Microwave Assisted Synthesis of New 1-{2, 4-Dihydroxy-5-[5-(aryl)-1-pyridine/pyrimidine-4-carbonyl]-4, 5-dihydro-1*H*-pyrazol-3-yl]-phenyl}-3-(aryl)-propenones and their Antibacterial Activity

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Abstract: A series of 1-{2, 4-dihydroxy-5-[5-(aryl)-1-pyridine/pyrimidine-4-carbonyl]-4, 5-dihydro-1*H*-pyrazol-3-yl]-phenyl}-3-(aryl)-propenones (2a-h) have been synthesized from 1-[2,4-dihydroxy-5-(aryl acryloyl)phenyl]-aryl propenones (**1a-h**) by Micheal addition with isoniazide/pyrazinic acid hydrazide under microwave irradiation and classical heating. The synthesized compounds were characterized by IR, ¹H-NMR, ¹³C-NMR and Mass spectral data. All the compounds were screened for their Antibacterial activity.

Keywords: Microwave assisted synthesis, Isoniazide, Pyrazinic acid hydrazide, Pyrazolines and Antibacterial activity.

Introduction

Driven by the increased demand of pyrazolines exhibiting biological activities like anti-inflammatory¹⁻³, antidepressant⁴, antimicrobial⁵⁻¹⁴, antitumor¹⁵⁻¹⁷, antitubercular¹⁸⁻¹⁹ drug activity as a stable fragment in biological moieties to synthesize new heterocyclic compounds which is a major topic in contemporary bioorganic synthesis. Microwave heating has proved as a powerful tool for organic synthesis and has found application in selective absorption of microwave energy for rapid reaction rate²⁰, ecofriendly synthesis of carbon-heteroatom, carbon-carbon bond formation²¹⁻²² in organic compounds.

In continuation of our work on microwave assisted synthesis of heterocycles²³⁻²⁶ and the synthetic utility of microwave induced organic reaction enhancement (MORE) chemistry

and keeping in view the biological activity prominence of isoniazide and pyrazinic acid hydrazide²⁷⁻²⁹ herein we wish to report microwave assisted synthesis of new “1-{2,4-dihydroxy-5-[5-(aryl)-1-pyridine/pyrimidine-4-carbonyl]-4,5-dihydro-1*H*-pyrazol-3-yl]-phenyl}-3-(aryl)-propenones” (**2a-h**) with comparative analysis through classical approach. 1, 3, 5-trisubstituted pyrazolines have been synthesized by Michael addition of 1-[2,4-dihydroxy-5-(aryl acryloyl)phenyl]-aryl propenones(**1a-h**) with isoniazide/pyrazinic acid hydrazide in catalytic amount of glacial acetic acid through conventional and non-conventional approach. The structural assignment of the title compounds (**2a-h**) has been made on the basis of IR, ¹H NMR, ¹³C NMR and Mass spectral studies.

Experimental

All the melting points were determined on open capillary tubes and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer spectrum FT-IR spectrophotometer. NMR spectra were recorded on ACF 200 Bruker. Mass spectra were recorded on LCMS-2010A Shimadzu Japan. Microwave reactions were carried out in a Multisynth series microwave system (Milestone). Reactions were monitored by using TLC Silica gel G plates (Merck).

Synthetic Protocol - Microwave irradiation method: Method A

*Synthetic Protocol for the Synthesis of 1-{2, 4-dihydroxy-5-[5-(aryl)-1-pyridine/pyrimidine-4-carbonyl]-4, 5 dihydro-1*H*-pyrazol-3-yl]-phenyl}-3-(aryl)-propenones (**2a-h**)*

A mixture of **1** (0.01 mol) and isoniazide/pyrazinic acid hydrazide (0.02 mol) in catalytic amount of glacial acetic acid was subjected to microwave irradiation for appropriate time given in the Table 1. The progress of the reaction was monitored with TLC. The reaction mixture was poured in ice water, resulting crude residue was dried and recrystallized from chloroform to give yellow solid crystals.

*Synthesis of 1-{2, 4-dihydroxy-5-[5-(aryl)-1-pyridine/pyrimidine-4-carbonyl]-4, 5 dihydro-1*H*-pyrazol-3-yl]-phenyl}-3-(aryl)-propenones (**2a-h**)*

Conventional method- Method B

A mixture of **1** (0.01 mol) and isoniazide/pyrazinic acid hydrazide (0.02 mol) in glacial acetic acid (20 mL) was refluxed for appropriate time given in the Table 1. The progress of the reaction was monitored with TLC. The reaction mixture was poured in ice water, resulting crude was dried and recrystallised from chloroform to give yellow solid crystals.

