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Microwave assisted Synthesis and Antimicrobial Activity of Substituted Pyrrolidinone derivatives

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Abstract : A microwave assisted green synthetic methodoloy was developed for the synthesis various substituted pyrrolidinones derivatives by the one-pot three component reaction of aromatic aldehydes, aniline with dialkylbut-2-ynedioate in the presence of *p*-TsOH in water medium. The compounds were screened for their *in vitro* antimicrobial activity against four bacterial organism and two fungal organisms, resulted moderate to good activity with compared to their standard drug.

Keywords: Pyrrolidinone, One-pot three component synthesis, Microwave irradiation, *p*-TsOH.

Introduction:

The 2-pyrrolidinone core is a well-known heterocyclic scaffold which is found in natural products and pharmaceuticals such as piracetam, oxiracetam, aniracetam, nefiracetam, and levetiracetam. They have been interested over the past few years owing to their notable pharmaceutical effects and the promising results in medicinal chemistry, and drug designing[1]. This fascinating scaffold has diverse pharmacological activities including antimicrobial[2], anti-HIV[3], anti-inflammatory[4], anticancer[5] and anticonvulsant[6]. Moreover, microwave assisted organic synthesis reaction condition is promising alternative to conventional methods as these reactions represent clean, effective, safe, economical and eco-friendly procedure[7] and is believed to be a step towards green chemistry. Furthermore, MCRs strategy attained greater value, as the target molecules are often obtained in a single step rather than multiple steps which minimize the tedious work-up procedures and environmental hazardous wastes. In addition, many procedures for the preparation of substituted pyrrolidinone have been reported and also their various reactions offer great scope in the field of medicinal chemistry[8-14]. However, many of the methods reported above suffer from one or more disadvantages such as the use of

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expensive moisture sensitive metallic reagents, longer reaction times, tedious separation procedures, and large amount of catalyst loadings which in turn results in the generation of huge amount of metal wastes into the environment. Owing to the above facts, our endeavor to decrease the reaction time, increase the yields, and develop an eco-friendly methodology for microwave assisted one-pot synthesis of pyrrolidinones derivatives by the reaction of aromatic aldehydes, aniline with dialkyl but-2-ynedioate in the presence of *p*-TsOH in water medium. (**Scheme-1** and **Table-1**).

Scheme-1: Synthesis of polysubstituted pyrrolidinones

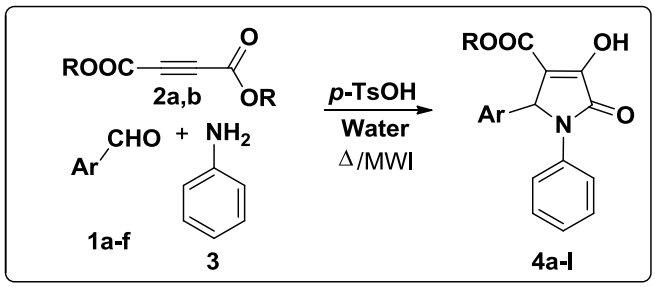

Table-1: Physical data of polysubstituted-pyrrolidinones:

Entry	Ar	R	Conventional heating		MWI	
			Reaction time	Yield	Reaction time	Yield
4a	Phenyl	Methyl	60	84	6	96
4b	4-methyl phenyl	Methyl	55	85	6	95
4c	4-methoxy phenyl	Methyl	55	82	6	95
4d	3,4-dimethoxy phenyl	Methyl	60	80	7	94
4e	2,4,6-trimethoxy phenyl	Methyl	60	80	7	94
4f	4-Chloro phenyl	Methyl	55	83	6	96
4g	Phenyl	Ethyl	60	85	6	97
4h	4-methyl phenyl	Ethyl	60	85	6	95
4i	4-methoxy phenyl	Ethyl	60	83	6	95
4j	3,4-dimethoxy phenyl	Ethyl	60	82	7	94
4k	2,4,6-trimethoxy phenyl	Ethyl	60	82	7	94
4l	4-Chloro phenyl	Ethyl	60	84	6	95

Result and discussion:

