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Microwave Mediated Synthesis and Antimicrobial Screening of 2,6-Diaryl-3-methyl-4-piperidyl carbazone Derivatives

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Microwave irradiation technique as a green chemistry procedure have been applied to the synthesis of a series of some new 2,6-diaryl-3-methyl-4-piperidyl carbazone derivatives (**2a-f**) which was obtained by the reaction of 2,6-diaryl-3-methyl-4-piperidone (**1a-c**) with semicarbazide or thiosemicarbazide respectively. The key intermediate **1a-c** were prepared in one step by reacting ethyl methyl ketone, various substituted aldehydes and ammonium acetate. The chemical structures of the synthesized compounds were confirmed by IR, ^{1}H NMR and mass spectral data. The compounds were screened for antibacterial and antifungal activity. Majority of the compounds showed significant antimicrobial activity.

Key Words: Piperidone, Semicarbazone, Thiosemicarbazone, Antimicrobial, Antifungal.

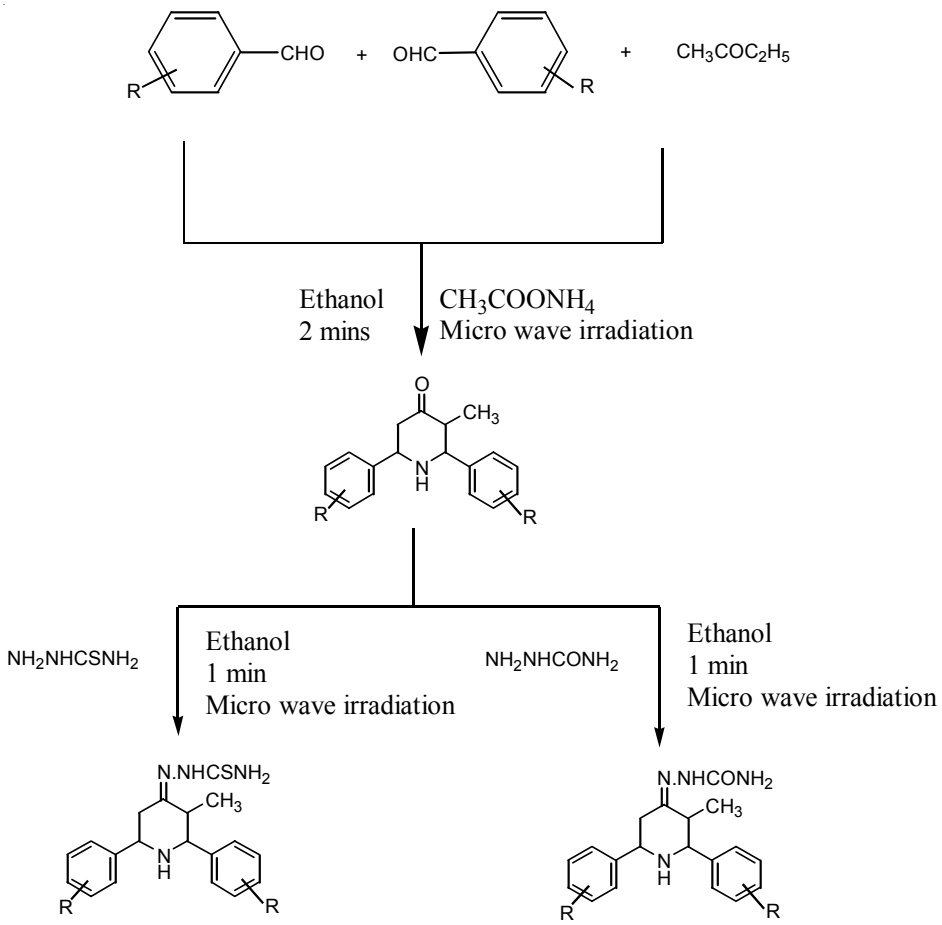
INTRODUCTION

Piperidines were reported to possess analgesic[1], antiinflammatory[2], central nervous system[3,4], local anaesthetic[1], anticancer[5] and antimicrobial[6] activity. Semicarbazone and thiosemicarbazone derivatives are also reported to have antibacterial[7], anticonvulsant[8], analgesic[9] and antiinflammatory[9] activities. The use of microwave (MW) for the assisting different organic reaction have become very popular in last few years and recently gained attraction due to its ecofriendliness and safety. Due to timeliness, easy of workability, dramatic rate enhancement and increase selectivity, microwave technology provides a promising alternative to environmentally unacceptable conventional procedure. So, we report here in a facile and enviro-economic synthesis of title compound **2a-f** in cooperating two biologically important moiety with the assumption that the combination of these moieties may enhance the biological profile of the compound many fold *versus* its parent nuclei.

