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Synthesis of Isoxazole, Pyrazole, Pyrimidone and Benzodiazepine from Bis-Chalcone

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Abstract

In this work Succinamide bis-chalcone 1 used for preparation of isoxazole 2, pyrazole 3, and pyrimidine 4 and benzodiazepine 5. Synthetic protocol involves microwave assisted reactions of Succinamide chalcone with ammonia derivatives like hydroxylamine hydrochloride, Phenyl hydrazine, Urea and Orthophenylene diamine resulted in the formation of target molecules. The structure of all synthesized compound have been determined by FT IR and ^{1}H NMR Spectral techniques

Key words: Pyrimidine, thiopyrimidine, urea , thiourea, Chalcones

Introduction

Chalcones are ordinary naturally occurring pigments and one of the most essential intermediate in biogenesis of Flavonoide. The general structural formula of chalcone is Ar-CH=CH-CO-Ar and name chalcone was given by Kostanecki and Tambor [1]. The Synthesis of chalcone involves cross Aldol Condensation reaction of suitable benzaldehyde with aldehyde or ketone having α hydrogen atom in presence of acid or base catalyst results in to formation α β unsaturated carbonyl compound due to loss of water molecule. Chalcone derivatives are broadly studied pharmacy because of the encompass antioxidant [2], antimalerial [3], anticancer [4].

The isoxazole is an important class of five member heterocyclic compounds that have paid attention of many research groups which engaged in synthesis and designing new drug molecules for treatment of multifaceted diseases like neurogenerative disorder the isoxazole is act as an Antagonist the function is neurotransmitter receptor [5]. The molecule built-in with isoxazole moiety found to possess Acetylcholinsterase inhibitor activity [6]

The pyrazole molecule is important five member heterocyclic compound of 1, 2 azol family that has antibacterial [7], fungicidal activities [8]. The molecules containing pyrazole nucleus serve as Anti-inflammatory agent [9]

The pyrimidone moiety is also present in vitamin B-9 i.e. folic acid is a valuable dietary supplement and important for healthy development of foetus during pregnancy and it act as Calcium Chanel modulator [10]. The pyrimidine derivatives like Zidovudine (AZT) and Idoxuridine are important class of anti-viral drugs which act as anti-HIV agents [11].

It is Benzos and class of psychoactive drugs containing benzene and diazepine ring system. It is belongs to seven member heterocyclic compounds containing two nitrogen atoms in their chemical structure. It was accidently discovered [12] 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 [13], Arfendazam [14], Lofendazam [15] particularly used in Pharmaco psychiatry.

The benzodiazepine derivatives are commonly known as tranquillizers. It increases the effect of neurotransmitter gamma amino butyric acid GABA at GABA receptor [16] results in the Sedative, hypnotics [17] anti-depressant [18], Anxiolytic [19] and in treatment of epileptic disorder [20]. On account of literature survey reveals that these seven member heterocyclic compounds of benzodiazepine family is most prescribed drug since 1977 globally. By considering such huge applications of heterocyclic compounds reasercher have developed greener method of synthesis from one synthon.

Experimental

Material and method

For synthesis of isoxazole N-phenyl substituted bis-chalcone condensed with hydroxylamine hydrochloride (A.R Grade) contain two nucleophilic site one is nitrogen atom and other is oxygen atom that able to react with α-β unsaturated carbonyl compounds. For formulation of pyrazole bis-chalcone have reacted with hydrazine hydrate (A.R Grade) and for synthesis of pyrimidone the starting precursor reacted with urea and for preparation of benzodiazepine orthophenylene diamine reacted with bis-chalcones all ammonia derivatives used in this synthesis are of high purity and analytical grade.

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 starting precursor succinimide chalcone **1** use in this synthesis was taken from our previously reported method [21]. 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.

General procedure for synthesis of 7-(p-tolyl)-7H-pyrrolo [2, 3-c: 5, 4-c'] isoxazole derivative

The 5 milimoles bis- chalcone **1** taken in presence of 2-2.5 grams of neutral alumina and 10 milimoles of hydroxylamine hydrochloride added then homogenized this mixture with morter. Then the reaction mixture taken in 100 ml borosilicate glass beakers and irradiated in microwave oven at 450 watt power for 4- 6 min thus brown colored fused solid derivatives of isoxazole derivatives **2** obtained and recrystallised it from ethanol

General procedure for Synthesis of 7-(p-tolyl)- [2,3-c:5,4c'] pyrazole derivative

The 5 milimole of chalcones **1** and 10 milimole of hydrazine hydrate in presence of 2 grams of neutral alumina and homogenized in a morter. Then reaction mixture taken in 100 ml borosilicate glass beaker and irradiated it in microwave oven at 450 watt for 2 to 3 min fused solid mixture of compounds **3** obtained recrystalised it from ethanol.

