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ARTICLE

Synthesis and Characterization of Novel Substituted 2,6-diarylpiperidine-4-one Derivatives

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ABSTRACT

In this article, new derivatives of 4-piperidinone nucleus *viz.*, substituted 2,6-diarylpiperidine-4-ones were synthesized using Mannich reaction. Eight compounds were synthesized and characterization by elemental analysis, FTIR and ^{1}H NMR spectral analysis.

KEYWORDS

Piperidione, Anti-inflammatory, Antihistamine, Mannich reaction, 2,6-Diarylpiperidine-4-ones.

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INTRODUCTION

Piperidine alkaloid occurs in few species of higher plants, microorganism and animal's lobe line is the main constituent of lobelia alkaloid (*Lobelia inflata*). Piperidine is an active ingredient in black pepper (*Piper nigrum*). It is respiratory stimulant in mammal on hydrolysis gives piperic acid and piperidine [1]. Other piperidine alkaloids are isopelletierine, coniine, arecoline and anabasine. 4-Piperidones are important piperidine derivatives. Other method available for their synthesis, *e.g.* Dieckmann cyclization of diesters, Thorpe-Ziegler cyclization of dinitriles and cyclization of dialkyl ketones or acetone dicarboxylic esters with aldehyde ad primary amines in Mannich reaction [2]. Among the various heterocyclic compounds, nitrogen containing heterocyclic especially piperidine-4-ones, have considerable importance because of their various biological properties such as antiviral, antitumour, anticancer and antidepressant activities. 4-Pyrodone pyridine-4(1*H*)-one are tautomeric with 4-hydroxypyridine [3].

4-Piperidinone is a derivative of piperidine ring, having molecular formulae C_5H_9NO. It is also named as azinane-4-one having molecular mass 99.13 g/mol [4]. A classic named reaction for the synthesis of piperidone is Petrenko-Kritschenko piperidone synthesis, which involves combination of alkyl-1,3-acetonedicarboxylate with benzaldehyde and an amine [5,6]. This multi-component reaction is related to the Hantzsch pyridine synthesis. The structure of piperidone nucleus also recognized in molecular framework of naturally occurring compound and synthetic compound. 2,6-Diarylpiperidine-4-one is a heterocyclic organic compound, in this piperidine ring contains diaryl

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group at position 2 and 6 carbonyl group at position number 4 and also possesses wide spectrum of activities [7,8].

EXPERIMENTAL

The chemicals and reagents *viz*. 4-nitrobenzaldehyde, 4-fluorobenzaldehyde, 4-chlorobenzaldehyde, anisaldehyde, acetone, 3-pentanone, ammonium acetate, acetyl chloride, 4-bromo-acetophenone, 2-chloro-4-bromoacetophenone, methanol, ethanol, diethyl ether, ethyl acetate, chloroform, *n*-hexane, silica gel were procured from Sigma-Aldrich company, India and used as such without further purification. Melting points of the synthesized compounds were determined by open capillary method using MAC melting point apparatus and are uncorrected.

Thin layer chromatography of compounds: Thin layer chromatographic analysis of compounds was performed on silica gel G coated glass plates. The adsorbent silica gel G was coated to a thickness of about 0.3 mm on previously cleaned TLC plates of 20 × 5 cm using conventional spreader. The plates were placed in hot air oven at 105°C for 30 min. The solution of compounds was applied as a spot on the activated plate about 2 cm above from the lower edge. The mobile phases were selected according to the polarity of compounds. Benzene:acetone, 8:2 v/v was used as mobile phase. The spots were visualized by exposure to iodine vapour.

Infrared (FT-IR) analysis of compounds was recorded on a Perkin Elmer Spectrum RXI FTIR spectrometer using KBr pellets. ^{1}H NMR spectra were recorded on Bruker Avance II 300 NMR in $CDCl_3$ using TMS as internal standard.