*1-{2, 4-Dihydroxy-5-[5-(anisyl)-1-pyridine-4-carbonyl]-4,5-dihydro-1*H*-pyrazol-3-yl]-phenyl}-3-(anisyl)-propenone (**2a**)*

IR (KBr)(cm⁻¹): 1695 (>C=O), 1636 (>C=O). ¹H NMR (CDCl₃, δ): 2.90 (dd, 1H, C_{4''}-H), 3.13 (dd, 1H, C_{4''}-H), 3.84 (s, 3H, -OCH₃), 3.88 (s, 3H, -OCH₃), 5.50 (dd, 1H, C_{5''}-H), 6.55 (s, 1H, C₃-H), 6.97 (d, 4H, Ar-H), 7.26 (s, 1H, C₂-H), 7.40 (d, 4H, Ar-H), 7.56 (d, 2H, Ar-H), 7.68 (s, 2H, C_{2''}, C_{6''}), 7.93 (d, 1H, C₃-H), 8.63(s,1H,C₆-H), 13.73 (s,1H, -OH): ¹³C NMR (CDCl₃, δ): 29.76, 44.05, 55.48, 55.57, 79.78, 105.3, 114.06, 114.40, 114.67, 116.17, 117.07, 127.25, 127.86, 130.19, 130.97, 131.21, 146.15, 160.24, 162.40, 166.70, 170.09, 190.40, 192.77: MS: *m/z* =549 (M⁺).

3-(2-Chloro-phenyl)-1-{5-[5-(2-chloro-phenyl)-1-(pyridine-4-carbonyl)-4,5-dihydro-1H-pyrazol-3-yl]-2,4-dihydroxy-phenyl}-propenone (2b)

IR (KBr)(cm⁻¹): 1690(>C=O), 1638(>C=O). ¹H NMR (CDCl₃, δ): 2.92 (dd, 1H, C_{4''}-H), 3.13 (dd, 1H, C_{4''}-H), 5.85 (dd, 1H, C_{5''}-H), 6.62 (s, 1H, C₃-H), 7.35-7.55 (m, 10H, Ar-H), 7.77-7.78 (m, 3H, C₂-H, & C_{2'''}, C_{6'''}-H), 8.40 (d, 1H, C₃-H), 8.65 (s, 1H, C₆-H), 13.52(s, 1H, -OH); MS: *m/z* = 557 (M⁺).

3-(4-Chloro-phenyl)-1-{5-[5-(4-chloro-phenyl)-1-(pyridine-4-carbonyl)-4,5-dihydro-1H-pyrazol-3-yl]-2,4-dihydroxy-phenyl}-propenone (2c)

IR (KBr) (cm⁻¹): 1690 (>C=O), 1635 (>C=O). ¹H NMR (CDCl₃, δ): 2.95 (dd, 1H, C_{4''}-H), 3.05 (d, 1H, C_{4''}-H), 5.52 (dd, 1H, C_{5''}-H), 7.25 (s, 1H, C₃-H), 7.35-7.50 (m, 9H, C₂-H & Ar-H), 7.60-7.80 (m, 4H, C_{2'''}, C_{3'''}, C_{5'''}, C_{6'''}-H), 7.90 (d, 1H, C₃-H), 8.58 (s, 1H, C₆-H), 13.42(s, 1H, -OH); MS: *m/z* = 557 (M⁺).

1-[2,4-Dihydroxy-5-[1-(pyridine-4-carbonyl)-5-p-tolyl-4,5-dihydro-1H-pyrazol-3-yl]-phenyl]-3-p-tolyl-propenone (2d)

IR (KBr) (cm⁻¹): 1667(>C=O), 1634(>C=O). ¹H NMR (CDCl₃, δ): 2.39 (s, 3H, -CH₃), 2.42 (s, 3H, -CH₃), 2.92 (dd, 1H, C_{4''}-H), 3.10 (dd, 1H, C_{4''}-H), 5.50 (dd, 1H, C_{5''}-H), 6.57 (s, 1H, C₃-H), 7.25-7.46 (m, 9H, C₂-H Ar-H), 7.59-7.69 (m, 4H, C_{2'''}, C_{6'''}-H, Ar-H), 7.95 (d, 1H, C₃-H), 8.63 (s, 1H, C₆-H), 13.65 (s, 1H, -OH), 13.67(s, 1H, -OH). ¹³C-NMR (CDCl₃, δ): 21.27, 21.69, 44.08, 79.93, 105.3, 114.0, 116.1, 116.5, 118.4, 126.2, 128.9, 129.9, 129.6, 129.9, 131.3, 131.7, 134.0, 135.1, 139.0, 142.0, 146.3, 146.1, 166.7, 170.0, 176.5, 190.3, 192.8. MS: *m/z* = 518 (M+H)⁺.

