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SYNTHESIS AND CHARECTERIZATION OF SOME NOVEL BIS-ISOXAZOLE FROM 3,4-DI ((Z)-BENZYLIDENE)-1-(5-METHYLPYRIDIN-2-YL) PYRROLIDINE-2,5-DIONE UNDER MICROWAVE IRRADIATION

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ABSTRACT
The new series of 3,4-di ((z)-benzylidene)-1-(5-methylpyridin-2-yl) pyrrolidine-2,5-dione (1a-e) was synthesized from the reaction of N-5-methyl pyridine succinimide and substituted benzaldehyde upon microwave irradiation in presence of neutral alumina. The synthesized chalcones (1a-e) underwent ring closer with hydroxyl amine hydrochloride in presence of neutral alumina upon irradiation in microwave afforded bis-isoxazole derivatives (2a-e). All these compounds were characterized by their spectral and elemental analysis.

KEYWORDS: Succinic anhydride, 1-(5-methyl pyridine-2-yl) pyrrolidine-2,5dione, Bis-Chalcone, Bis-isoxazole.

INTRODUCTION
Heterocyclic compounds are broadly occurring in nature and synthetic compounds are crucial to life in various ways. Particularly these heterocyclic compounds are important because of the variety of chemotherapeutic or pharmacological activities. Heterocyclic rings are present in several compounds. The Succinimide moiety of cyclic imide appears as an interesting pioneer for the synthesis of many biologically active heterocyclic compounds. The cyclic imides and its derivatives are important compounds of many drugs. One of the most fundamental objectives of organic and medicinal chemistry is the design and synthesis of molecules having value as human therapeutic agents. Cyclic imides and their derivatives contain an imide ring and the general structure –CO–N(R)–CO–, so they are cross biological membranes in vivo.[1] The succinimide is a part of many active molecules possessing activities such as CNS depressant, analgesic, antitumor, cytostatic, anorectic, nerve conduction blocking, antispasmodic, bacteriostatic, muscle relaxant, hypotensive, antibacterial, antifungal, anti-convulsant and anti-tubercular.

Chalcones are natural products found in various plant species with the general formula Ar-CH=CH-CO-Ar. The two aromatic rings in chalcones are joined by an α, β-unsaturated carbonyl system. Chalcones belongs to an important group of natural compounds with diverse biological activities. Chalcones are vital intermediates during the synthesis of many pharmaceuticals such as flavonoids. Chalcones are generally synthesized with the Claisen-Schmidt condensation between substituted acetophenone and benzaldehyde and catalyzed by base and acid under homogenous conditions. Chalcones have a large range of biological activities and some possible uses are anti-bacterial[1], anti-inflammatory[2], anti-malarial[3], anti-protozoal[4], immunodulatory[5], cytotoxic[6] and their anticancer[7] activities.

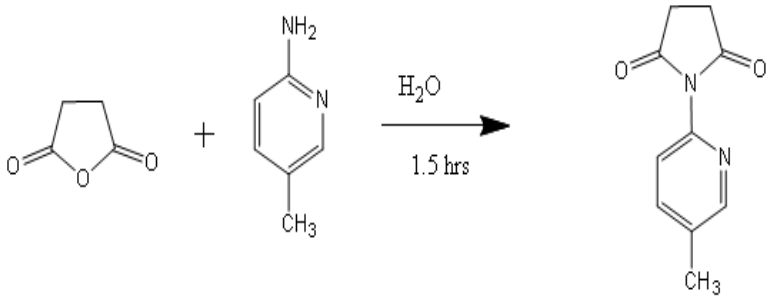
Isoxazole derivatives have played an vital role in the medicinal chemistry. They are reported to acquire a broad spectrum of biological activities such as antimicrobial[1], anti-inflammatory[2], antimalarial[3], anthelmentic[8], analgesic[9], anticancer[7], antiviral[10] and antitubercular[10].