General procedure for Synthesis of 4,5-bis-(p-tolyl)- [2,3-d:5,4-d'] pyrimidine-dione

The 5 milimole of chalcone **1** and 10 milimole of urea taken in presence of 2 gm of neutral alumina then homogenized this mixture in morter and taken in 100 ml borosilicate glass beaker covered it with glass petridish then irradiated reaction mixture in microwave oven at 450 watt power for 5-6 min as solvent free condition thus fused solid pyrimidine-dione **5** obtained and recrystalised it from ethyl acohol.

General procedure for synthesis of 6-(p-tolyl) - pyrrolo [2,3-e] bis[1,4]diazepine

The 5 milimole of chalcone **1** and 10 milimole of Ortho phenylenediamine and 2 gm of neutral alumina then homogenized this mixture in morter and taken in 100 ml borosilicate glass beaker covered with glass petridish then irradiated reaction mixture in microwave oven at 450 watt power for 4-6 min as solvent free condition thus fused solid derivatives of benzodiazepine **5** obtained and recrystalised it from ethyl acohol

2,2'-(7-(p-tolyl)-3,3a,3b,4-tetrahydro-7H-pyrrolo[2,3-c:5,4-c']diisoxazole-3,4-diyl) diphenol

M.F: $C_{25}H_{19}Cl_2N_3O_2$, brown solid, M.P (^{0}C): 112-114, M.W: 464.35, Yield (%): 71.55, C H N Analysis: Cal.:C, 64.67; H, 4.12; N, 9.05. Obs.: C, 64.85; H, 4.332; N, 9.35. FTIR (KBr, cm^{-1}): 1537.88 (C=N), 2937(-CH_3), 713 (C-Cl), 925.83(N-O)., ^{1}H NMR (500 MH_Z ; DMSO d_6 ; δ ppm): 7.29-7.15 (m, 6H, Ar-H), 4.19 (d, 1H, CH isoxazole), 2.89 (d, 1H , CH isoxazole),2.32 (s, 3H, CH_3)

2,2'-(7-(p-tolyl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c:5,4c']dipyrazole-3,4diyl)diphenol