3-(2,4-Dimethoxy-3-methyl-phenyl)-1-{5-[5-(2,4-dimethoxy-3-methyl-phenyl)-1-(pyridine-4-carbonyl)-4,5-dihydro-1-pyrazol-3-yl]-2,4-dihydroxy-phenyl}-propenone (2e)

IR (KBr) (cm⁻¹): 1684(>C=O), 1637(>C=O). ¹H NMR (CDCl₃, δ): 2.14 (s, 3H, CH₃), 2.18 (s, 3H, CH₃), 2.76 (dd, 1H, C_{4''}-H), 3.12 (dd, 1H, C_{4''}-H), 3.79 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 3.92 (s, 3H, OCH₃), 5.74 (dd, 1H, C_{5''}-H), 6.49 (s, 1H, C₃-H), 6.75 (d, 2H, Ar-H), 7.25 (d, 1H, Ar-H), 7.50 (d, 1H, C₂-H), 7.70 (m, 3H, Ar-H), 8.00 (d, 2H, Ar-H), 8.20 (d, 1H, C₃-H), 8.60 (s, 1H, C₆-H), 13.64 (s, 1H, -OH), 13.72 (s, 1H, -OH); MS: *m/z* = 638 (M+H)⁺.

1-[2,4-Dihydroxy-5-[5-phenyl-1-(pyridine-4-carbonyl)-4,5-dihydro-1H-pyrazol-3-yl]-phenyl]-3-phenyl-propenone (2f)

IR (KBr) (cm⁻¹): 1683 (>C=O), 1635 (>C=O). ¹H NMR(CDCl₃ δ): 3.10 (dd, 1H, C_{4''}-H), 3.65 (dd, 1H, C_{4''}-H), 5.70 (dd, 1H, C_{5''}-H), 6.85 (d, 4H, Ar-H), 7.08 (s, 1H, C₃-H), 7.26-7.50 (m, 7H, C₂-H, Ar-H), 7.58-7.66 (m, 2H, Ar-H), 7.68 (s, 2H, C_{2'''}, C_{6'''} Ar-H), 7.70-7.72 (d, 1H, C₃-H), 8.74 (d, 1H, C₆-H); MS: *m/z* = 489 (M)⁺.

1-[2,4-Dihydroxy-5-[1-(pyrimidine-4-carbonyl)-5-p-tolyl-4,5-dihydro-1H-pyrazol-3-yl]-phenyl]-3-p-tolyl-propenone (2g)

IR (KBr) (cm⁻¹): 1684(>C=O), 1635 (>C=O). ¹H NMR(CDCl₃ δ): 2.42 (s, 3H, CH₃), 2.46 (s, 3H, CH₃), 2.92 (dd, 1H, C_{4''}-H), 3.08 (dd, 1H, C_{4''}-H), 5.52 (dd, 1H, C_{5''}-H), 6.55 (s,

1H, C₃-H), 7.26 (m, 5H, C₂-H, Ar-H), 7.35 (d, 3H, Ar-H), 7.64 (d, 4H, Ar-H), 7.92 (d, 1H, C₃-H), 8.62 (s, 1H, C₆-H), 13.52 (s, 1H, -OH): MS: *m/z*=517 (M-H).

3-(2,4-Dimethoxy-3-methyl-phenyl)-1-[5-[-(2,4-dimethoxy-3-methyl-phenyl)-1-(pyrimidine-4-carbonyl)-4,5-dihydro-1H-pyrazol-3-yl]-2,4-dihydroxy-phenyl]-propenone (2h)

IR (KBr) (cm⁻¹): 1682(>C=O), 1634(>C=O). ¹H NMR(CDCl₃ δ): 2.16 (s, 3H, CH₃), 2.18 (s, 3H, CH₃), 2.82 (dd, 1H, C₄^{''}-H), 3.12 (dd, 1H, C₄^{''}-H), 3.80 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 3.84(s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 5.74 (dd, 1H, C₅^{''}-H), 6.48 (s, 1H, C₃-H), 6.69 (m, 2H, Ar-H), 7.26 (d, 2H, Ar-H), 7.48 (d, 1H, C₂-H), 7.68 (d, 1H, C₂^{''} Ar-H), 7.70 (d, 1H, Ar-H), 7.97 (d, 1H, C₆^{''} Ar-H), 8.15 (d, 1H, C₃-H), 8.59 (s 1H, C₆-H), 13.62 (s, 1H, -OH), 13.70 (s, 1H, -OH): MS: *m/z* =639 (M+H)⁺.

