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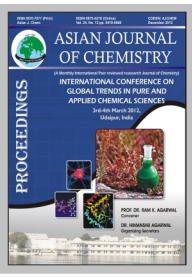

Synthetic Studies on *N*-Methyl Piperazine Containing Pyrazoles and Their Ethoxyphthalimide Derivatives†

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In the present investigation, synthesis of 1-{4-[5-aryl-1-(*N*-ethoxyphthalimido)-4,5-dihydro-1*H*-pyrazol-3-yl]-2-nitrophenyl}-4-methyl-piperazine (**6a-d**) *via* a series of reactions was carried out. For this purpose 4-*N*-methyl piperazinyl-3-nitro acetophenone (**2**) was prepared by the nitration of 4-chloroacetophenone, followed by addition reaction with *N*-methyl piperazine in isopropanol, which on condensation with various aldehydes (**3a-d**) gave 3-aryl-1-[4-(4-methylpiperazin-1-yl)-3-nitrophenyl]prop-2-en-1-one (**4a-d**). Arylidine derivatives (**4a-d**) were further cyclized to their corresponding pyrazole derivatives (**5a-d**) by reaction with hydrazine hydrochloride in DMF. Furnished the final compounds (**6a-d**) through subsequent treatment of 1-{4-[5- aryl -4,5-dihydro-1*H*-pyrazol-3-yl]-2-nitrophenyl}-4-methylpiperazine (**5a-d**) with *N*-hydroxyphthalimide in the presence of NaH in DMF. All the synthesized compounds have been characterized by elemental analysis and spectral data.

Key Words: 4-Chloroacetophenone, Nitration, *N*-Hydroxyphthalimide, Pyrazol and *N*-methyl piperazine.

INTRODUCTION

Piperazine derivatives have also attracted more and more attention due to their excellent activities. Piperazines have paved their way to become the most important blocks in modern day drug discovery. Piperazine and its congeners are important pharmacophores that can also found in biologically actives compounds across a number of different therapeutic areas such as antifungal, antibacterial, antimalarial, antipsychotic, HIV protease inhibitors, antidepressant and antitumor[1]. They express partial agoinst activity at the 5-HT1A receptors and stronger antagonism at the 5-HT2A than at the D_2 receptors, which is also suggested in literature as a suitablemodel of interactions for some newly synthesized DA/5-HT ligands which are considered for their atypical neuroleptic potential[2-4]. Previous studies on benzimidazole type of dopaminergic/ serotonergic ligands[5-7] showed that the affinity and DA/5-HT ratio can be fine tuned by small changes in the structure of the ligand. It is also reported that this derivatives are biological screening across a number of different therapeutic areas such as antifungal[8], antidepressant, anticonvulsant[9-12], antiinflammatory[13], antibacterial[14,15] and antitumor[16], antitubercular[17] and insecticidal[18] properties. Pyrazole compounds are a kind of important compounds, which have good biological activity and used widely in the field of coordination, agriculture, medicine and coordination chemistry. Today heterocyclic compounds especially heterocyclic with *N* occupy the important position in the research and development of pesticide.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The time required for completion of the reaction was monitored by TLC using Silica gel-G plates and spots were exposed in iodine chamber. IR spectra were recorded on a Perkin Elmer 1800 (FTIR) spectrometer ^{1}H NMR spectra (DMSO) were taken on a DRX-300 spectrometer (300 MHz) using TMS as internal standard and chemical shifts are expressed in δ ppm. Mass spectra were taken on a jeol SX-102/DA-6000 spectrometer. Phthalimidoxyethylbromide was prepared[19] by reported methods.

Synthesis of 4-chloro-3-nitroacetophenone (I): To 4-chloroacetophenone (0.08 mol), suspended in conc. H_2SO_4 at -12 to -10 ºC, a mixture of HNO_3 and conc. H_2SO_4 (1:2 v/v) was added dropwise with constant stirring. The temperature was kept below 0 ºC and stirring was continued for further 10 min, during which the nitration product separated out. The suspension was poured on crushed ice and the obtained solid was recrystallized from ice cold methanol to give colourless

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TABLE-1
CHARACTERIZATION DATA OF SYNTHESIZED COMPOUNDS [**I** to **(VIa-d)**]