In order to study and achieve the optimized reaction, benzaldehyde, aniline and dialkylacetylene carboxylate were chosen as the model reactants and their one-pot reaction was studied at different reaction conditions. Initially, the experiment was carried out under conventional heating methods in different reaction conditions afford lower yields. Then, the model reaction was carried out under microwave irradiation at 360W in the presence of different catalysts. Surprisingly, improved yields were obtained under MWI in the presence of *p*-TsOH. Encouraged by utility of *p*-TsOH under MWI, we have screened the reaction condition under different solvent system, maximum yields were obtained water medium (Table-2). Structures of the pyrrolidinone derivatives were successfully established by using different analytical data**.**

Table-2: The effect of the solvent on the synthesis of polysubstituted-pyrrolidinones:

Entry	Catalyst	Solvent	Yield (%)
1	*p*-TsOH	MeOH	62
2	*p*-TsOH	EtOH	64
3	*p*-TsOH	THF	58
4	*p*-TsOH	TEA	45
5	*p*-TsOH	Acetic acid	70
6	*p*-TsOH	DMSO	44
7	*p*-TsOH (1 mol)	Water	80
8	*p*-TsOH (2 mol)	Water	87
9	***p*-TsOH (3 mol)**	**Water**	**96**
10	*p*-TsOH (4 mol)	Water	95

Antimicrobial activity:-

Antibacterial activity: The compounds **(4a-l)** were tested thier *in vitro* antibacterial activity against four bacterial organisms such as *B. faecalis, S. aeureus, K. pneumonia and E. coli*, ampicillin used as standard drug. The activity was determined using cup plate agar diffusion method by measuring the zone of inhibition in mm at the concentration 100µg/ml in DMSO. The synthesized compounds **4e**, **4f** and **4k** showed good activity against the tested bacterial organisms and the remaining compounds showed low to moderate activity against the tested organisms compared with standard drug Ampicilin.

Antifungal activity: The compounds **(4a-l)** were tested thier *in vitro* antifungal activity against *Aspergillus niger* and *Candida metapsilosis* using grieseofulvin as standard drug. The activity was determined using cup plate agar diffusion method by measuring the zone of inhibition in mm at the concentration 500µg/ml in DMSO. The synthesized compounds **4a**, **4b, 4g** and **4l** showed good activity against tested fungal organisms and the reaming synthesized compound showed low to moderate antifungal activity.

Experimental:

The purity of the compounds was checked by TLC using precoated silica gel plates 60_{254}(Merck). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II 400 MHz spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer.

General procedure for the synthesis of polysubstituted-pyrrolidinones (4a-l):

To a mixture of arylaldehydes **(1a-f)** (1 mmol), dialkylbut-2-ynedioate **(2a,b)** (1 mmol), aniline **(3)** (1 mmol), and *p*-TsOH (3 mmol) in water (2 ml)was taken into a quartz tube, inserted into a screw-capped Teflon vial and then subjected to microwave irradiation at 320 W for 6-7 min. Reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice cold water. The product was extracted with ethyl acetate, washed with water and brine solution and the organic solvent concentrated under reduced pressure. The product purified by column chromatography using n-hexane: ethyl acetate to afford pure polysubstituted pyrrolidinones **(4a-l)**.

Spectal Data:

Methyl 4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4a): ^{1}H NMR (400 MHz) δ: 3.52 (s, 3H, OCH_3), 5.91 (s, 1H, CH), 7.08-7.11 (t, 1H, ArH), 7.16-7.19 (m, 3H, ArH), 7.31-7.35 (m, 2H,OH), 7.41-7.45 (m, 4H, ArH), 8.11 (brs, 1H, OH); ^{13}C NMR (100 MHz) δ: 50.9, 63.0, 109.1, 122.7, 124.6, 125.5, 127.4, 127.9, 128.6, 136.3, 138.4, 141.8, 163.9, 164.4; ESI-MS: 310 $(M+H)^{+}$.