Synthesis of 4-piperidinone nucleus using Mannich reaction (1a-d): Ammonium acetate (0.05 M), appropriate aromatic aldehyde (0.1M) and respective ketones (acetone or 3-pentanone) (0.05 M) were added to a round bottomed flask containing 30 mL of ethanol. The mixture was refluxed for 3 h and allowed to stand at room temperature overnight. Then conc. HCl (5 mL) was added and the precipitated hydrochloride was collected, washed with ethanol:ether mixture (1:5). A suspension of hydrochloride in acetone was treated with strong liquid NH_3 and the free base was obtained by pouring in ice-cold water. The crude product was recrystallized with ethanol.

N^1-Acetylation of 3,5-(disubstituted)-2,6-diarylpiperidin-4-one derivatives (2a-d): To a well stirred solution of 2,6-diarylpiperidin-4-one (0.05 M) in 15 mL of dry benzene, acetyl chloride (0.05 M) in 15 mL of benzene was added dropwise through the addition funnel for about 0.5 h. Stirring was continued with mild heating using a magnetic stirrer. After completion of reaction, it was poured into water and extracted with ether in three 30 mL portions. The combined ether extract was then washed with 3 % sodium carbonate and dried over anhydrous sodium sulfate. This upon evaporation and subsequent recrystallization in distilled ethanol gave the compound (**2a-b**) in pure form with good yield.