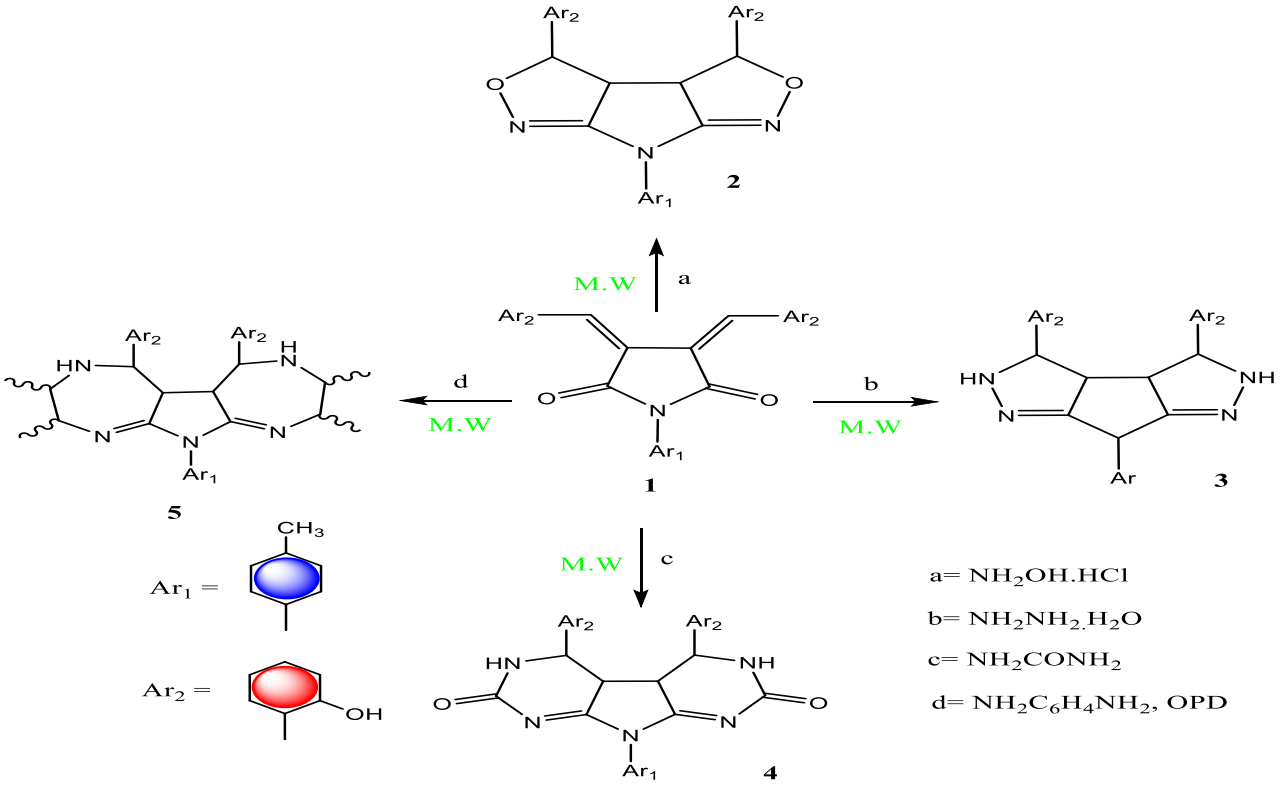
M.F:$C_{25}H_{23}N_5O_2$, Yellow solid, M.P (^{0}C):120-123, M.W: 425.48, Yield (%): 74.28, C H N Analysis: Cal.:C, 70.57; H, 5.45; N, 16.46. Obs.: C, 70.18; H, 5.65; N, 16.76. FTIR (KBr, cm^{-1}): 3460.30 (-OH) , 3292.49 (NH), 2935.66 (Ar-CH_3) , 1496.76 (C=N). ^{1}H NMR (500 MH_Z ; DMSO d_6 ; δ ppm) : 2.34 (s, 3H, CH_3) , 2.50 (d, 1H, -CH Pyrazole) , 3.34 (d, 1H, -CH Pyrazole) , 7.7-6.9 (m , 6H, Ar-H) , 9.0 (s, 1H, -NH Pyrazole), 11.1(s, 1H, -OH). ^{13}C NMR (400 MH_Z ; DMSO d_6 ; δ ppm):20.68 (CH_3), 39.99, 116.50, 118.17, 119.58, 126.84, 129.23,130.08,130.79,133.27,137.55,158.6 1,162.75,176.96(C=N).

4,5-bis(2-hydroxyphenyl)-9-(p-tolyl)-3,4,4a,4b,5,6-hexahydro-2H-pyrrolo[2,3d:5,4-d']dipyrimidine-2,7(9H)-dione

M.F: $C_{27}H_{23}N_5O_4$, Radish yellow solid, M.P(^{0}C): 140-142, M.W: 481.51, Yield (%): 72.12, C H N Analysis: Cal.: C, 67.35; H, 4.81; N, 14.54 Obs.: C, 67.65; H, 4.91; N, 14.84 FTIR (KBr, Cm^{-1}): 3734.19 (-OH), 3456.44 (-NH), 1512.19 (C=N), 1705.07 (C=O), 2918.30 (CH_3, Ar-CH_3). ^{1}H NMR (500 MH_Z; DMSO d_6 ; δ ppm) : 2.34 (s, 3H, -CH_3), 2.76 (d, 1H, -CH, pyrimidone), 3.37 (d,1H, -CH, pyrimidone), 9.56 (s, 1H, OH),7.29-7.11 (m, 6H, Ar-H), 8.41 (s, 1H, -NH, pyrimidone).

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

M.F.: $C_{37}H_{31}N_5O_2$, Reddish Brown Solid, M.P. (^{0}C): 93-95 ^{0}C, M.W: 577.67, Yield (%): 70.32, 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}): 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 d6 ; δ ppm): 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). ^{13}C NMR (400 MH_Z ; DMSO d_6 ; δ ppm): 20.68(-CH_3) 39.89, 112.56, 117.75,118.95,119.09,121.14,126.20, 126.84,129.01,129.23,130.08,131.71,137.55,157.98 (C-N), 176.97 (C=N).



