Bulgarian Chemical Communications, Volume 47, Number 2 (pp. 502 – 508) 2015

$NaBH_4/I_2$ mediated one-pot synthesis of 4-(substituted-anilinomethyl-3-(6-methoxy-2-naphthyl)-1-phenyl-1*H*-pyrazoles and their antimicrobial screening

N. Goel[1], S. Kumar[2], S. Bawa[*2]

[1] *Maharaja Surajmal Institute of Pharmacy, (Affiliated to GGSIP University, New Delhi) C-4, Janakpuri, New Delhi*

[2] *Dept. Of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi*

Received January 6, 2014; Revised March 4, 2014

A series of compounds (**Va-Vl**) was synthesized *via* direct reductive amination of 3-(naphthalen-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde with various substituted aromatic amines using $NaBH_4$ in the presence of I_2 as a reducing agent. The reaction was carried out in anhydrous methanol under neutral conditions at room temperature. The structures of the synthesized compounds (**Va-Vl**) were established on the basis of IR, ^1H and ^{13}C-NMR, and mass spectral data. All 4-(substituted-anilinomethyl-3-(2-naphthyl)-1-phenyl-1*H*-pyrazole derivatives (**Va-Vl**) were tested *in vitro* for antifungal and antibacterial activities against different fungal and bacterial strains. Most of the compounds exhibited considerable antifungal activity but poor antibacterial activity against the test strains. The compounds **Vg**, **Vj** and **Vk** showed excellent antifungal activity against the fungal strain *Aspergillus niger* MTCC 281 and *Aspergillus flavus* MTCC 277 (% inhibition in the range of 47.7-52.8).

Keywards; Reductive amination, Pyrazole, Naphthalene, Antimicrobial activity

INTRODUCTION

Pyrazole scaffold represent one of the most active class of heterocyclic compounds possessing a wide spectrum of biological activities including anti-inflammatory–analgesic [1-3], antimicrobial [4,5], antihypertensive [6,7] etc. Some of the analogues have also shown potent antitumor [8,9], antidepressant - anticonvulsant [10,11] and hypoglycemic activities [12,13]. The significance of pyrazole scaffold may be realized by the fact that, there are numerous pyrazole containing drugs has been approved by USFDA for appropriate therapeutic indications some of which includes Celecoxib, Lanazolac, Sulphinpyrazone and Cefoselis etc. Crizotinib (Xalkori) an anticancer drug recently approved by USFDA for the treatment of non-small cell lung carcinoma (NSCLC) is pyrazole derivative [14]. Fig. 1 shows some of the pyrazole derived therapeutic agents and represent the molecular varsity of pyrazole nucleus. Owing to the immense importance and varied bioactivities of pyrazole scaffold and in the continuation of our ongoing research on biologically active pyrazole derivatives [15, 16], it was thought of interest to synthesized some new 6-methoxy naphthalene incorporated pyrazole derivatives. In the present study

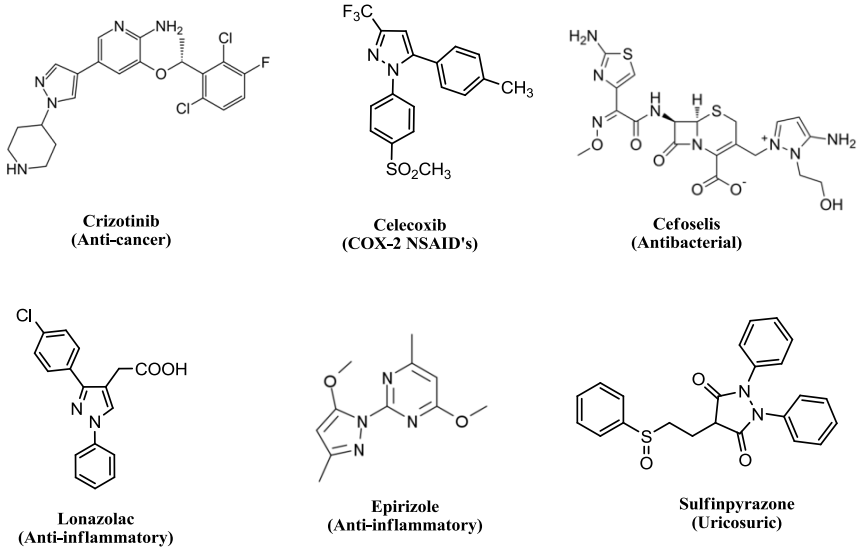

Fig. 1. Chemical structures of various pyrazole containing drugs.

