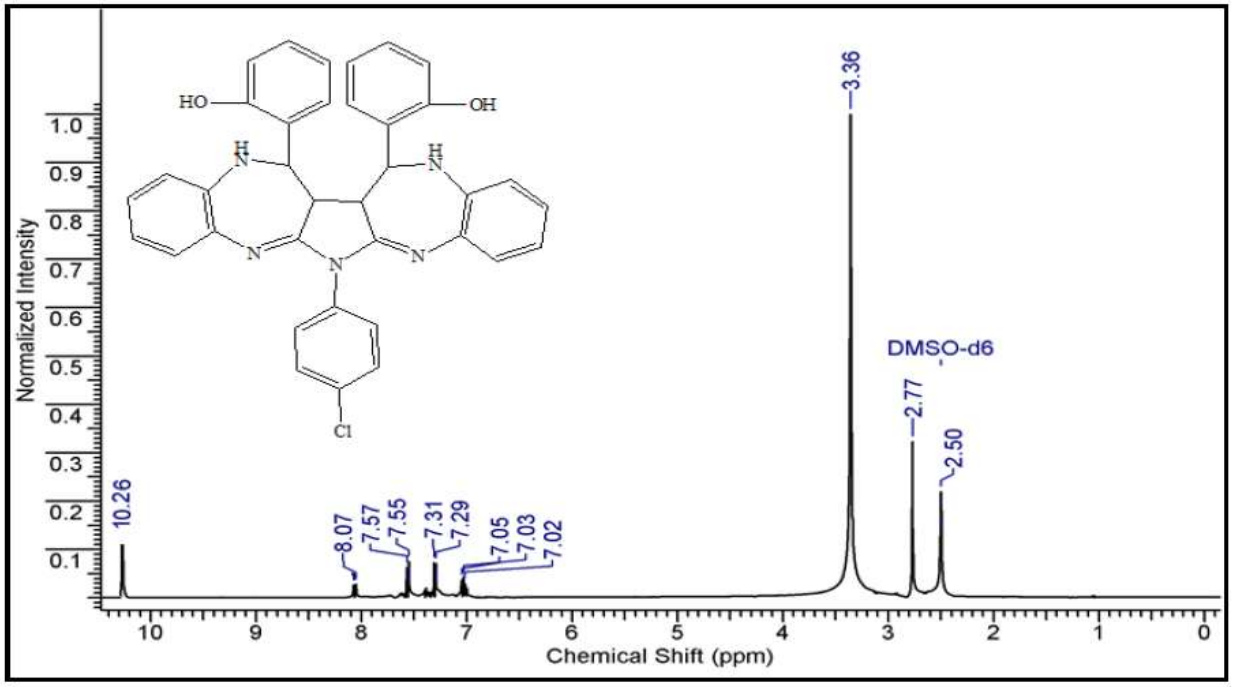


Fig:3- ^{1}H NMR Spectrum of compound 2,2'-(6-(p-chloro)-12,13,13a,13b,14,15-hexahydro-6H-benzo[b] benzo[6',7']azepino[3',4':4,5] pyrrolo[2,3-e]bis[1,4]diazepine-13,14-diyl)diphenol (9a)

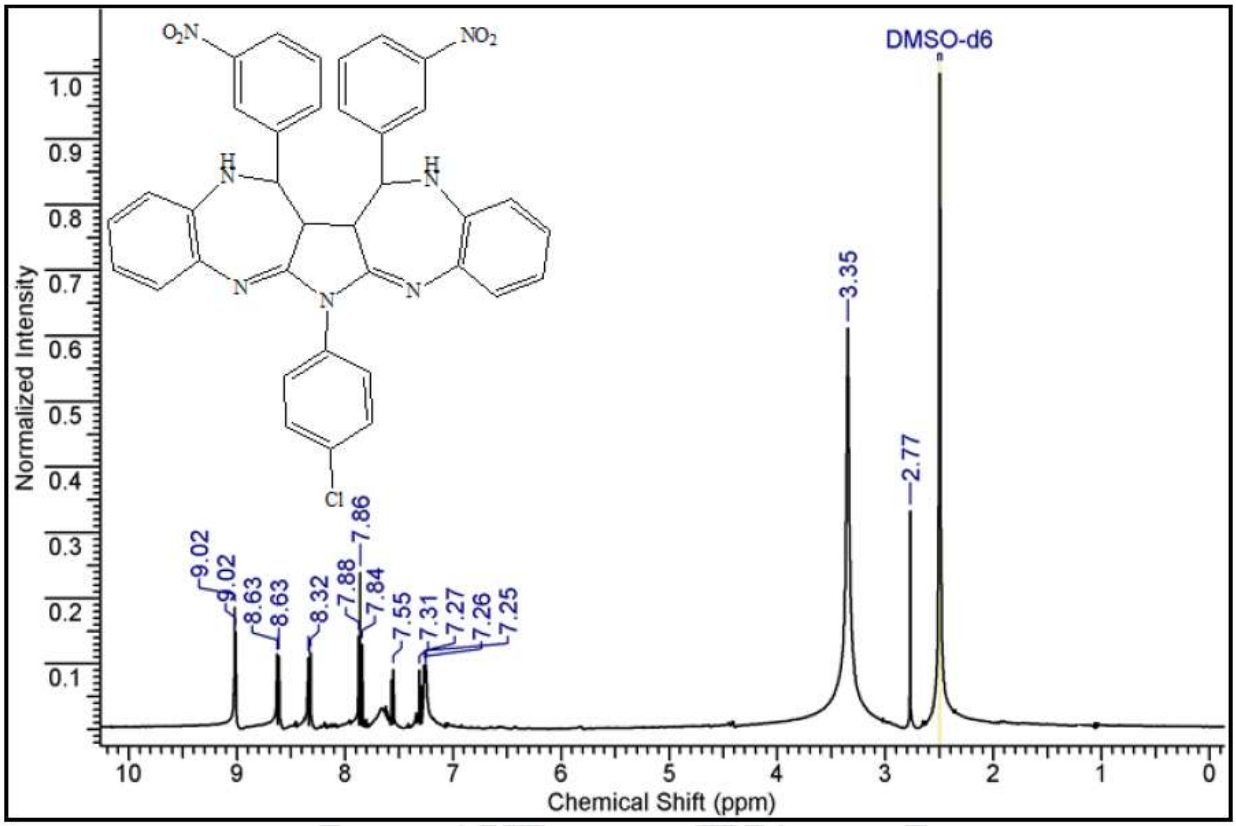


Fig:4- ^{1}H NMR Spectrum of compound 13,14-bis(3-nitrophenyl)-6-(p- chloro)-12,13,13a,13b,14,15-hexahydro-6H-benzo [b] benzo [6',7'] azepino[3',4':4,5]pyrrolo[2,3-e]bis[1,4]diazepine (9b)

5. CONCLUSION

This study concluded that this green synthetic protocol provide simple workup for production of such intricate seven member heterocyclic compounds. The ^{1}H NMR spectrums confirmed that by this synthetic approach benzodiazepine have been easily synthesized in short period of time. All synthesized derivatives showed promising microbial activity against bacterial stain S. aureus and fungal strain C. Albicans. The synthesized bis-benzodiazepine derivatives have greater hope extent in pharmaceutical chemistry for the expansion of new drug molecule.

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