Synthesis of thiosemicarbazone derivatives (3a-d): Compounds (**2a-d**, 0.02 M) were dissolved 20 mL of methanol in separate round bottomed flask and heat to get the clear solution. Few drops of conc. thiosemicarbazide (0.02 M) and few drops of HCl were added to it with constant stirring. Reaction mixture was refluxed for 3 h on a water bath with constant stirring. Reaction was monitored by TLC. After the completion of reaction, the content were brought to room temperature, solid thus separated (**3a-d**) was filtered. The crude product was purified and used for the synthesis of final compounds. The physico-chemical data are reported along with analytical data.

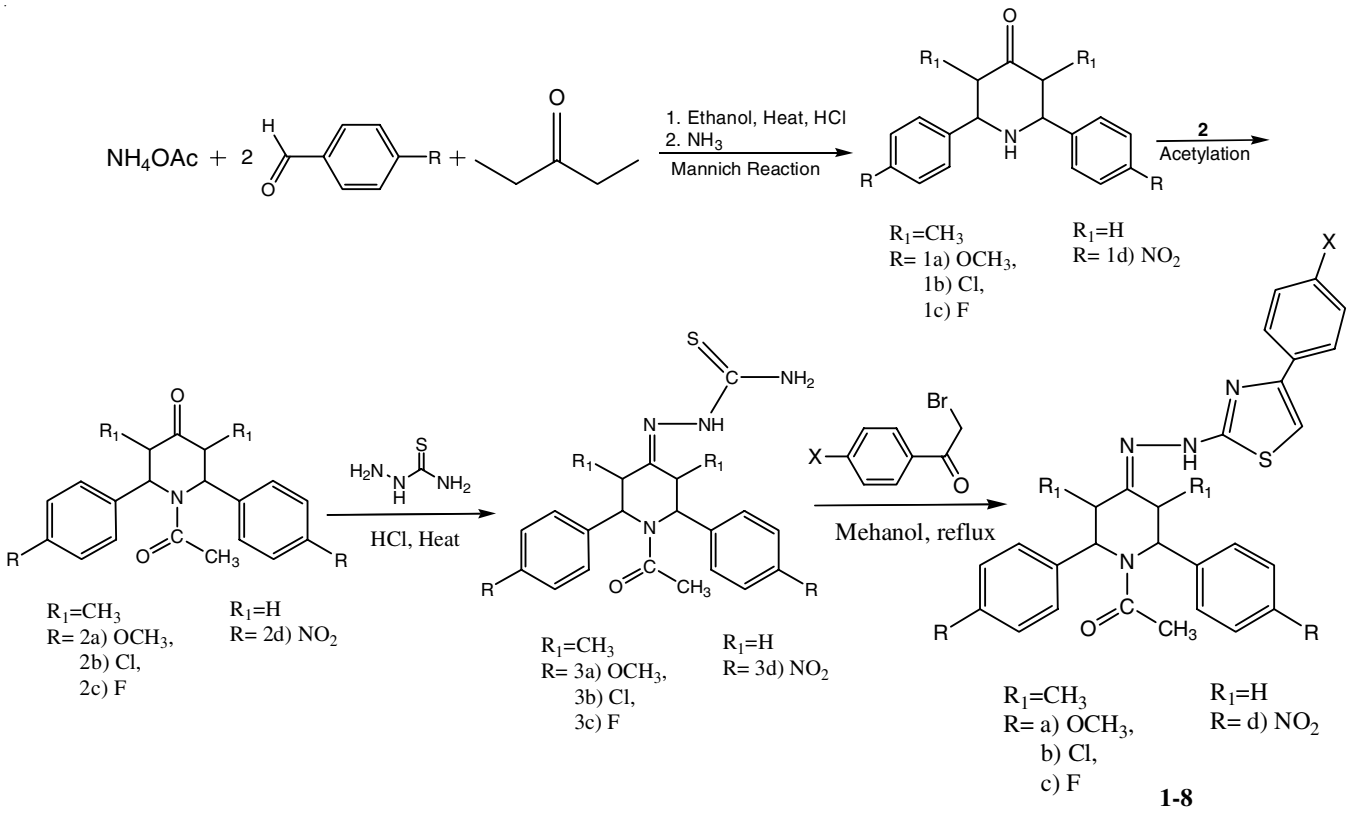
Synthesis of substituted phenacylbromide: A mixture of equimolar quantities of thiosemicarbazone (**3a-d**, 0.01 M) in ethanol/methanol (20 mL) and substituted phenacylbromide (0.01 mol) in methanol was refluxed on a water bath for 4-10 h. The progress of reaction was monitored by TLC at appropriate time interval. The excess of solvent was distilled off and the solid that separated was collected by filtration, suspended in water and neutralized with $NaHCO_3$/K_2CO_3 and finally extracted with ethyl acetate (25 mL). The combined organic layers were washed with distilled water, brine and dried over sodium sulphate to get the desired product (**Scheme-I**). The product was recrystallized from ethanol [9]. The physico-chemical data are reported in Table-1.