* To whom all correspondence should be sent:
E-mail: drsbawa@reffimail.com

we performed the one-pot synthesis of 4-(substituted-anilinomethyl-3-(6-methoxy-2-naphthyl)-1-phenyl-1H-pyrazoles and their antimicrobial screening against a panel of bacterial and fungal strains.

EXPERIMENTAL

Melting points were determined by the open capillary method with electrical melting point apparatus and are uncorrected. IR spectra were recorded as KBr (pallet) on Nicolet, Protege 460 FTIR spectrophotometer and ^{1}H & ^{13}C-NMR spectra recorded on Bruker DPX 300 MHz spectrophotometer using DMSO-d_6 or $CDCl_3$ as a NMR solvent. TMS used as internal standard and chemical shift data reported in parts per million (in ppm) where s, bs, d, t, and m designated as singlet, broad singlet, doublet, triplet and multiplet respectively. Mass spectra (MS-ESI) were recorded on a JEOL-AccuTOF JMS-T100LS mass spectrometer with a DART (Direct Analysis in Real Time) and elemental analysis on C,H,N Analyzer Perkin Elmer 2400. Thin Layer Chromatography (TLC) was performed to monitor progress of the reaction and purity of the compounds, spot being located under iodine vapour or UV-light.

Synthesis of 1-[1-(6-methoxynaphthalen-2-yl)ethylidene]-2-phenylhydrazine (**III**).

A mixture of 2-acetyl-6-methoxynaphthalene **I** (2.0 g or 0.01 mol) and phenyl hydrazine (**II**) (0.012 mol) was refluxed in round bottom flask containing absolute ethanol (30 ml) for 2.0 hrs in presence of few drops of acetic acid. The content of the flask was cooled to give solid product which was filtered, washed with water, dried and recrystallized from ethanol as a yellow crystalline solid. The purity of compound was checked by TLC using (TEF) (5:4:1) as mobile phase.

1-[1-(6-Methoxynaphthalen-2-yl)ethylidene]-2-phenylhydrazine **(III)**. Yellowish white solid, yield 90 %; m.p. 183 ºC**;** IR (KBr) ν_{max} (cm $^{-1}$) : 3357 (NH), 1605 (C=C), 1590 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.36 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 6.77-6.82 (m, 1H, Ar-H), 7.10-7.18 (m, 1H, Ar-H), 7.21-7.34 (m, 4H, Ar-H), 7.69-7.79 (m, 3H, Ar-H), 7.93 (s, 1H, Ar-H), 8.14-8.17 (d, 1H, Ar-H, *J* = 8.7 Hz), 10.4 (bs, 1H, NH) Anal. calcd. for : $C_{19}H_{18}N_2O$; C 78.59, H 6.25, N 9.65 % Found : C 78.33, H 6.29, N 9.72 %.

Synthesis of 3-(6-methoxynaphthalen-2-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (**IV**).

To a cold solution of 6-methoxy naphthyl hydrazones **III** (4.35 g or 0.015 mol) in DMF (25 ml) was added $POCl_3$ (5 ml) and resulting mixture was stirred at 55-60 ˚C for 6 hrs. The mixture was cooled to room temperature and poured in to ice-cold water, latter a saturated solution of sodium bicarbonate was added to neutralize the solution. The precipitate so formed was filtered, washed with water, dried and recrystallized from ethanol as crystalline solid.

3-(6-Methoxynaphthalen-2-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (**IV**). Light yellow solid, yield 70%, m. P. 152 ºC**;** IR (KBr) ν_{max} (cm $^{-1}$) : 1671 (C=O), 1610 (C=C), 1595 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_3) δ (ppm): 3.97 (s, 3H, OCH_3), 7.19-7.21 (m, 2H, Ar-H), 7.37-7.42 (m, 1H, Ar-H), 7.49-7.55 (m, 2H, Ar-H). 7.81-7.93 (m, 5H, Ar-H), 8.25 (s, 1H, Ar-H), 8.56 (s, 1H, Ar-H), 10.15 (s, 1H, CHO). ^{13}C-NMR (DMSO-d_6, 75 MHz) δ (ppm) : 55.4 (OCH_3), 103.6,114.5, 116.9, 119.7, 125.8, 126.6, 128.0, 128.9, 129.5, 130.2, 131.8, 132.0, 137.6, 141.2, 157.5, 162.4, 184.0 (CHO). MS (ESI) m/z: 328 (M^+), 300 (M-28), Anal. calcd. for : $C_{21}H_{16}N_2O_2$, C 76.81, H 4.91, N 8.53 %, Found C 76.48, H 4.95, N 8.61.