Protocol for Antibacterial activity

The *in vitro* antibacterial activities of the synthesized compounds were evaluated by disc diffusion method using standard literature protocol³⁰. Nutrient agar was melted on a water bath and cooled to 45 °C with gentle shaking to bring about uniform cooling. It was inoculated with 0.5-0.6 mL of culture and mixed by gentle shaking before pouring onto a sterilized petri dish. The poured material was allowed to set and the Whatman no.1 paper discs containing test solutions of 12.5, 25.0, 50.0, 100.0 and 200.0 µg/mL were introduced under sterile condition on to the nutrient agar plates. The test compounds at five different concentrations ranging from (12.5 µg/mL, 25.0 µg/mL, 50.0 µg/mL, 100.0 µg/mL, 200.0 µg/mL) taken from stock concentration of 2 mg/mL solution (*i.e.*, 2 mg/mL analysis compounds dissolved in dimethyl sulfoxide (DMSO 1%) was used as solvent to prepare the stock solution of the test compounds. The drug was allowed to diffuse for about 4 h into the agar medium before adding the suspension of the test bacteria. The test was carried out in duplicate. Apart from running controls of standard drugs (Ampicillin, Carbencillin), controls with DMSO (positive control) and without DMSO (negative control) were also included in the test. The plates were incubated at 37°C for 48 h and the results were recorded. The zones of inhibition of the microbial growth (100 µg/disc) produced by different concentration of compounds were measured in millimeters (mm).

Results and Discussion

1-[2,4-Dihydroxy-5-[5-(aryl)-1-pyridine/pyrimidine-4-carbonyl]-4,5dihydro-1H-pyrazol-3-yl]-phenyl]-3-(aryl)-propenones (**2a-h**) were synthesized by Micheal addition involving 1-[2, 4-dihydroxy-5-(aryl acryloyl)phenyl]-aryl propenones (**1a-h**) with isoniazide/ pyrazinic acid hydrazide under microwave irradiation (Method A) and conventional heating (Method B). The synthesized compounds were characterized by IR, ¹H-NMR, ¹³C-NMR and Mass spectral data.

IR spectra of **2** showed two carbonyl peaks in the range 1667-1695 cm⁻¹ and 1634-1638 cm⁻¹ due to two different carbonyl groups. ¹H NMR spectra of **2** showed three double doublets in the range δ 2.76-3.10, δ 3.05-3.65 and δ 5.50-5.85 integrating for one proton each and involving coupling of both geminal and vicinal protons. These signals clearly indicate the formation of mono pyrazoline moiety. The spectrum also exhibited two doublets around δ 7.38 and δ 7.70 integrating for one proton each due to C₂-H & C₃-H respectively of α,β-unsaturated carbonyl moiety. The ¹³C NMR spectrum of **2** exhibited three characteristic signals in the aliphatic region around δ 29.76, δ 44.05 and δ 79.78 due to

pyrazoline moiety. In mass spectra of **2** showed the molecular ion peak as base peak (100%), which provides evidence for the formation of 1-{2, 4-dihydroxy-5-[5-(aryl)-1-pyridine/pyrimidine-4-carbonyl]-4,5-dihydro-1*H*-pyrazol-3-yl]-phenyl}-3-(aryl)-propenones (**2a-h**). This can lead further scope for the construction of new heterocyclic rings, on free α,β -unsaturated carbonyl moiety which could contribute towards biodynamic heterocycles. The yields obtained under microwave assisted synthesis are high when compared to conventional method (Table 1).

Table 1. Physical and analytical data of 1-{2, 4-dihydroxy-5-[5-(aryl)-1-pyridine/pyrimidine-4-carbonyl]-4, 5-dihydro-1*H*-pyrazol-3-yl]-phenyl}-3-(aryl)-propenones (**2a-h**)

S.No	Compounds	Mol. Formula (M.Wt.)	M.P. °C	Comparative study			
				Conventional		Microwave	
				Time, h	Yield %	Time, min	Yield %
1	2a	C ₃₂ H ₂₇ N ₃ O ₆ (549)	192	18	65	4	85
2	2b	C ₃₀ H ₂₁ Cl ₂ N ₃ O ₄ (557)	167	19	60	5	75
3	2c	C ₃₀ H ₂₁ Cl ₂ N ₃ O ₄ (557)	160	18	65	4	70
4	2d	C ₃₂ H ₂₇ N ₂ O ₄ (517)	140	18	70	3	85
5	2e	C ₃₆ H ₃₅ N ₃ O ₈ (637)	210	20	65	4	80
6	2f	C ₃₀ H ₂₃ N ₃ O ₄ (489)	165	18	60	5	75
7	2g	C ₃₁ H ₂₆ N ₄ O ₄ (518)	180	18	70	4	85
8	2h	C ₃₅ H ₃₄ N ₄ O ₈ (638)	240	19	65	4	80