1-[4-{[4-Phenylthiazol-2-yl]hydrazono}-2,6-*bis*-(4-methoxyphenyl)-3,5-dimethyl-piperidin-1-yl]ethanone (1): Elemental analysis: Calcd. (Found) %: C 69.29 (69.20), H 6.18 (6.15), N 10.10 (10.03). IR (ν_{max}, KBr, cm^{-1}): 3364 (NH), 3075 (Ar-H), 2980, 2950, 2887, 2855 (C-H *str.*), 1653 (N-C=O *str.*), 1606 (C=C), 1518, 1410, 1250, 1217, 1175, 1097, 1032, 830, 769, 669, 507. ^{1}H NMR (δ, $CDCl_3$): 0.97 (d, 6H, *J* = 12 Hz, -CH_3 at C3 and C5), 1.57 (s, 6H, 2 *p*-OCH_3 groups), 2.67-2.77 (m, 2H, H_{3a} and H_{5a}), 3.58-3.62 (d, 2H, H2 and H6), 4.23 (s, 3H, N-$COCH_3$), 6.91-7.15 (m, 9H, aromatic protons of *p*-OCH_3 phenyl ring merged with H5 of thiazole ring), 7.40-7.72 (m, 5H, aromatic protons).

1-[4-{[4-(4-Chloro phenyl)thiazol-2-yl]hydrazono}-2,6-*bis*-(4-methoxy phenyl)-3,5-dimethylpiperidin-1-yl]ethanone (2): Elemental analysis: Calcd. (Found) %: C 65.24 (65.18), H 5.65 (5.71), N 9.51 (9.55). IR (ν_{max}, KBr, cm^{-1}): 3398 (N-H), 3071(Ar-H), 2969, 2940, 2897, 2854, (C-H *str.*),

TABLE-1
PHYSICO-CHEMICAL DATA OF SYNTHESIZED COMPOUNDS

Code	Substituent			m.f.	m.p. (°C)	Yield (%)	m.w.	R_f value#	Colour
	R	R_1	X						
1	OCH_3	CH_3	H	$C_{32}H_{34}N_4O_3S$	120	60	554.70	0.65	Dark brown
2	OCH_3	CH_3	Cl	$C_{32}H_{33}N_4O_3SCl$	130	40	589.15	0.60	Dark brown
3	-F	CH_3	H	$C_{30}H_{28}N_4OSF_2$	100	40	530.64	0.55	Light yellow
4	-F	CH_3	Cl	$C_{30}H_{27}N_4OSClF_2$	80	30	565.09	0.60	Dark brown
5	$-NO_2$	H	H	$C_{28}H_{24}N_6O_5S$	70	30	556.59	0.70	Dark brown
6	$-NO_2$	H	Cl	$C_{28}H_{23}N_6O_5SCl$	60	30	591.04	0.75	Dark brown
7	-Cl	CH_3	H	$C_{30}H_{28}N_4OSCl_2$	140	40	562.14	0.60	Dark brown
8	-Cl	CH_3	Cl	$C_{34}H_{38}N_4OSCl_3$	130	40	596.10	0.65	Dark brown



Scheme-I

1643 (N-C=O *str*.), 1609, 1513, 1459, 1416, 1298, 1248, 1179, 1116, 1029, 926, 869, 835, 771, 741, 630, 559. ^{1}H NMR (δ, $CDCl_3$): 1.00 (d, 6H, *J* = 12 Hz, -CH_3 at C3 and C5), 1.59 (s, 6H, 2 *p*-OCH_3 groups), 2.05 (Br, 1H, NH), 2.59-2.77 (m, 2H, H_{3a} and H_{5a}), 3.58-3.66 (d, 2H, H2 and H6), 5.40 (s, 3H, N-$COCH_3$), 6.91-7.06 (m, 5H, aromatic protons close to -OCH_3 merged with H5 of thiazole ring), 7.40-7.53 (m, 6H, aromatic protons not close to -OCH_3, aromatic proton close to Cl); 7.86-7.92 (d, 2H, aromatic proton not close to Cl).

1-[4-{[4-Phenyl thiazol-2-yl]-hydrazono}-2,6-*bis*-(4-fluoro phenyl)-3,5-dimethyl piperidin-1-yl]ethanone (3): Elemental analysis: Calcd. (Found) %: C 67.91 (67.86), H 5.32 (5.31), N 10.56 (10.52). IR (ν_{max}, KBr, cm^{-1}): 3065 (Ar-H), 2940, 2897, (C-H *str*.), 1655 (N-C=O *str*.), 1615, 1515, 1450, 1423, 1276, 1250, 1169, 1100, 1020, 915, 866, 775, 740, 610, 540. ^{1}H NMR (δ, $CDCl_3$): 0.96 (d, 6H, *J* = 18 Hz, -CH_3 at C3 and C5), 1.26-1.30 (br/m, 1H, H_{2ax}), 1.59 (s, 3H, -N-$COCH_3$) 2.67-2.77 (m, 2H, H_{3a} and H_{5a}), 2.74 (s, 3H, N-$COCH_3$), 3.58-3.67 (d, 1H, H_{6ax}, 4.68 (s, 1H, H5-thiazole); 7.01-7.06 (m, 7H, aromatic protons close to F and H3, H4, H5 proton of phenylthiazole ring), 7.35-750 (m, 6H, aromatic protons not close to F and H2, H6 proton of phenylthiazole ring), 7.89 (s/br, 1H, NH).

1-[4-{[4-(4-Chloro phenyl)thiazol-2-yl]hydrazono}-2,6-*bis*-(4-fluoro phenyl)-3,5-dimethyl piperidin-1-yl]ethanone (4): Elemental analysis: Calcd. (Found) %: C 63.77 (63.83), H 4.82 (4.80), N 9.91 (9.92). IR (ν_{max}, KBr, cm^{-1}): 3400 (N-H), 3029 (Ar-H), 2945, 2876 (C-H *str*.), 1650 (N-C=O *str*.), 1620, 1522, 1449, 1435, 1267, 1245, 1178, 1112, 1030, 925, 860, 705, 743, 621, 542.