General procedure for the synthesis of compounds **(Va-Vl).**

To a solution of 3-(6-methoxynaphthalen-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **IV** (1.0 mmol) in 10 ml of methanol, substituted aniline (1.2 mmol) was added and then 50 mg iodine (0.4 mmol) was added with stirring at room temperature. To the stirred solution 55 mg of sodium borohydride (1.4 mmol) was added slowly, stirring further for 3-6 hrs. The precipitate was formed which was filtered, washed with water, dried and recrystallized from ethanol/methanol to give crystalline product (**Va-Vl**). The progress of reaction and purity of the compound was checked by (TLC), using benzene: acetone (9.5:0.5) as mobile phase.

4-Anilinomethyl-3-(6-methoxy-2-naphthyl)-1-phenyl-1H-pyrazole **(Va)**. Light brown solid**,** yield 75%, m. P. 130-132 ºC**;** IR (KBr) ν_{max} (cm $^{-1}$) 3406 (N–H), 1619 (C=C), 1596 (C=(Vmax), 1021 (C–N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) : 3.90 (s, 3H, OCH_3), 4.47 (s, 2H, CH_2), 4.72 (s, 1H, NH, D_2O-exchangeble), 6.61-6.64 (d, 2H, Ar-H, *J* = 8.4 Hz), 7.04-7.07 (d, 2H, Ar-H, *J* = 8.1 Hz), 7.10-7.15 (m, 3H, Ar-H), 7.29-7.35 (m, 2H, Ar-H), 7.46-7.55 (m, 3H, Ar-H), 7.70-7.81 (m, 2H, Ar-H), 7.98-8.09 (m, 2H, Ar-H), 8.21 (s, 1H, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) : 38.4 (CH_2), 55.4 (OCH_3), 103.2, 114.6, 116.4, 117.8, 119.2, 120.0, 125.3, 126.4, 127.6, 129.5, 128.2, 128.9, 129.5, 130.7, 132.1, 138.6, 140.9, 142.3, 149.4, 162.4. DEPT-135; (-ve) 38.6 (CH_2). MS (ESI) m/z: 405 (M)$^+$. Anal. calcd. for $C_{27}H_{23}N_3O$: C 79. 97, H 5.72, N 10.39 % ; Found: C 79.73, H 5.76, N 10.44%.

4-(4-Chloroanilinomethyl-3-(6-methoxy-2-naphthyl)-1-phenyl-1H-pyrazole (**Vb**). Cream colored solid, yield 70%, m. P. 119-121 ºC**;** IR (KBr) ν_{max} (cm $^{-1}$) : 3411 (N–H), 1612 (C=C), 1596 (C=N), 1036 (C–N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) : 3.93 (s, 3H, OCH_3), 4.46 (s, 2H, CH_2), 4.78 (bs, 1H, NH, D_2O-exchangeble), 6.67-6.69 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.09-7.17 (d, 4H, Ar-H, *J* = 7.8 Hz), 7.22-7.29 (m, 2H, Ar-H), 7.40-7.48 (m, 3H, Ar-H), 7.69-7.74 (m, 2H, Ar-H), 7.95-8.03 (m, 2H, Ar-H), 8.16 (s, 1H, Ar-H). MS (ESI) m/z: 439 $(M)^+$, 441 (M+2). Anal. calcd. for $C_{27}H_{22}ClN_3O$: C 73.71, H 5.04, N 9.55 %, Found : C 73.82, H 5.09, N 9.62 %.

3-(6-Methoxy-2-naphthyl)-1-phenyl-4-(4-toluidinomethyl)-1H-pyrazole. (**Vc**). Yellowish brown solid, yield 74%, m. P. 144 ºC**;** IR (KBr) ν_{max} (cm $^{-1}$) : 3433 (N–H), 1620 (C=C), 1591 (C=N), 1030 (C–N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) : 2.26 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 4.46 (s, 2H, CH_2), 4.80 (s, 1H, NH, D_2O-exchangeble), 6.61-6.64 (d, 2H, Ar-H, *J* = 8.4 Hz), 7.01-7.03 (d, 2H, Ar-H, *J* = 8.1 Hz), 7.12-7.15 (m, 2H, Ar-H), 7.25-7.30 (m, 2H, Ar-H), 7.43-7.48 (m, 2H, Ar-H), 7.68-7.80 (m, 3H, Ar-H), 7.92-7.99 (m, 2H, Ar-H), 8.16 (s, 1H, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.4 (CH_3), 37.9 (CH_2), 55.4 (OCH_3), 104.1, 114.4, 116.6, 117.4, 119.2, 120.6, 125.7, 126.3, 127.2, 127.8, 128.2, 128.8, 129.6, 130.2, 132.6, 135.8, 137.1, 138.2, 140.5, 142.8, 149.1, 162.8. DEPT-135; (-ve) 37.9 (CH_2). MS (ESI) m/z: 419 $(M)^+$, Anal. calcd. for $C_{28}H_{25}N_3O$: C 80.16, H 6.01, N 10.02 %, Found : C 80.34, H 6.06, N 10.7 %.