Compd. no.	Ar	m.f.	m.w.	m.p. (ºC)	Yield (%)	Calcd./found (%) N
I	–	$C_8H_6NO_3Cl$	199	104	80	7.02 (6.98)
II	–	$C_{13}H_{17}N_3O_3$	263	72	76	15.96 (15.88)
IVa	4-Cl-C_6H_4	$C_{20}H_{20}N_3O_3Cl$	386	130	85	10.89 (10.91)
IVb	4-CH_3O-C_6H_4	$C_{21}H_{23}N_3O_4$	381	150	70	11.02 (10.88)
IVc	-C_6H_5	$C_{20}H_{21}N_3O_3$	351	115	68	11.96 (11.89)
IVd	2,4-$(CH_3)_2C_6H_3$	$C_{22}H_{25}N_3O_3$	379	180	73	14.20 (14.05)
Va	4-Cl-C_6H_4	$C_{20}H_{22}N_5O_2Cl$	399	195	77	17.51 (17.40)
Vb	4-CH_3O-C_6H_4	$C_{21}H_{25}N_5O_3$	395	220	61	17.71 (17.79)
Vc	-C_6H_5	$C_{20}H_{23}N_5O_2$	365	205	60	19.16 (19.12)
Vd	2,4-$(CH_3)_2C_6H_3$	$C_{22}H_{27}N_5O_2$	393	233	69	20.57 (20.50)
VIa	4-Cl-C_6H_4	$C_{30}H_{29}N_6O_5Cl$	589	228	64	14.27 (14.11)
VIb	4-CH_3O-C_6H_4	$C_{31}H_{32}N_6O_6$	584	160	56	14.38 (14.29)
VIc	-C_6H_5	$C_{30}H_{30}N_6O_5$	554	195	62	15.15 (15.00)
VId	2,4-$(CH_3)_2C_6H_3$	$C_{32}H_{34}N_6O_5$	582	265	51	16.40 (16.22)

crystals of 4-chloro-3-nitroacetophenone (I). IR (ν_{max}, cm^{-1}): 1677 (C=O str.), 1578, 1390 (NO_2 str.), 3088 (Ar-H str.), 778 (C-Cl str.), ^{1}H NMR (δ): 2.6 (s, 3H, CH_3), 7.24-7.33 (m, 3H, Ar-H);

Synthesis of 4-*N*-methylpiperazinyl-3-nitro acetophenone (II): 4-Chloro-3-nitroacetophenone (I, 0.01 mol) in isopropanol (30-40 mL) was refluxed with *N*-methyl piperazine (0.02 mol) for 10-12 h. Excess of solvent was evaporated and water added to it. The crystals of 4-*N*-methylpiperazinyl-3-nitro acetophenone (**II**) thus separated were filtered and recrystallized from ethanol. IR (ν_{max}, cm^{-1}): 1692 (C=O str.), 1530, 1349 (NO_2 str.), 3070 (Ar-H str.), 1225 (C-N str.), 2989 (C-H str.).

Synthesis of 3-(4-chlorophenyl)-1-[4-(4-methyl-piperazin-1-yl)-3-nitrophenyl]prop-2-en-1-one (IVa): To a well stirred and cooled equimolar solution of (**II**) and chlorobenzaldehyde (**IIIa**) in ethanol, 30 % aq. NaOH was added during a period of 0.5 h. The reaction mixture was further stirred for 4 h at room temperature, poured on crushed ice and then acidified with 1*N* HCl. The resulting solid was washed with water, dried and recrystallized from ethanol as needle shaped crystals. With minor changes in reaction process compounds (**IVb-d**) were obtained. IR (ν_{max}, cm^{-1}): 1660 (C=O str.), 3047 (Ar-H str.), 1210 (C-N str.), 775 (C-Cl str.); ^{1}H NMR (δ): 6.32 (s, 1H, Ar-CH=CH), 6.63 (s, 1H, Ar-CH=CH), 7.16 -7.8 (m, 7H, Ar-H), (**IVb**) : IR (cm^{-1}): 1590 (C=O str.), 3020 (Ar-H str.), 1187 (C-N str.), 730 (C-Cl str.), 1080 (C-O str.); ^{1}H NMR (δ): 6. 5.78 (s, 1H, Ar-CH=CH), 6.47 (s, 1H, Ar-CH=CH), 6.96-7.84 (m, 7H, Ar-H), (**IVc**) : IR (cm^{-1}): 1648 (C=O str.), 3078 (Ar-H str.), 1244 (C-N str.), 789 (C-Cl str.), ^{1}H NMR (δ): 5.97 (s, 1H, Ar-CH=CH), 6.53 (s, 1H, Ar-CH=CH), 7.43 -7.91 (m, 8H, Ar-H), (**IVd**) : IR (cm^{-1}): 1683 (C=O str.), 3055 (Ar-H str.), 1238 (C-N str.), 728 (C-Cl str.), ^{1}H NMR (δ): 6.10 (s, 1H, Ar-CH=CH), 6.29 (s, 1H, Ar-CH=CH), 7.22 -7.87 (m, 7H, Ar-H),