Methyl 4-hydroxy-5-oxo-1-phenyl-2-(*p*-tolyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4b): IR (KBr): 3438, 2110, 1708 and 1650 cm^{-1}; ^{1}H NMR (400 MHz) δ: 2.25 (s, 3H, CH_3), 3.52 (s, 3H, OCH_3), 5.78 (s, 1H), 7.04-7.09 (m, 3H, ArH), 7.22-7.32 (m, 3H, ArH), 7.45-7.47 (d, 2H, ArH), 8.10 (brs, 1H, OH); ^{13}C NMR (100 MHz) δ: 21.3, 51.5, 63.0, 110.4, 123.8, 124.4, 127.5, 128.7, 129.6, 131.2, 133.2, 135.2, 137.2, 138.3, 163.9, 164.8;

ESI-MS: 324 $(M+H)^+$.**Methyl 4-hydroxy-2-(4-methoxyphenyl)-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4c):** ^{1}H NMR (400 MHz) δ: 3.52 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 5.77 (s, 1H, CH), 6.74-6.77 (d, 2H, ArH), 7.06-7.08 (m, 1H, ArH), 7.24-7.36 (m, 4H, ArH), 7.43-7.45 (d, ArH), 8.01 (brs, 1H, OH); ^{13}C NMR (100 MHz) δ: 51.0, 55.0, 62.6, 109.4, 113.7, 122.7, 124.6, 125.6, 128.3, 128.7, 136.3, 138.5, 141.7, 159.1, 163.9, 164.6; ESI-MS: 340 $(M+H)^+$.

Methyl 2-(3,4-dimethoxyphenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4d): ^{1}H NMR (400 MHz) δ: 3.53 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 5.76 (s, 1H, CH), 6.71-6.73 (d, 1H, ArH), 6.84-6.89 (t, 1H, ArH), 7.09-7.23 (m, 4H, ArH), 7.42-7.44 (d, 2H, ArH), 8.13 (brs, 1H, OH); ^{13}C NMR (100 MHz) δ: 51.1, 55.6, 55.8, 63.0, 109.7, 110.6, 120.5, 122.6, 124.6, 125.8, 128.3, 128.7, 136.3, 138.5, 141.6, 152.0, 163.9, 164.6; ESI-MS: 370 $(M+H)^+$.

Methyl 2-(2,4,6-trimethoxyphenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4e): ^{1}H NMR (400 MHz) δ: 3.56 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.77 (6H, s, 2 X OCH_3), 5.75 (s, 1H, CH), 6.64 (s, 2H, ArH), 7.10-7.18 (m, 3H, ArH), 7.43-7.45 (d, 2H, ArH), 8.17 (brs, 1H, OH); ^{13}C NMR (100 MHz) δ: 51.5, 55.6, 55.8, 63.2, 104.2, 110.1, 124.1, 126.0, 127.5, 128.4, 136.7, 138.3, 141.5,152.5, 153.0, 163.7, 164.3; ESI-MS: 400 $(M+H)^+$.

Methyl 2-(4-chlorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4f): ^{1}H NMR (400 MHz) δ: 3.57 (3H, s, OCH_3), 5.71 (s, 1H), 6.84-6.86 (d, 2H, ArH), 7.08-7.13 (m, 2H, ArH), 7.19-7.32 (m, 4H, ArH), 8.16 (brs, 1H, OH); ^{13}C NMR (100 MHz) δ: 51.5, 63.0, 110.4, 123.8, 124.4, 127.5, 128.7, 129.6, 131.2, 133.2, 135.2, 137.2, 142.1, 163.9, 164.8; ESI-MS: 344 $(M+H)^+$.

Ethyl 4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4g): ^{1}H NMR (400 MHz) δ: 1.03-1.07 (t, 3H, CH_3), 4.00-4.07 (q, 3H, CH_3), 5.71 (s, 1H, CH), 7.06-7.42 (m, 10H, ArH), 8.20 (brs, 1H, OH); ^{13}C NMR (100 MHz) δ: 13.8, 60.3, 62.4, 110.5, 123.6, 127.9, 128.4, 128.8, 129.8, 130.8, 132.9, 134.9, 137.0, 141.5, 163.6, 164.2; ESI-MS: 324 $(M+H)^+$.