4-(4-Bromoanilinomethyl-3-(6-methoxy-2-naphthyl)-1-phenyl-1H-pyrazole. (**Vd**). brownish solid, yield 68%, m. P. 189-192 ºC**;** IR (KBr) ν_{max} (cm $^{-1}$) : 3424 (N–H), 1624 (C=C), 1596 (C=N), 1028 (C–N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) : 3.90 (s, 3H, OCH_3), 4.49 (s, 2H, CH_2), 5.01 (bs, 1H, NH, D_2O-exchangeble), 6.70-6.73 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.08-7.15 (m, 3H, Ar-H, *J* = 7.8 Hz), 7.20-7.25 (m, 2H, Ar-H), 7.30-7.34 (m, 1H, Ar-H), 7.42-7.51 (m, 3H, Ar-H), 7.72-7.78 (m, 2H, Ar-H), 7.90-7.98 (m, 2H, Ar-H), 8.18 (s, 1H, Ar-H). Anal. calcd. for $C_{27}H_{22}BrN_3O$: C 66.95, H 4.58, N 8.67 % Found : C 66.72, H 4.63, N 8.73 %.

4-(3-Chloroanilinomethyl-3-(6-methoxy-2-naphthyl)-1-phenyl-1H-pyrazole. (**Ve**). Beize colored solid, yield 65%, m. P. 110-112 ºC**;** IR (KBr) ν_{max} (cm $^{-1}$) : 3418 (N–H), 1621 (C=C), 1593 (C=N), 1027 (C–N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) : 3.94 (s, 3H, OCH_3), 4.47 (s, 2H, CH_2), 4.82 (bs, 1H, NH, D_2O-exchangeble), 6.69-6.72 (d, 2H, Ar-H, *J* = 8.0 Hz), 6.83-6.87 (m, 1H, Ar-H), 7.01-7.08 (m, 3H, Ar-H), 7.18-7.25 (m, 2H, Ar-H), 7.37-7.45 (m, 3H, Ar-H), 7.68-7.78 (m, 2H, Ar-H), 6.97-7.03 (m, 2H, Ar-H), 8.20 (s, 1H, Ar-H). Anal. calcd. for $C_{27}H_{22}ClN_3O$: C 73.71, H 5.04, N 9.55 % Found : C 73.54, H 5.01, N 9.62 %.

4-(4-Methoxyanilinomethyl)-3-(6-methoxy-2-naphthyl)-1-phenyl-1H-pyrazole (**Vf**). Yellowish brown solid**,** yield 71%, m. P. 103-105 ºC**;** IR (KBr) ν_{max} (cm $^{-1}$) : 3420 (N–H), 1628 (C=C), 1597 (C=N), 1029 (C–N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) : 3.69 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.50 (s, 2H, CH_2), 4.78 (bs, 1H, NH, D_2O-exchangeble), 6.60-6.72 (d, 2H, Ar-H, *J* = 8.0 Hz), 6.96-6.98 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.10-7.19 (m, 3H, Ar-H), 7.23-7.27 (m, 1H, Ar-H), 7.36-7.48 (m, 3H, Ar-H), 7.71-7.79 (m, 2H, Ar-H), 6.98-7.05 (m, 2H, Ar-H), 8.19 (s, 1H, Ar-H). Anal. calcd. for $C_{28}H_{25}N_3O_2$: C 77.22, H 5.79, N 9.65 % Found C 77.47, H 5.82, N 9.73 %.

4-(4-Fluoroanilinomethyl-3-(6-methoxy-2-naphthyl)-1-phenyl-1H-pyrazole (**Vg**). Light brown solid, yield 78%, m. P. 134-136 ºC**;** IR (KBr) ν_{max} (cm $^{-1}$) : 3420 (N–H), 1628 (C=C), 1597 (C=N), 1029 (C–N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) : 3.91 (s, 3H, OCH_3), 4.52 (s, 2H, CH_2), 4.79 (bs, 1H, NH, D_2O-exchangeble), 6.63-6.65 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.01-7.04 (m, 1H, Ar-H), 7.09-7.15 (m, 2H, Ar-H), 7.24-7.30 (m, 3H, Ar-H), 7.41-7.45 (m, 2H, Ar-H), 7.73-7.80 (m, 3H, Ar-H), 7.01-7.06 (m, 2H, Ar-H), 8.15 (s, 1H, Ar-H). Anal. calcd. for $C_{27}H_{22}FN_3O$: C 76.58, H 5.24, N 9.92 % Found C 76.27, H 5.29, N 9.97 %.