MATERIALS AND METHODS
All the research chemicals were purchased from S. D. Fine and Sigma Aldrich chemicals india Pvt. Ltd. All the melting points of synthesized compounds were determined by open capillaries method and are uncorrected. The reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel plates. The IR spectra of synthesized compounds were taken on FTIR Agilent technologies spectrometer at 4000-650.The ^{1}H NMR were recorded on 500 MHz by Bruker spectrophotometer. The chemical shifts are expressed in ð ppm, using tetra methyl silane (TMS) as internal

reference. The purity of compounds were checked by TLC on pre-coated silica gel plates.

Preparation of 1-(5-methylpyridin-2-yl)pyrrolidine-2,5-dione

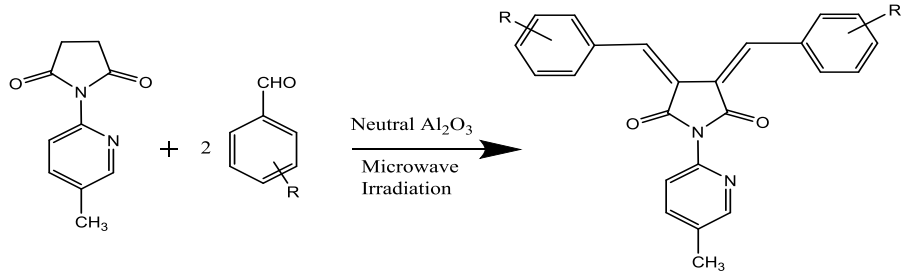
0.01 mole of the properly 5-methyl 2-amino pyridine was dissolved in 20 ml of water and 0.01 mole of succinic anhydride was slowly added. The mixture was heated in oil bath with concurrent distillation of water. The water complete removed, the temperature of the reaction mixture was maintained at 180 ^{0}C about 1.5 hr. the crude product was separated and recrystallized from isopropyl alcohol **(Scheme-I).**



Scheme-I.

Preparation of 3,4-di((Z)-benzylidene)-1-(5-methylpyridin-2-yl)pyrrolidine-2,5-dione (1a-e):

The bis-chalcones (1a-e) derivatives were synthesized by the mixture of 0.01 moles N-5-Methyl pyridine succinimide and 0.02 mole of substituted benzaldehyde in 1 gm of Neutral Al_2O_3 with the assist of microwave irradiations. This mixture is placed in microwave at 750-850 W power for 3-6 min. in solvent free conditions. The bis-chalcone derivatives were separated. The crude product was washed with hot water for elimination of neutral Al_2O_3 **(Scheme-II).**



Scheme-II.

Preparation of 7-(5-methylpyridin-2-yl)-3,4-diphenyl-3,3a,3b,4-tetrahydro-7H-pyrrolo[2,3-c:5,4-c']diisoxazole(2 a-e)

The bis-isoxazole (2 a-e) derivatives were synthesized by 0.1 mole of bis-chalcone (1 a-e) and 0.2 moles hydroxyl amine hydrochloride in 1 gm of neutral Al_2O_3 under microwave supported solvent free condition using 600 W power for 3-5 min. The afforded coloured compounds were recrystallized by ethanol solvents. The purity of synthesized compounds were confirmed by TLC. (Scheme-III).

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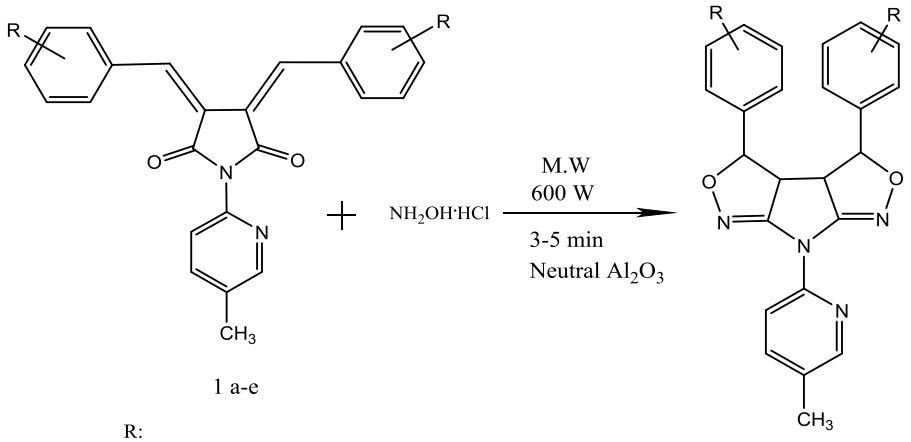