SCHEME 1

Result and Discussion

An isoxazole derivative 2 was carried out by reaction of chalcone with hydroxyl amine hydrochloride in presence of neutral alumina as solid support under microwave irradiation. The IR spectral data of diisoxazole 2 showed stretching frequency at 1537.32 Cm^{-1} indicate the presence of C=N group. The IR Spectrum showed streaching frequency at 1588.48 Cm^{-1} corresponds to C=N group and ^1H NMR spectrum in DMSO d_6 of compound 2 showed peak at 3.34 δ doublet 1H for -CH of isoxazole and 2.76 δ doublet 1H for -CH of isoxazole ring. The structure of compound 2 was characterized by spectral techniques and data found consistent with considered structure of compound.

The reaction of chalcones with hydrazine hydrate underwent ring formation reaction afforded pyrazole derivatives **3** .The IR spectra of this compounds showed stretching frequency at 3292.49 Cm^{-1} indicates the presence of (N-H) group and 1591.33 Cm^{-1} indicates presence of (C=N) group. The ^1H NMR Spectrum in DMSO d_6 showed peak around 2.50 δ doublets for 1H -CH of pyrazole ring, 3.34 δ doublet for 1H -CH pyrazole ring. This data gave evidences of formation of pyrazole ring system.

The Pyrimidone derivative **4** have been synthesized from reaction of chalcone **1** urea irradiated in microwave oven in presence of neutral alumina as solid support. This leads to cyclisation and formation of six member ring. IR spectra of compound **4** showed stretching frequency at 3456.44 cm^{-1} indicates -NH, 1705.07 cm^{-1} for C=O, and 1512.19 cm^{-1} indicates C=N groups this characteristic IR bands give evidence of formation of pyrimidone ring. The ^1H NMR Spectrum in DMSO d_6 of compound **4** appeared a peak around 2.77 δ doublets and 3.36 δ doublet indicates the presence of –CH groups of dipyrimidone ring. This data gave strong evidence of formation of six member dipyrimidone derivatives.

The synthesis of benzodiazepine **5** was carried out from reaction of chalcone **1** with OPD in presence of neutral alumina as solid support under microwave irradiation. IR spectra of compound 5 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 ^{1}H NMR Spectrum compound **5** in DMSO d_6 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 some proton resonance spectrum of synthesized compounds shown here in figures.

Figure: 1:- ^{1}H NMR Spectrum of Isoxazole compound (2)