3-(6-Methoxy-2-naphthyl)-4-(4-nitroanilino methyl)-1-phenyl-1H-pyrazole (**Vh**). Yellowish brown solid, yield 75%, m. P. 168170 ºC**;** IR (KBr) cm ν_{max} (cm $^{-1}$) : 3428 (N–H), 1631 (C=C), 1590 (C=N), 1033 (C–N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) : 3.92 (s, 3H, OCH_3), 4.48 (s, 2H, CH_2), 4.76 (bs, 1H, NH, D_2O-exchangeble), 6.60-6.63 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.06-7.11 (m, 2H, Ar-H), 7.17-7.20 (m, 1H, Ar-H), 7.28-7.33 (m, 3H, Ar-H), 7.43-7.47 (m, 2H, Ar-H), 7.80-7.88 (m, 3H, Ar-H), 8.02-8.07 (m, 2H, Ar-H), 8.21 (s, 1H, Ar-H). Anal. calcd. for $C_{27}H_{22}N_4O_3$: C 71.99, H 4.92, N 12.44 % Found : C 72.21, H 4.96, N 12.51 %.

3-(6-Methoxy-2-naphthyl)-1-phenyl-4-(3-toluidinomethyl)-1H-pyrazole (**Vi**). Light brown solid, yield 75%, m. P. 106-107 ºC**;** IR (KBr) ν_{max} (cm $^{-1}$) : 3417 (N–H), 1625 (C=C), 1594 (C=N), 1031 (C–N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) : 2.24 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 4.50 (s, 2H, CH_2), 4.81 (bs, 1H, NH, D_2O-exchangeble), 6.59-6.62 (d, 2H, Ar-H, *J* = 8.0 Hz), 6.93-6.97 (m, 2H, Ar-H), 7.07-7.13 (m, 2H, Ar-H), 7.21-7.24 (m, 1H, Ar-H), 7.40-7.49 (m, 3H, Ar-H), 7.68-7.77 (m, 3H, Ar-H), 8.01-8.07 (m, 2H, Ar-H), 8.17 (s, 1H, Ar-H). Anal. calcd. for

$C_{28}H_{25}N_3O$: C 80.16, H 6.01, N 10.02 %, Found : C 80.01, H 6.06, N 10.08 %.

4-(3-Chloro-4-fluoroanilinomethyl-3-(6-methoxy-2-naphthyl)-1-phenyl-1H-pyrazole (**Vj**). Brownish solid, yield 67%, m. P. 124-125 ºC**;** IR (KBr) ν_{max} (cm $^{-1}$) : 3422 (N–H), 1630 (C=C), 1593 (C=N), 1034 (C–N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) : 3.92 (s, 3H, OCH_3), 4.48 (bs, 2H, CH_2), 4.71 (bs, 1H, NH, D_2O-exchangeable), 6.50-6.53 (m, 1H, Ar-H), 6.68-6.70 (m, 1H, Ar-H), 6.91-6.97 (m, 1H, Ar-H), 7.07-7.23 (m, 3H, Ar-H), 7.39-7.54 (m, 3H, Ar-H), 7.67-7.96 (m, 4H, Ar-H), 8.04 (s, 1H, Ar-H), 8.12 (s, 1H, Ar-H), Anal. calcd. for $C_{27}H_{21}ClFN_3O$: C 70.82, H 4.62, N 9.18% Found : C 70.63, H 4.67, N 9.24 %.

4-(3,4-Dichloroanilinomethyl-3-(6-methoxy-2-naphthyl)-1-phenyl-1H-pyrazole (**Vk**). Light brown solid, yield 69 %, m. P. 176-177 ºC**;** IR (KBr) ν_{max} (cm $^{-1}$) : 3428 (N–H), 1631 (C=C), 1598 (C=N), 1033 (C–N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) : 3.93 (s, 3H, OCH_3), 4.46 (s, 2H, CH_2), 4.86 (bs, 1H, NH, D2o-exchangeable), 6.52-6.55 (m, 1H, Ar-H), 6.70-6.72 (m, 1H, Ar-H), 6.91-6.97 (m,1H,), 7.10-7.24 (m, 3H, Ar-H), 7.42-7.51 (m, 3H, Ar-H), 7.70-7.98 (m, 4H, Ar-H), 8.06 (s, 1H, Ar-H), 8.18 (s, 1H, Ar-H), Anal. calcd. for $C_{27}H_{21}Cl_2N_3O$: C 68.36, H 4.46, N 8.86 Found : C 68.15, H 4.49, N 8.92 %.