1 a-e

R:
a=4-Br
b=4-CN
c=4-NO_2
d=4-OH
e=2-Br

2 a-e

Scheme-III.

Physiochemical and analytical data for compounds
1-(5-methylpyridin-2-yl) pyrrolidine-2, 5-dione
Molecular formula: $C_{10}H_{10}O_2N_2$, Whitish Solid, **Percent Yield**:81%, **Molecular weight:** 190.20, **Melting point:** 145-147^{0}C, **Elemental Analysis: Calculated-** C. 63.13%,H. 5.29%,N. 14.75%,**Found-** C. 63.28%, H. 5.15%,N. 14.71%; **IR:** 1709, 2448, 2932, 1567, 1594, 2740, 1323, 1316, 3033, 2975 cm^{-1}; **^{1}H NMR (500 MHz, DMSO-d6,δ ppm):** 2.33(S, 3H, CH_3-Pyridine), 2.81(S, 4H, imide), 7.71-8.57(m, 2H, pyridine), 8.35(d, 1H, pyridine).

3,4-bis((Z)-4-bromobenzylidene)-1-(5-methylpyridin-2-yl)pyrrolidine-2,5-dione(1a)
Molecular formula: $C_{24}H_{16}Br_2N_2O_2$, Yellowish solid, **Percent Yield:** 86%, **Molecular weight:**524; **Melting point:**142-146^{0}C, **Elemental Analysis: Calculated**-C. 54.93%, H. 3.10%, N. 5.37%, **Found-** C. 54.73%, H. 3.31%, N. 5.59%. **IR:** 1719, 741, 845, 1333, 1311, 3031, 2962, 2933, 1538, 1609, 2726 cm^{-1}. **^{1}H-NMR (500 MHz, DMSO-d6,δ ppm):** 6.51-8.32 (m, 7H, Ar-H and =C-H), 2.69 (S, 3H, -CH_3).

3,4-bis((Z)-4-cyanobenzylidene)-1-(5-methylpyridin-2-yl)pyrrolidine-2,5-dione(1b)
Molecular formula: $C_{26}H_{16}N_4O_2$, Yellowish solid, **Percent Yield:** 92%, **Molecular weight:** 416, **Melting point:** 123-125^{0}C, **Elemental Analysis: Calculated**-C. 74.92%, H. 3.81%, N. 13.41%, **Found**-C. 74.33%, H. 3.87%, N. 13.66%, **IR:** 1722, 2489, 2215, 1312, 3043, 2957, 2933, 1566, 1612, 2737 cm^{-1}. **^{1}H-NMR (500 MHz, DMSOd^6,δ ppm):** 6.44-8.18 (m, 7H, Ar-H and =C-H), 2.60 (S, 3H, -CH_3).

3,4-bis((Z)-4-nitrobenzylidene)-1-(5-methylpyridin-2-yl)pyrrolidine-2,5-dione(1c)
Molecular formula: $C_{24}H_{16}N_4O_6$, Brownish solid, **Percent Yield**: 89%, **Molecular weight:** 456, **Melting point:** 126-130^{0}C, **Elemental Analysis: Calculated**-C. 63.19%, H. 3.57%, N. 12.32%, **Found**-C. 63.31%, H. 3.21%, N. 12.51%, **IR:** 1725, 1357, 1317, 3046, 2943, 2931, 1597, 2761 cm^{-1}. **^{1}H-NMR (500 MHz, DMSO-d^6,δ ppm):** 7.23-8.26 (m,7H, Ar-H and =C-H), 2.57 (S, 3H, -CH_3).