1-{2,6-*Bis*-(4-Nitro phenyl)-4-[(4-phenylthiazol-2-yl)-hydrazono]piperidin-1-yl}ethanone (5): Elemental analysis: Calcd. (Found) %: C 60.42 (60.45), H 4.35 (4.32), N 15.10 15.12). IR (ν_{max}, KBr, cm^{-1}): 3386 (N-H), 3025 (Ar-H), 2940 2897, 2820 (CH *str*.), 1666 (N-C=O *str*.), 1625, 1550, 1517, 1450, 1430, 1280, 1262, 1172, 1105, 1032, 905, 868, 777, 741, 615, 560. ^{1}H NMR (δ, $CDCl_3$): 1.07-1.35 [br/m, 2H, H_{3ax} and H_{5ax}), 2.40-2.50 (d, 2H, H_{2a} and H_{6a}), 2.5-2.70 (dd/m, 2H, H_{3eq} and H_{5eq}), 2.74 (s, 3H, N-$COCH_3$), 5.64 (s, 1H, H5- thiazole), 7.30-7.65 (m, 5H, aromatic protons of 4-phenylthiazole ring), 7.70-8.05 (m, 4H, aromatic protons not close to -NO_2), 8.10-8.50 (m, 4H, aromatic proton close to -NO_2), 9.38 (s/br, 1H, NH).

1-{2,6-*bis*-(4-Nitro phenyl)-4-[(4-(*p*-chloro phenyl)thiazol-2-yl)hydrazono]piperidin-1-yl}-ethanone (6): Elemental analysis: Calcd. (Found) %: C 56.90 (56.88), H 3.93 (3.92), N 14.22 (14.24). IR (ν_{max}, KBr, cm^{-1}): 3425 (N-H), 3071(Ar-H), 2942, 2870, 2840 (C-H *str*.), 1665 (N-C=O *str.*), 1620, 1555, 1519, 1453, 1420, 1290, 1272, 1174, 1112, 1034, 906, 860, 770, 745, 606, 550.

1-{2,6-*bis*-(4-Chloro phenyl)-3,5-dimethyl-4-[(4-phenyl-thiazol-2-yl)hydrazono]piperidin-1-yl}ethanone (7): Elemental analysis: Calcd. (Found) %: C 63.94 (63.90), H 5.01 (5.01), N 9.94 (9.93). IR (ν_{max}, KBr, cm^{-1}): 3385 (N-H), 3010 (Ar-H), 2936, 2875 (C-H *str*.), 1655 (N-C=O *str*.), 1610, 1545, 1523, 1455, 1424, 1283, 1270, 1170, 1102, 1032, 910, 855, 740, 535.

1-(2,6-*bis*-(4-Chloro phenyl)-4-{[4-(4-chloro phenyl)-thiazol-2-yl]hydrazono}-3,5-dimethyl piperidin-1-yl)ethanone (8): Elemental analysis: Calcd. (Found) %: C 60.26 (60.27), H 4.55 (4.54), N 9.37 (9.36). IR (ν_{max}, KBr, cm^{-1}): 3401(N-H), 3025(Ar-H), 2950, 2880 (C-H *str*.), 1665 (N-C=O *str.*), 1620, 1540, 1529, 1449, 1415, 1290, 1250, 1183, 1100, 1035, 915, 850, 745, 550.

RESULTS AND DISCUSSION

The synthesis of substituted 2,6-diarylpiperidine-4-one derivatives (**1-8**) was accomplished by Mannich reaction as shown in **Scheme-I** using ketone, arylaldehyde and ammonium acetate. The product obtained was subjected to column chromatography using benzene-acetone (8:2) v/v as eluent. The IR and ^{1}H NMR spectral analysis data confirmed the structures of substituted 2,6-diarylpiperidine-4-one derivatives.

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