3-(6-Methoxy-2-naphthyl)-4-(4-hydroxyanilino methyl)-1-phenyl-1H-pyrazole (**Vh**). Dark yellowish solid, yield 65 %, m. P. 165-166 ºC**;** IR (KBr) cm ν_{max} (cm $^{-1}$) : 3432 (N–H), 3389(OH) 1634 (C=C), 1594 (C=N), 1031 (C–N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) : 3.93 (s, 3H, OCH_3), 4.46 (s, 2H, CH_2), 4.82 (bs, 1H, NH, D_2O-exchangeble), 6.74-6.76 (d, 2H, Ar-H, *J* = 7.4 Hz), 7.09-7.12 (m, 2H, Ar-H), 7.18-7.20 (m, 1H, Ar-H), 7.30-7.36 (m, 3H, Ar-H), 7.42-7.48 (m, 2H, Ar-H), 7.86-7.93 (m, 3H, Ar-H), 8.03-8.07 (m, 2H, Ar-H), 8.24 (s, 1H, Ar-H), 9.79 (bs, 1H, OH). Anal. calcd. for $C_{27}H_{23}N_3O_2$: C 76.94, H 5.50, N 9.97 % Found : C 76.73, H 5.52, N 10.02 %.

Antimicrobial activity

The newly synthesized compounds were screened for their antifungal and antibacterial activities against the test organism *viz. Candida albicans* MTCC-183, *Aspergillus niger* MTCC 281, *Aspergillus flavus* MTCC 277, *Escherichia coli* NCTC 10418, *Staphylococus aureus* NCTC 6571, *Pseudomonas aeruginosa* NCTC 10662 in DMSO by cup plate method [17]. Potato dextrose agar and nutrient agar were used as culture medium for antibacterial and antifungal activity respectively. Using an agar punch, wells were made on these seeded agar plates and dilution of 500 µg/ml of test compounds in DMSO was added into each well, labeled previously. A control was also prepared using solvent DMSO. The petri plate were prepared and maintained at 30° for 72 hrs for fungi and at 37 ºC for 24 hrs for bacteria. Each experiment was repeated twice and the average of the two independent determinations was recorded. Antimicrobial activity was determined by measuring zone of inhibition and results were reported as percentage inhibition and calculated as 100(C–T)/C, where C is the average diameter of fungal or bacterial growth on the control plate and T is the average diameter of fungal or bacterial growth on test plate. Activity of each compound was compared with standard Fluconazole for antifungal and Ciprofloxacin for antibacterial activity. Results of antimicrobial activity have been summarized in Table 1

Table 1. *In-vitro* antimicrobial activity data of compounds (**Va-Vl**).

Compd. No.	Antimicrobial activity as % inhibition					
	Antifungal activity			Antibacterial activity		
	C. albicans	A. flavus	A. niger	E. coli	S. aureus	P. auroginosa
Va	28.1	33.8	31.7	19.6	13.7	—
Vb	38.2	42.0	43.6	16.9	17.4	—
Vc	26.0	30.8	32.3	22.5	13.8	—
Vd	31.8	39.6	38.0	21.7	18.7	—
Ve	38.4	45.7	46.1	18.6	14.3	—
Vf	26.1	32.5	30.3	24.9	18.2	—
Vg	38.9	48.9	48.7	20.9	15.6	—
Vh	14.8	18.6	15.7	32.3	21.5	—
Vi	24.7	26.8	28.8	15.7	10.8	—
Vj	42.2	49.6	51.0	22.9	18.2	—
Vk	44.8	52.8	50.3	23.7	20.4	—
Vl	34.6	38.3	40.6	33.6	27.9	—
Ciprofloxacin	NT	NT	NT	84.8	78.7	80.6
Fluconazole	81.5	89.8	92.6	NT	NT	NT

NT: not tested, (—): no activity observed.