Ethyl 4-hydroxy-5-oxo-1-phenyl-2-(p-tolyl)-2,5-dihydro-1H-pyrrole-3-carboxylate (4h): IR (KBr): 3400, 2088, 1707 and 1644 cm^{-1}; ^{1}H NMR (400 MHz) δ: 0.99-1.02 (t, 3H, CH_3), 2.17 (s, 3H, CH_3), 3.99-4.01 (q, 3H, CH_3), 5.78 (s, 1H, CH), 7.02-7.18 (m, 6H, ArH), 7.46-7.48 (d, ArH), 8.12 (bs, 1H, OH); ^{13}C NMR (100 MHz) δ: 13.6, 21.0, 60.0, 62.8, 109.9, 122.4, 125.4, 127.4, 128.6, 129.0, 133.4, 136.4, 138.7, 141.1, 164.0, 164.2; ESI-MS: 348 $(M+H)^+$.

Ethyl 4-hydroxy-2-(4-methoxyphenyl)-5-oxo-1-(*p*-tolyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4i): ^{1}H NMR (400 MHz) δ: 1.03-1.07 (t, 3H, CH_3), 3.78 (3H, s, OCH_3), 4.00-4.07 (q, 3H, CH_3), 5.71 (s, 1H, CH), 6.77-6.80 (d, 2H, ArH), 7.19-7.28 (m, 4H, ArH), 7.40-7.42 (d, 2H, ArH), 8.20 (brs, 1H, OH); ^{13}C NMR (100 MHz) δ:14.3, 56.3, 60.9, 63.6, 104.8, 109.3, 123.1, 125.0, 126.1, 129.0, 132.3, 136.6, 138.7, 142.0, 153.3, 164.2, 164.8; ESI-MS: 354 $(M+H)^+$.

Ethyl 2-(3,4-dimethoxyphenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4j): ^{1}H NMR (400 MHz) δ: 1.02-1.07 (t, 3H, CH_3), 3.72 (6H, s, 2 X OCH_3), 4.00-4.06 (q, 3H, CH_3), 5.72 (s, 1H, CH), 6.98-7.25 (m, 5H, ArH), 7.42-7.44 (d, 2H, ArH), 8.21 (brs, 1H, OH); ^{13}C NMR (100 MHz) δ: 13.8, 55.3, 56.0, 60.7, 63.0, 109.5, 110.2, 121.1, 122.3, 125.0, 126.7, 128.5, 128.8, 132.6, 136.3, 138.0, 141.2, 152.0, 153.1, 163.7, 164.4; ESI-MS: 414 $(M+H)^+$.

Ethyl 4-hydroxy-5-oxo-1-phenyl-2-(2,4,6-trimethoxyphenyl)-2,5-dihydro-1H-pyrrole-3-carboxylate (4k): ^{1}H NMR (400 MHz) δ: 1.08-1.13 (t, 3H, CH_3), 3.78 (9H, s, 3 X OCH_3), 4.05-4.12 (q, 3H, CH_3), 5.70 (s, 1H, CH), 6.40 (s, 2H, Ar-H), 7.09-7.12 (d, 2H, ArH), 7.41-7.44 (d, 2H, ArH), 8.26 (brs, 1H, OH); ^{13}C NMR (100 MHz) δ:14.1, 55.2, 56.3, 60.6, 63.2, 98.6, 107.8, 122.5, 124.9, 125.7, 128.3, 132.3, 137.1, 142.0, 151.4, 153.3, 162.7, 164.1; ESI-MS: 414 $(M+H)^+$.

Fthyl 2-(4-chlorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4l): ^{1}H NMR (400 MHz) δ: 0.99-1.03 (t, 3H, CH_3), 3.97-4.04 (q, 3H, CH_3), 5.70 (s, 1H, CH), 7.04-7.33 (m, 7H, ArH), 7.42-7.46 (d, 2H, ArH), 8.20 (brs, 1H, OH); ^{13}C NMR (100 MHz) δ: 13.9, 60.4, 62.8, 110.2, 122.6, 124.0, 126.3, 127.1, 128.3, 129.3, 133.2, 135.2, 137.5, 141.9, 162.7, 164.5; ESI-MS: 358 $(M+H)^+$.