EXPERIMENTAL

Scientific microwave synthetic system (700 W) was used for microwave irradiation. All the melting points were measured on Veego digital melting point apparatus and are uncorrected. The infrared spectra were recorded on Perkin FT-IR instrument in KBr. The ^{1}H NMR was recorded on 400 caps FT-NMR and chemical shift was

measured as parts per million downfield from tetra methyl silane. The mass spectra were recorded on LC-MSD Trap-SL. The purity of the synthesized compounds were checked by Thin layer chromatography (TLC) using precoated silica gel-G plate using chloroform: methanol (9:1) as the mobile phase.



Scheme

Synthesis of 3-methyl-2,6-(diaryl)-4-piperidone (1a-b): A mixture of ethyl methyl ketone (0.01 mol), dried ammonium acetate (0.01 mol) and *p*-nitro benzaldehyde or 3-hydroxy benzaldehyde (0.02 mol) in ethanol (6 mL) were taken in a 250 mL beaker. Reaction mixture was irradiated in microwave (700 W) for 2 min, cooled to room temperature and neutralized with conc. hydrochloric acid. The compound so formed was filtered, washed with water and finally recrystallized from ethanol.

1a: Yield 75 %; m.p. 89 ºC; IR (KBr, ν_{max}, cm^{-1}): 3478 (NH *str.*), 1707 (C=O *str.*), 1508 (C=C, aromatic *str.*); ^{1}H NMR (δ) 7.5-8.5 (m, 9H, Ar-H), 2.5 (S, 2H, CS-$NHNH_2$); MS: m/z = 355.

1b: Yield 66 %; m.p. 170 ºC, IR (KBr, ν_{max}, cm^{-1}): 3210 (NH *str.*), 1581 (C=C *str.*), 3287 (OH *str.*), 1669 (C=O *str.*); ^{1}H NMR (δ) 7.5-8.5 (m, 9H, ArH), 5.2 (S, 1H, OH), 2 (S, 1H, NH); MS: m/z = 297.

Synthesis of 3-methyl-2,6-*bis*(3-nitrophenyl)piperidine-4-one (1c): A mixture of ethyl methyl ketone (0.01 mol), dried ammonium acetate (0.01 mol), *m*-nitrobenzaldehyde (0.01 mol) in ethanol (6 mL) were irradiated under microwave for 1 min. It was kept at room temperature and dry ether (5 mL) was added followed by conc. HCl (3 mL) and cooled in ice water. The precipitated hydrochloride salt was filtered and washed repeatedly with ethanol and ether (1:5) mixture. Then it was suspended in acetone and made alkaline with ammonia to get precipitate, filtered, vaccum dried and recrystallized from ethanol.

1c: Yield 55 %; m.p. 78 ºC; IR (KBr, ν_{max}, cm^{-1}): 3238 (NH *str.*), 1659 (C=O *str.*), 1533 (C=C *str.*), 1352 (C-NO_2 *str.*); ^{1}H NMR (δ): 7.5-8.5 (m, 9H, ArH), 2.5 (s, H, NH); MS: m/z = 356.

Synthesis of 3-methyl-2,6-(diaryl)-4-carbazones (2a-f): A mixture of 3-methyl-2,6-(diaryl)-4- piperidone (**1a-c**, 0.01mol) and thiosemicarbazide/semicarbazide (0.01 mol) dissolved in ethanol (6 mL) and was irradiated under microwave (700 W) for 1 min. The contents were cooled and poured into ice water. The precipitate obtained, was filtered, washed with water, vaccum dried and recrystallized from ethanol.

2a: Yellow crystals; Yield 65 %; m.p. 188 ºC; IR (KBr, ν_{max}, cm^{-1}): 3478 (NH *str.*), 1576 (C=N *str.*), 1508 (C=C *str.*), 848 (C-S *str.*), 1343 (C-N-O); ^{1}H NMR (δ) 7.5-8.5 (m, 9H, ArH), 2.5 (s, 1H, CS-NH); MS: m/z = 422.

2b: Green crystals; Yield 65%; m.p. 201 ºC; IR (KBr, ν_{max}, cm^{-1}): 3396 (N-H *str.*), 1526 (C=C *str.*), 1471 (C=N *str.*), 1050 (C=S *str.*), 1347 (C-N-O *str.*); ^{1}H NMR (δ) 7.5-8.5 (m, 9H, ArH), 2.5 (s, 1H, CS-NH), 2 (s, 1H, NH); MS: m/z = 425.