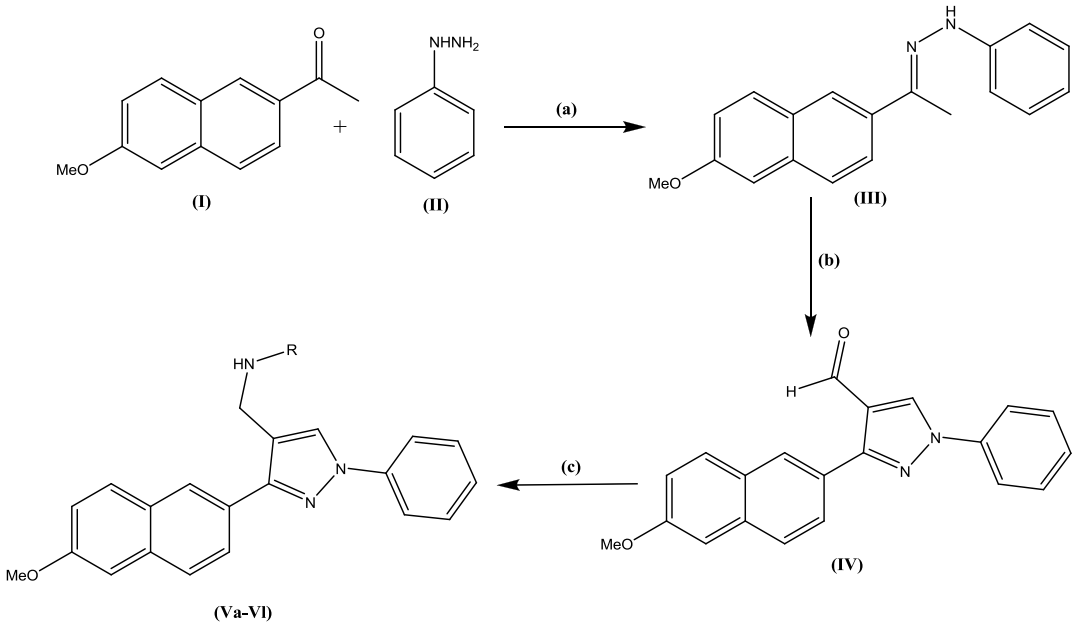

Fig. 2. Route of synthesis for compounds **(Va-Vl).** Reagent and conditions: (a) Abs. EtOH, reflux (b) DMF/$POCl_3$, 55-60 ºC, warm (c) aromatic amines, $NaBH_4/I_2$, MeOH, stirring

RESULTS AND DISCUSSION

Chemistry

The compounds **(Va-Vl)** were synthesized by direct reductive amination of 3-(6-methoxynaphthalen-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde with suitable aromatic amine using $NaBH_4$ in the presence of I_2 as reducing agent in absolute methanol as outlined in Fig. 2. The structure of synthesized amines **(Va-Vl)** were elucidated by combined use of IR, ^1H & ^{13}C-NMR and mass spectral data. Combustion analysis of compounds was found to be within the range of ±0.4 %. The synthesis of compounds was confirmed on the basis of functional group transformation of –CHO in compound **IV** into –CH_2NH– in compounds **(Va-Vl)** and this was established on the basis of IR, ^1H, ^{13}C-NMR including mass spectral data. In FTIR the characteristic carbonyl (C=O) stretching band which was observed at 1671 cm^{-1} in compound **IV** disappeared in FTIR spectra of compounds **(Va-Vl).** This was further supported by ^1H-NMR spectra. The ^1H-NMR spectrum of compound **IV**, the signal due to aldehydic proton which resonated as a singlet at δ value 10.15, disappeared in spectra of compounds **(Va-Vl)** and a new signal observed at high upfield δ values ranging from 4.46 to 4.52 integrating for two protons. The signal due to the NH proton was observed at δ value 4.72–5.01. The methylene group of –CH_2NH– appeared as a singlet or broad singlet (bs) due to coupling effect of NH proton whereas the NH signal was observed as a broad singlet. Furthermore in the ^{13}C-NMR spectrum of the compound **IV** the signal due to the carbonyl carbon observed at δ value 184.0. No carbonyl carbon signal was found in the spectra of compounds **(Va-Vl)** and a new signal due to methylene carbon of –CH_2NH– appeared at δ value 38.4 and 38.9 in compound **Va** and **Vc** respectively. The functional group transformation was again inveterate by ^{13}C-NMR spectra using DEPT-135 techaniqe, which records inverse (-ve) peak for CH_2 carban. The DEPT-135 spectra of compound **Va** and **Vc** exhibit inverse (-ve) peak at 38.6 and 37.9 respectively. The above spectral analysis suggest the successful reductive amination of pyrazole carbaldehydes **IV**. This fact was further supported by MS(ESI) spectra of prototype compounds **Va, Vb** and **Vc,** in which M+ ion peak was observed at m/z 405, 439 and 419 respectively. In ^1H-NMR the protons of naphthalene and phenyl rings were observed in aromatic region as multiplets due to coupling and overlapping of signals. While a singlets integrating for one proton appeared at δ value 8.12-8.24 arising due to H-5 proton of the pyrazole nucleus. These data are in agreement with structures assigned to the compounds **(Va-Vl).**