Graphical representations (Figure 1) of antibacterial activity as zone of inhibition (mm) on y-axis and concentration on x-axis. All the test compounds synthesized were evaluated for their antimicrobial activity against *Pseudomonas aeruginosa* Gram (+) and *Escherichia coli* Gram (-) strains by filter paper disc diffusion method³⁰ at five different concentrations ranging from (12.5 µg/mL, 25.0 µg/mL, 50.0 µg/mL, 100.0 µg/mL and 200.0 µg/mL) taken through stock concentration of 2 mg/mL solution. (i.e., 2 mg/mL analysis compounds dissolved in DMSO solvent. It's evident from the Table 2. **2a**, **2c**, found to be active, and moderately active at 12.5, 25 and 50 µg/mL concentrations and against gram-positive *Pseudomonas aeruginosa* strain with ampicillin, carbencillin as standard drugs respectively. Compounds **2b**, **2e**, **2f**, **2h** were considered to be very less active even at higher concentrations, compounds **2d**, **2g** shows no activity. Similarly among all the compounds only **2g**, **2h** shows increase in the zone of inhibition value uniformly at 12.5, 25 and 50 µg/mL concentrations against gram-negative *E. coli* strain with ampicillin, carbencillin respectively, indicates nominal activity. Compounds **2a**, **2b**, **2c**, **2d**, **2e**, **2f** shows no activity (Figure 2).

Among all the compounds screened, **2h** showed highest antibacterial activity and its activity was found to be comparable with that of standard drugs tested. Although with respect to standard drugs, all the test compounds were found to less potent but results of our preliminary study clearly indicated that the chalcone containing 1,3,5-trisubstituted pyrazoline moiety represent a new class of pharmacophore for broad spectrum antibacterial activity. Further studies related to the lead optimization and mechanistic studies to understand the exact mode of action of this new class of compounds are in progress.

Table 2. Antibacterial activity of compounds **2a-h**.

No Compd.		Antibacterial (zone of inhibition mm)										
		<i>Pseudomonas aeruginosa</i>					<i>E. coli</i>					
		Conc. µg/mL	Conc. µg/mL	12.5	25.0	50.0	100.0	200.0	12.5	25.0	50.0	100.0
1	2a		0.2	0.4	0.4	0.6	0.7	0.1	0.2	0.2	0.3	0.3
2	2b		0.1	0.1	0.2	0.2	0.2	0.1	0.1	0.2	0.3	0.4
3	2c		0.3	0.5	0.6	0.8	0.8	0.1	0.1	0.2	0.2	0.3
4	2d		-	-	-	-	-	-	-	-	-	-
5	2e		0.1	0.1	0.2	0.2	0.4	-	-	-	-	-
6	2f		0.1	0.3	0.3	0.3	0.5	0.2	0.2	0.2	0.4	0.4
7	2g		-	-	-	-	0.1	0.2	0.3	0.3	0.3	0.5
8	2h		0.1	0.1	0.1	0.1	0.3	0.1	0.3	0.4	0.4	0.6
Std.	Ampicillin		0.2	0.4	0.5	1.5	2.0	0.2	0.4	0.6	1.5	0.2
Drugs	Carbencillin		0.4	0.8	1.0	1.5	2.3	0.4	1.8	1.0	1.5	2.3

Scheme 1. Synthesis of 1-[2, 4-dihydroxy-5-[5-(aryl)-1-pyridine/pyrimidine -4-carbonyl]-4, 5 dihydro-1H-pyrazol-3-yl]-3-(aryl)-propanones (**2a-h**).

Figure 1. Antibacterial activity (**2a-h**) *pseudomonas* gram (+)

Figure 2. Antibacterial activity (**2a-h**) *E. coli*

Conclusion

In summary, this work demonstrates a rapid, efficient and environmentally friendly method for the synthesis of title compounds (**2a-h**) under microwave irradiation and results obtained confirm the superiority of microwave irradiation method over the conventional method. Above all it is a selective synthesis of 1-{2, 4-dihydroxy-5-[5-(aryl)-1-pyridine/pyrimidine-4-carbonyl]-4, 5 dihydro-1*H*-pyrazol-3-yl]-phenyl}-3-(aryl)-propenones, and are potential intermediates for the synthesis of various mixed heterocyclic compounds and metal complexes.

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