3,4-bis((Z)-4-hydroxybenzylidene)-1-(5-methylpyridin-2-yl)pyrrolidine-2,5-dione(1d)
Molecular formula: $C_{24}H_{18}N_2O_4$, Orange solid, **Percent Yield**:62%,**Molecular weight:** 398, **Melting point:** 137-141^{0}C, **Elemental Analysis: Calculated**-C. 72.30%, H. 4.51%, N. 7.09%, **Found**-C.72.41%, H. 4.62%, N. 7.21%, **IR:** 1718, 1338, 1313, 3109, 2923, 1557, 1602, 2767 cm^{-1}. **^{1}H-NMR (500 MHz, DMSO-d^6, δ ppm):** 7.19-8.23 (m, 7H, Ar-H and =C-H), 2.43 (S, 3H, -CH_3), 10.09 (S, 1H, OH).

3,4-bis((Z)- 2-bromo benzylidene)-1-(5-methylpyridin-2-yl)pyrrolidine-2,5-dione(1e)
Molecular formula: $C_{24}H_{16}Br_2N_2O_2$, Light Yellow solid, **Percent Yield**: 85%, **Molecular weight:** 524, **Melting point:** 84-86^{0}C, **Elemental Analysis: Calculated**-C. 54.92%, H. 3.09%, N. 5.39%, **Found**- C. 54.42%, H. 3.25%, N. 5.33%, **IR:** 1731, 749, 867, 2498, 1323, 3035, 2961, 2922, 1545, 1610cm^{-1}. **^{1}H-NMR (500 MHz, DMSO-d6, δ ppm):** 6.93-8.51 (m, 7H, Ar-H and =C-H), 2.59 (S, 3H, -CH_3).

3,4-bis(4-bromophenyl)-7-(5-methylpyridin-2-yl)-3,3a,3b,4-tetrahydro-7H-pyrrolo[2,3-c:5,4-c']diisoxazole (2a)
Molecular formula: $C_{24}H_{18}Br_2N_4O_2$, Whitish yellow solid, **Percent yield**: 78 %, **Molecular weight**: 554.24, **Melting point(^{0}C)**: 144-146 ^{0}C, **Elemental analysis: Calculated**- C (52.01%), H (3.27%), N (10.11%), **Found**- C (52.23%), H (3.30%), N (10.31%), **IR**:2970,3059,1633,1072,1316,721,1661,1693 cm^{-1};**1H NMR (500 MHz,DMSO-d^6,δ ppm)**:2.17(S,3H,-

CH_3),6.59-8.1(m,7H,Ar-H),2.37(d,1H,-CH),4.2(d,1H,-CH).

4,4'-(7-(5-methylpyridin-2-yl)-3,3a,3b,4-tetrahydro-7H-pyrrolo[2,3-c:5,4-c']diisoxazole-3,4-diyl)dibenzonitrile (2b)

Molecular formula: $C_{26}H_{18}N_6O_2$, White yellowish solid, **Percent yield**: 78 %, Molecular weight: 446.47, **Melting point(^{0}C)**: 108-112^{0}C,**Elemental analysis**: **Calculated**-C (69.95%),H (4.06%), N(18.82%), **Found**-C (69.23%),H (4.47%), N(18.83%), **IR:** 2965,3000,1645,1088,1330,735,1644,1680 cm^{-1}. **^{1}H NMR (500 MHz, DMSO-d^6,δ ppm)**:2.13 (S,3H,-CH_3),6.35-7.90(m,7H,Ar-H),2.37(d,1H,-CH), 4.9(d,1H,-CH).