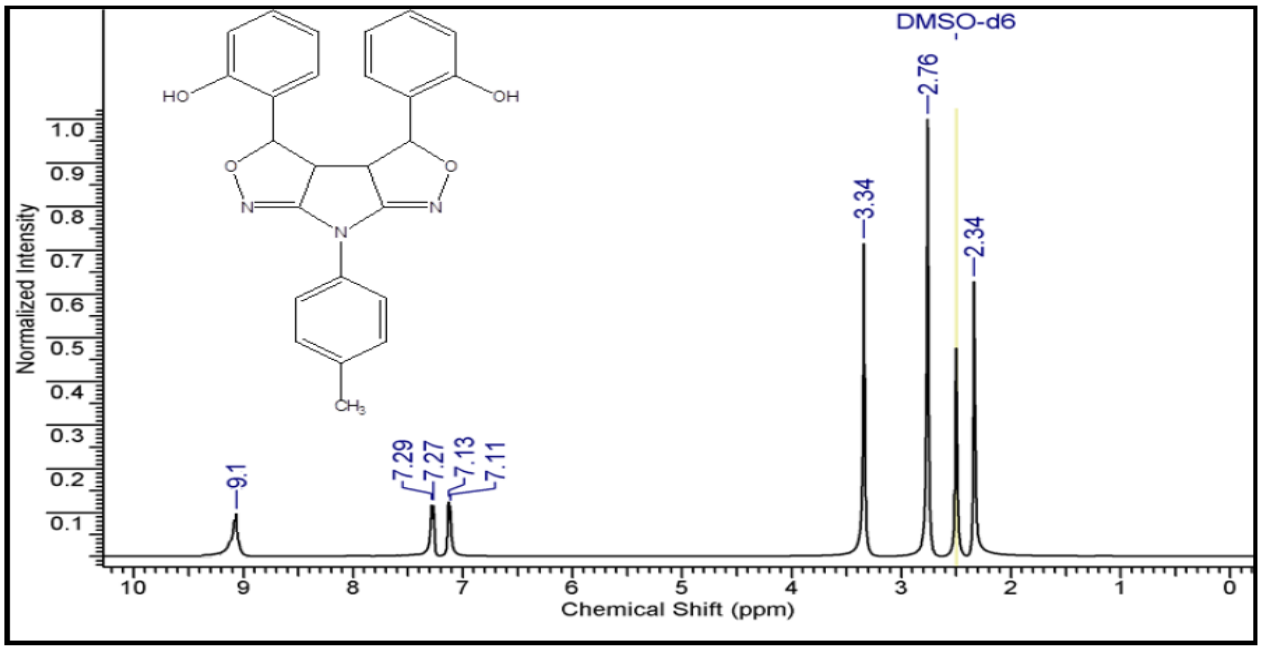
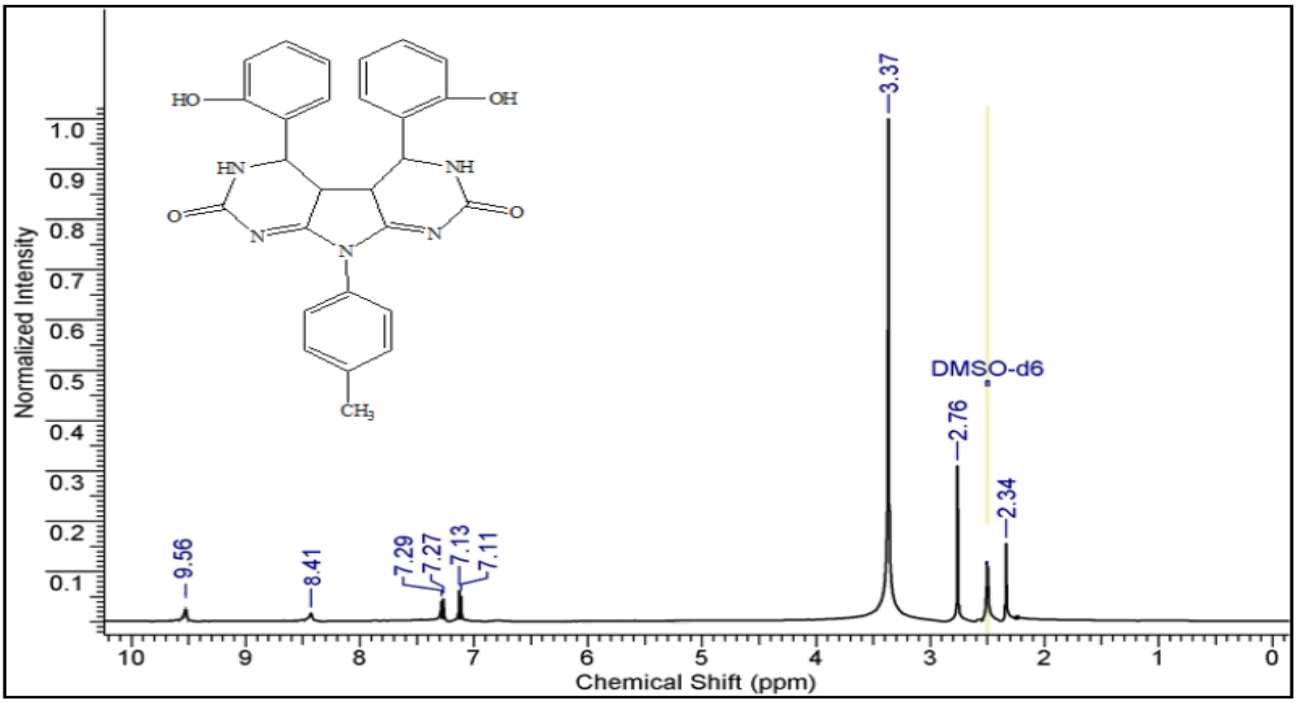


Figure: 2:- ^{1}H NMR Spectrum of Pyrimidone compound (4)



Conclusion

This study concluded that formation of five six and seven member heterocyclic compounds from bis-chalcone have successfully achieved by using this environmental friendly greener synthetic protocol. Spectral analysis suggested that formation of isoxazole, pyrazole, pyrimidone and benzodiazepine molecules have effortlessly formulated with simple workup.

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