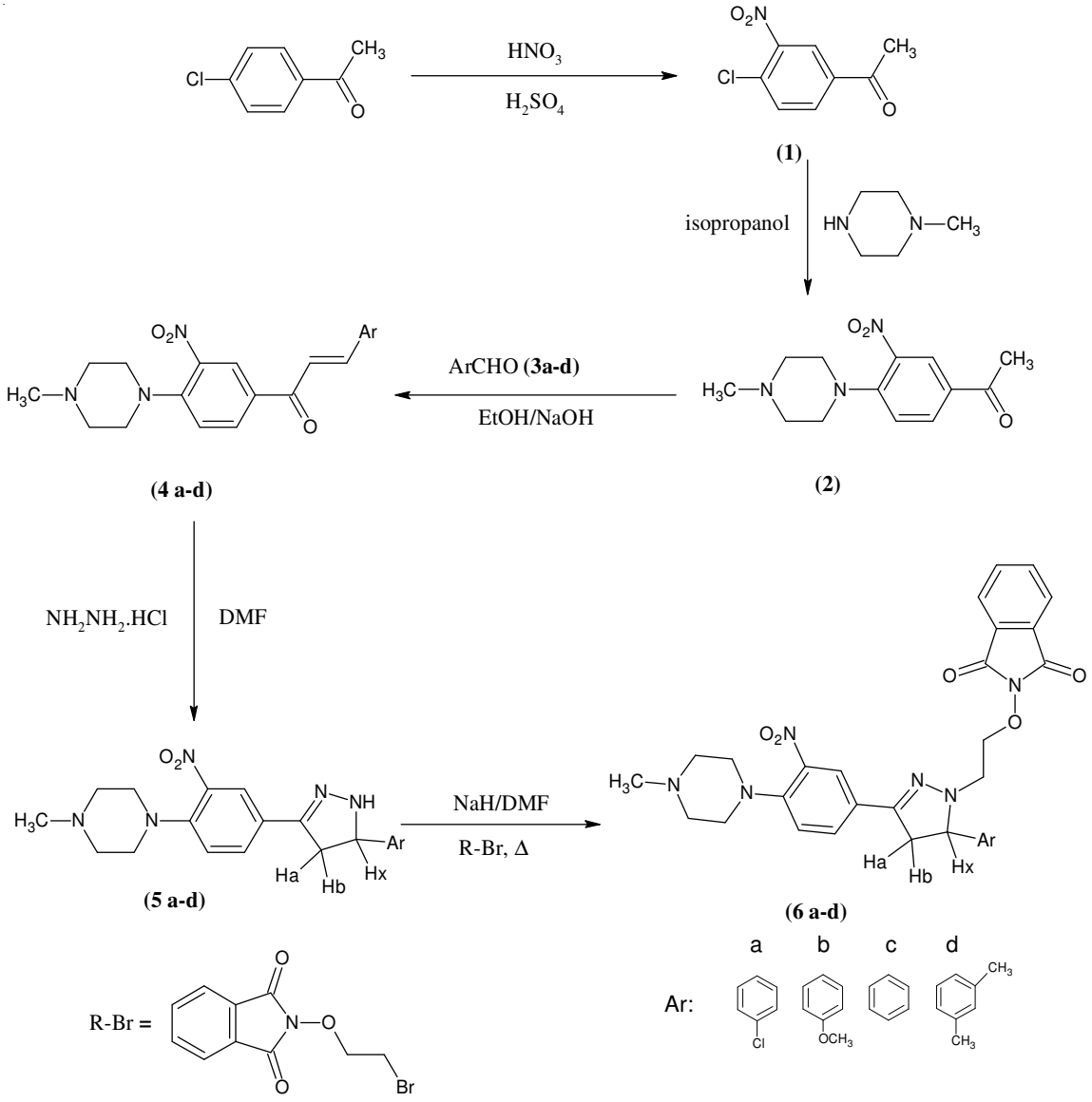
Synthesis of 1-{4-[5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-2-nitrophenyl}4-methylpiperazine (Va): Compound (**IVa**) was refluxed with hydrazine hydrochloride (1:4 molar ratio) in DMF for 8 h. The reaction mixture was cooled and filtered. Filtrate thus obtained was poured on crushed ice. Solid obtained was washed with cold water and recrystallized from ethanol. Compounds (**Vb-d**) were also synthesized by similar method using appropriate reactants with required change in reflux time. IR (ν_{max}, cm^{-1}): 3075(Ar-H str.), 1266 (C-N str.), 819 (C-Cl str.), 3435 (N-H str.), 1612 (C=N str.), 1120 (N-N str.); ^{1}H NMR (δ): 7.16 -7.76 (m, 7H, Ar-H), 2.70 (s, 3H, CH_3), 8.21 (s, 1H, NH), 5.47 (dd, 1H, Hx), 3.68 (dd, 1H, Ha), 4.07 (dd, 1H, Hb).