2c: Light brown crystals; Yield 51 %; m.p. 230 ºC; IR (KBr, ν_{max}, cm^{-1}): 3420 (N-H *str.*), 1542 (C=C *str.*), 1595 (C=N *str.*), 834 (C=S *str.*), 3287 (O-H *str.*); ^{1}H NMR (δ) 7.5-8.5 (m, 9H, ArH), 5.2 (s, 1H, C-NH), 2 (s, 1H, NH); MS: m/z = 364.

2d: Light yellow crystals; Yield 60 %; m.p. 210 ºC; IR (KBr, ν_{max}, cm^{-1}): 3449 (N-H *str.*), 1537 (C=C *str.*), 1707 (C=O *str.*), 1397 (C-N-O_2 *str.*), 1586 (C=N *str.*) ^{1}H NMR (δ) 7.5-8.5 (m, 9H, ArH), 6.1 (s, 1H, CONH-NH^2), 2 (s, 1H, NH); MS: m/z = 409.

2e: White crystals; Yield 64 %; m.p. 188 ºC; IR (KBr, ν_{max}, cm^{-1}): 3464 (NH *str.*), 1580 (C=C *str.*), 1531 (C=N *str.*), 1715 (C=O *str.*), 1347 (C-N-O_2 *str.*); ^{1}H NMR (δ) 7.5-8.5 (m, 9H, ArH), 2.5 (s, 1H, CO-NH), 2 (s, 1H, NH); MS: m/z = 410.

2f: Yellow crystals; Yield 55 %; m.p. 200 ºC; IR (KBr, ν_{max}, cm^{-1}): 3469 (NH *str.*), 1525 (C=C *str.*), 1050 (C=O *str.*), 1587 (C=N *str.*), 3220 (O-H *str.*); ^{1}H NMR (δ) 7.5-8.5 (m, 9H, ArH), 6.1 (s, 1H, C-NH), 2 (s, 1H, NH); MS: m/z = 353.

Antimicrobial activity: Antibacterial activities of the synthesized compounds were screened against gram-positive bacterial strains, *Saphylococcus aureus*, *Klebsiella pneumoniae* and gram-negative bacterial strains *Pseudomonas aeruginosa*, *Escherichia*

coli at different concentration. The antibacterial activity was determined by cup-plate diffusion method[10]. Ciprofloxacin (10 µg/mL) was used as standard. The antifungal activity was also determined by similar procedure[10] against *Aspergillus niger* using ketoconazole (10 µg/mL) as standard. After 24 h of incubation at 37 ºC, the MIC was measured.

TABLE-1
ANTIMICROBIAL ACTIVITY OF 2,6-DIARYL-3-METHYL-4-PIPERIDYL CARBAZONE DERIVATIVES

Compd.	R	Minimum inhibitory concentration (drug conc. in µg/mL)				
		Antibacterial				Antifungal
		E. coli	*S. aureus*	*P. aeruginosa*	*K. pneumonia*	*A. niger*
1a	4-NO_2	50.0	20.0	36.0	21.5	45.0
1b	3-OH	65.0	66.0	68.0	75.5	76.0
1c	3-NO_2	68.5	40.5	85.0	72.0	82.0
2a	4-NO_2	70.0	82.0	52.6	65.5	65.5
2b	3-NO_2	30.0	76.0	96.0	86.0	76.0
2c	3-OH	66.0	88.5	68.5	70.0	92.0
2d	4-NO_2	40.0	22.5	21.0	36.0	25.0
2e	3-NO_2	82.0	55.5	77.0	70.5	75.0
2f	3-OH	21.5	20.5	28.6	30.0	22.0

RESULTS AND DISCUSSION

The compounds **1a-2f** have been characterized on the basis of satisfactory analytical and spectral data. The IR spectra exhibited bands between 1670 to 1600, 800-700 and 3200-3100 has been assigned due to C=C stretching, C-H deformation and NH bonding, respectively. One more absorption band at 1700 ± 10 and between 1200-1230 is due to C=O and C=S stretching, respectively. The NH proton appeared as a broad singlet in offset (δ 9.7-9.8) region of PMR spectrum. The doublet found between δ 0.9-1.3 confirms the presence of CH_3 proton. The methyne and methylene protons signal is found between δ 1.5-2 and δ 2.4-2.6, respectively.

Out of the nine compounds synthesized in the series the compound **2f** showed MIC value at 21.5, 20.5 and 22 µg/mL against *E. coli*, *S. aureus* and *Aspergillus niger*, respectively. The compound **1a** exhibited antibacterial activity against *K. pneumonia*, at MIC value 21.5 µg/mL and *S. aureus* at 20 µg/mL. The compound **2d** show potency against *S. aureus* and *P. aeruginosa* at MIC value 22.5 and 21 µg/mL, respectively. The compound **2f** found to have more significant antibacterial and antifungal activities.

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