7-(5-methylpyridin-2-yl)-3,4-bis(4-nitrophenyl)-3,3a,3b,4-tetrahydro-7H-pyrrolo[2,3-c:5,4-c']diisoxazole(2c)

Molecular formula: $C_{24}H_{18}N_6O_6$, Light yellow solid, **Percent yield**: 80 %, **Molecular weight**: 486.44, **Melting point(^{0}C)**: 82-86^{0}C,**Elemental analysis**: **Calculated**-C (59.26%), H (3.73%), N(17.28%), **Found**-C (59.13%), H (3.46%), N(17.68%), **IR:** 2968,3038,1659,1069,1318,742,1659,1672 cm^{-1} **^{1}H NMR (500 MHz, DMSO-d^6,δ ppm)**:2.21 (S,3H,-CH_3),6.50-8.81(m,7H,Ar-H),2.35(d,1H,-CH), 4.4(d,1H,-CH).

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

Molecular formula: $C_{24}H_{20}N_4O_4$, Brown solid, **Percent yield**:79 %, **Molecular weight**:428.45,**Melting point(^{0}C)**:177-181^{0}C,**Elemental analysis**: **Calculated**-C (67.28%), H(4.71%), N(13.08%), **Found**:C(67.32%), H(4.69%), N(13.21%); **IR**:2962,3029,1646,1067,1318,717,1645,1678 cm^{-1}; **^{1}H NMR (500MHz,DMSO-d^6,δppm)**:2.14(S,3H,-CH_3),6.31-7.90(m,7H,Ar-H),2.35(d,1H,-CH), 5.1(d,1H,-CH),9.3(S,1H,-OH).

3,4-bis(2-bromophenyl)-7-(5-methylpyridin-2-yl)-3,3a,3b,4-tetrahydro-7H-pyrrolo[2,3-c:5,4-c']diisoxazole(2e)

Molecular formula: $C_{24}H_{18}Br_2N_4O_2$, Brown solid, **Percent yield**: 80 %, **Molecular weight**: 554.24, **Melting point(^{0}C)**: 138-142 ^{0}C,**Elemental analysis**: **Calculated**-C (52.01%), H (3.27%), N(10.11%), **Found**-C (52.14%), H (3.48%), N(10.15%), **IR**:2960,3055,1633,1069,1311,719,1668,1687 cm^{-1}; **1H NMR (500 MHz, DMSO-d^6,δ ppm)**:2.16 (S,3H,-CH_3), 6.52-7.95(m,7H,Ar-H),2.35(d,1H,-CH), 4.5(d,1H,-CH).

Physical standard of the synthesized compounds (1a-e, 2a-e)

Compound code	Molecular formula	Molecular weight	% Yield	M.P.(^{0}c)	Colour
-	$C_{10}H_{10}O_2N_2$	190.20	81	145-147	Whitish Solid
1a	$C_{24}H_{16}Br_2N_2O_2$	524	86	142-146	Yellowish solid
1b	$C_{26}H_{16}N_4O_2$	416	92	123-125	Yellowish solid
1c	$C_{24}H_{16}N_4O_6$	456	89	126-130	Brownish solid
1d	$C_{24}H_{18}N_2O_4$	398	62	137-141	orange solid
1e	$C_{24}H_{16}Br_2N_2O_2$	524	85	84-86	Light Yellow solid
2a	$C_{24}H_{18}Br_2N_4O_2$	554.24	78	144-146	Whitish yellow solid
2b	$C_{26}H_{18}N_6O_2$	446.47	78	108-112	White yellowish
2c	$C_{24}H_{18}N_6O_6$	486.44	80	82-86	Light yellow solid
2d	$C_{24}H_{20}N_4O_4$	428.45	79	177-181	Brown solid
2e	$C_{24}H_{18}Br_2N_4O_2$	554.24	80	138-142	Brownish solid

CONCLUSION

Bis-isoxazoles (2a-e) have been synthesized by the treatment of bis-chalcone of succinimide and hydroxyl amine hydrochloride with neutral alumina in microwave supported solvent free method. All the synthesized compounds (1a-e, 2a-e) were characterized by their physical, spectral and elemental analysis. The ecofriendly microwave supported solvent free method can be used for the preparation of different substituted heterocyclic synthones.

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