(**Vb**)**:** IR (ν_{max}, cm^{-1}): 3050 (Ar-H str.), 1280 (C-N str.), 1081 (C-O str.), 3445 (N-H str.), 1619 (C=N str.), 1100 (N-N str.), ^{1}H NMR (δ): 7.83 -7.99 (m, 7H, Ar-H), 2.66 (s, 3H, CH_3), 7.97 (s, 1H, NH), 5.52 (dd, 1H, Hx) 3.71 (dd, 1H, Ha), 4.01 (dd, 1H, Hb), 3.58 (s, 3H, OCH_3).

(**Vc**)**:** IR (ν_{max}, cm^{-1}): 3078 (Ar-H str.), 1210 (C-N str.), 3414 (N-H str.), 1585 (C=N str.), 1145 (N-N str.); ^{1}H NMR (δ): 7.04-7.79 (m, 8H, Ar-H), 2.68 (s, 3H, CH_3), 8.10 (s, 1H, NH), 5.59 (dd, 1H, Hx), 3.63 (dd, 1H, Ha), 4.11 (dd, 1H, Hb).

(**Vd**)**:** IR (ν_{max}, cm^{-1}): 3084 (Ar-H str.), 1230 (C-N str.), 3430 (N-H str.), 1650 (C=N str.), 1132 (N-N str.); ^{1}H NMR (δ): 7.21 -7.93 (m, 7H, Ar-H), 2.74 (s, 3H, CH_3), 8.17 (s, 1H, NH), 5.38 (dd, 1H, Hx), 3.58 (dd, 1H, Ha), 4.17 (dd, 1H, Hb), 2.97 {s, 6H, $N(CH_3)_2$}.

Synthesis of 1-{4-[5-(4-chlorophenyl)-1-(*N*-ethoxyphthalimido)-4,5-dihydro-1*H*-pyrazol-3-yl]-2-nitrophenyl}-4-methylpiperazine (VI a): To a solution of compound (**Va**, 0.01 mol) in 20 mL DMF, NaH (0.02 mol) was added drop wise with constant stirring for 1 h ω-bromo ethoxyphthalimide (0.02 mol) was added to above mixture with constant stirring for 2 h and stirring was further continued for 6 h. The resultant reaction mixture was filtered under reduced pressure. The filtered solid was washed with water and recrystallized from ethanol. Compounds (**VI b-d**) were also prepared in a similar manner with minor changes with reaction workout. IR (ν_{max}, cm^{-1}): 3020 (Ar-H str.), 1422, 1570 (NO_2 str.), 762 (C-Cl str.), 1525 (C=C str), 1230 (C-N str.), 1658, 1717 (C=O str), 1607 (C=N str.), 1130 (N-N str.), 1044 (C-O str.), 1335 (N-O str.), 2976 (C-H str.); ^{1}H NMR (δ): 2.50 (s, 3H, CH_3), 7.19 -7.66 (m, 11H, Ar-H), 5.50 (dd, 1H, Hx), 3.75 (dd, 1H, Ha), 4.47 (dd, 1H, Hb), 3.82 (t, 2H, O-CH_2), 2.67 (t, 2H, N-CH_2), 3.12 -3.48 (m, 8H, CH piperazinyl); Mass (*m/z*): 588 $[M]^+$, 590 $[M+2]^+$, 489, 477, 398, 331, 315, 301, 298, 287, 220, 188.