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References:

1. Hosseinzadeh Z., Ramazani A., Hosseinzadeh K., Razzaghi-Asl N., Gouranlou F., An overview on chemistry and biological importance of pyrrolidinone. Current Org. Syn., 2018, 15, 166-178.
2. Gein V.L., Armisheva M.N., Rassudikhina N.A., Vakhrin M.I., Voronina E.V., Synthesis and antimicrobial activity of 1-(4-hydroxyphenyl)-4-acyl-5-aryl-3-hydroxy-3-pyrrolin-2-ones. Pharm. Chem. J., 2011, 45, 162-164.
3. Ma K., Wang P., Fu W., Wan X., Zhou L., Chu Y., et al., Rational design of 2-pyrrolinones as inhibitors of HIV-1 integrase. Bioorg. Med. Chem. Lett., 2011, 21, 6724-6727.
4. Lauro G, Cantone V, Potenza M, Fischer K, Koeberle A, Werz O, Riccio R, Bifulco G., Med chem. comm. 2018 Nov 20;9(12):2028-2036
5. Geng Y., Wang X., Yang L., Sun H., Wang Y., Zhao Y., et al., Antitumor activity of a 5-hydroxy-1H-Pyrrol-2-(5H)-one-based synthetic small molecule in vitro and in vivo PLoS One, 2015, 10, 1-15.
6. Kamiński K, Zagaja M, Łuszczki JJ, Rapacz A, Andres-Mach M, Latacz G, Kieć-Kononowicz K., Design, synthesis, and anticonvulsant activity of new hybrid compounds derived from 2-(2,5-dioxopyrrolidin-1-yl)propanamides and 2-(2,5-dioxopyrrolidin-1-yl)butanamides. J Med Chem. 2015 Jul 9;58(13):5274-86
7. Santagada V., Frecentese F., Perissutti E., Fiorino F., Severino B., Caliendo G., Microwave assisted synthesis: A new technology in drug discovery. Mini-Rev. Med. Chem., 2009, 9, 340-358.
8. Franco M.S.F., Casagrande G.A., Raminelli C., Moura S., Rossatto M., Quina F.H., et al., Ultrasound-promoted environmentally friendly synthesis of 5-(3,3,3-trifluoro-2-oxopropylidene) pyrrolidin-2-ones. Synth. Commun., 2015, 45, 692-701.
9. Choi D.R., Lee K.Y., Chung Y.S., Joo J.E., Kim Y.H., Oh C.Y., et al., Diastereoselective synthesis of polysubstituted pyrrolidinone as a key intermediate for the anticancer agents by palladium(II)-catalyzed carboxylation. Arch. Pharm. Res., 2005, 28, 151-158.
10. Overman L.E., Remarchuk T.P., Catalytic asymmetric intramolecular aminopalladation: Enantioselective synthesis of vinyl-substituted 2-oxazolidinones, 2-imidazolidinones, and 2-pyrrolidinones. J. Am. Chem. Soc., 2002, 124, 12-13.
11. Singh V., Saxena R., Batra S., Simple and efficient synthesis of substituted 2-pyrrolidinones, 2-pyrrolones, and pyrrolidines from enaminones of Baylis−Hillman derivatives of 3-isoxazolecarbaldehydes. J. Org. Chem., 2005, 70, 353-356.
12. Sarkar R., Mukhopadhyay C., Admicellar catalysis in multicomponent synthesis of polysubstituted pyrrolidinones. Tetrahedron Lett., 2013, 54, 3706-3711.
13. Sun J., Wu Q., Xia E.Y., Yan C.G., Molecular diversity of three- component reactions of aromatic aldehydes, arylamines, and acetylenedicarboxylates. Eur. J. Org. Chem., 2011, 2011, 2981-2986.
14. Zhu Q., Jiang H., Li J., Liu S., Xia C., Zhang M., Concise and versatile multicomponent synthesis of multisubstituted polyfunctional dihydropyrroles. J. Comb. Chem., 2009, 11, 685-696.

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