Scheme-IV: Reaction

(**VI b**)**:** IR (ν_{max}, cm^{-1}): 3044 (Ar-H str.), 1410, 1600 (NO_2 str.), 1570 (C=C str), 1260 (C-N str.), 1670, 1710 (C=O str), 1655 (C=N str.), 1183 (N-N str.), 1025 (C-O str.), 1290 (N-O str.), 2918 (C-H str.), ^{1}H NMR (δ): 2.79 (s, 3H, CH_3), 6.98 -7.76 (m, 11H, Ar-H), 5.48 (dd, 1H, Hx), 3.68 (dd, 1H, Ha), 4.32 (dd, 1H, Hb), 3.79 (t, 2H, O-CH_2), 2.49 (t, 2H, N-CH_2), 2.87 -3.60 (m, 8H, CH piperazinyl), 3.64 (s, 3H, O-CH_3); Mass (*m/z*): 584 $[M]^+$, 477, 394, 331, 301, 294, 287, 99.

(**VI c**)**:** IR (ν_{max}, cm^{-1}): 3145 (Ar-H str.), 1395, 1555 (NO_2 str.), 1530 (C=C str), 1248 (C-N str.), 1697, 1740 (C=O str), 1680 (C=N str.), 1210 (N-N str.), 1078 (C-O str.), 1358 (N-O str.), 2990 (C-H str.); ^{1}H NMR (δ): 2.68 (s, 3H, CH_3), 7.08-7.63 (m, 12H, Ar-H), 5.67 (dd, 1H, Hx), 3.88 (dd, 1H, Ha), 4.43 (dd, 1H, Hb), 4.12 (t, 2H, O-CH_2), 2.64 (t, 2H, N-CH_2), 2.72-3.48 (m, 8H, CH piperazinyl), Mass (*m/z*): 554 $[M]^+$, 477, 455, 364, 331, 301, 290, 66.

(**VI d**)**:** IR (ν_{max}, cm^{-1}): 3084 (Ar-H str.), 1470, 1590 (NO_2 str.), 1579 (C=C str), 1288 (C-N str.), 1676, 1782 (C=O str), 1630 (C=N str.), 1168 (N-N str.), 1047 (C-O str.), 1310 (N-O str.), 2898 (C-H str.), ^{1}H NMR (δ): 2.81 (s, 3H, CH_3), 7.32-7.84 (m, 11H, Ar-H), 5.61 (dd, 1H, Hx), 3.95 (dd, 1H, Ha), 4.37 (dd, 1H, Hb), 3.81 (t, 2H, O-CH_2), 2.73 (t, 2H, N-CH_2), 2.95 -3.78 (m, 8H, CH piperazinyl), 2.66 (s, 6H, N $(CH_3)_2$). Mass (*m/z*): 582 $[M]^+$, 498, 477, 307, 220,130,107.

RESULTS AND DISCUSSION

In the present investigation, synthesis of ethoxyphthalimide derivatives of some pyrazolyl piperazines (**VI a-d**) *via* a series of reactions was carried out. For this purpose 4-chloroacetophenone, as starting material, was treated with conc. HNO_3 and H_2SO_4 to furnish 4-chloro-3-nitro acetophenone (**I**). Formation of (**I**) was confirmed by appearance of two stretching bands at 1578 and 1390 cm^{-1} in IR spectrum for NO_2 moiety. Treatment of (**I**) with *N*-methyl piperazine in isopropanol afforded 4-*N*-methyl piperazinyl-3-nitro acetophenone (**II**). This was characterized by disappearance of C-Cl stretching band in IR spectrum. Compound (**II**) was converted to arylidine derivatives (**IVa-d**) when treated with various araldehydes (**IIIa-d**) which were further cyclized to their corresponding pyrazole derivatives (**Va-d**). IR and ^{1}H NMR

spectral data established the structure of these compounds. IR absorption at 1683-1590 cm^{-1} indicated the presence of α,β-unsaturated carbonyl functionality. Formation of pyrazole derivatives (**Va-d**) was confirmed by disappearance of C=O stretching bands at 1683-1590 cm^{-1}, appearance of a stretching band at 3400-3445 cm^{-1} in IR spectrum and double doublets for hydrogens Ha, Hb and Hx of pyrazole ring at δ 3.58-3.71, 4.02-4.17 and 5.38-5.59 respectively in ^1H NMR spectrum. Formation of final compounds (**VIa-d**) inferred by disappearance of IR peaks for NH, appearance of C-O and N-O stretching bands at 1044 and 1335 cm^{-1} respectively and two triplets at δ 2.67 and 3.82 for N-CH_2 and OCH_2 of ethoxyphthalimide moiety in ^1H NMR spectrum.

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