*Antimicrobial activity of (**Va-Vl**).*

All the pyrazolyl amines **(Va-Vl)** displayed variable growth inhibitory effects against the fungal strains at concentration of 500 mg/ml in DMSO as shown in Table No 1 Among the series of compounds **(Va-Vl)** compounds **Vb, Ve, Vg, Vj** and **Vk** showed good antifungal activity against Candida albicans. The

growth inhibitory effect of compounds **(Va-Vl)** was more pronounced against the fungal strain *Aspergillus niger* MTCC 281 and *Aspergillus flavus* MTCC 277. In this series compound **Vg, Vj** and **Vk** showed excellent antifungal activity against the fungal strain Aspergillus niger MTCC 281 and *Aspergillus flavus* MTCC 277 (% inhibition in the range of 47.7-52.8). While rest of the compounds such as **Va, Vc, Vd, Vf, Vi** and **Vl** displayed moderate antifungal activity. Only one derivative expressed weak antifungal activity viz. **Vh**.

All the pyrazolyl amines **(Va-Vl)** were also evaluated for antibacterial activity against the strains *Escherichia coli* NCTC 10418, *Staphylococus aureus* NCTC 6571, *Pseudomonas aeruginosa* NCTC 10662 at concentration of 500 mg/ml in DMSO by cup plate method. A careful examination of Table revealed that most of molecules of series **(Va-Vl)** exhibited moderate to weak antibacterial activity against the test organism *E. coli* NCTC 10418, *Staphylococus aureus* NCTC 6571 at the conc. of 500 µg/ml. Compounds were completely inactive against the strain *Pseudomonas aeruginosa* NCTC 10662.

CONCLUSION

The study provides successful one-pot synthesis 4-(substituted-anilinomethyl-3-(6-methoxy-2-naphthyl)-1-phenyl-1*H*-pyrazols (**Va-Vl**) using $NaBH_4/I_2$ as reducing agent. The process offers advantages such as good yield, simple procedure, use easily available reagents etc. The results of antimicrobial screening suggest that compounds were more active towards the fungal strains compared to the bacterial strains, In the series compound **Vg, Vj, Vk,** showed excellent antifungal activity against the fungal strain *Aspergillus niger* MTCC 281 and *Aspergillus flavus* MTCC 277 (% inhibition in the range of 47.7-52.8).

Acknowledgment: *The author (NG) expresses sincere thanks to Maharaja Surajmal Institute of Pharmacy, Janakpuri, New Delhi for providing necessary facilities. Thanks are due to CDRI, Lucknow, India and IIT for recording spectral data.*

REFERENCES

1. S. Sugiura, S. Ohno, O. Ohtani, K. Izumi, T. Kitamikado, H. Asai, K. Kato, M. Hori, M. Fujimura. *J. Med. Chem*., **20**, 80 (1977).
2. T.D. Penning, J.J. Talley, S.R. Bertenshaw, J.S. Carter, P. W. Collins, S. Docter, M.J. Graneto, L.F. Lee, J.W. Malecha, J.M. Miyashiro, R.S. Rogers. *J. Med. Chem*., **40**, 1347 (1997).
3. A.A. Bekhit, H.M. Ashour, A-D. Bekhit, S.A. Bekhit. *Med. Chem*., **05**, 103 (2009).
4. A. Tanitame, O. Keiko, Y. Hiyama, S. Kenji, *et. al.*. *J. Med. Chem.*, **47**, 3693 (2004).
5. A.M. Gilbert, Y. Yang, A. Failli, J. Shumsky, A. Severin, G. Singh, *et al.*, e. *J. Med. Chem.*, **49**, 6027 (2006).
6. L.M. Bonesi, G.A. Statti, S. Michel, F. Tillequin, F. Menichini. *Bioorg. Med. Chem. Lett.*, **20**, 1990 (2010).
7. A. Monge, I. Aldana, T. Alvarez, M.J. Losa, M. Font, E. Cenarruzabeiti, B. Lasheras, D. Frechill, E. Castiella, E. Fernandez-Alvarez. *Eur. J. Med. Chem*., **26**, 655 (1991).
8. M. Anzaldi, A.C. Macciò, M. Mazzei, R. Gangemi, P. Castagnola, M. Miele, C. Rosano, M. Viale. *Eur. J. Med. Chem*., **46**, 5293 (2011).
9. X. Li, X. Lu, M. Xing, X. Yang, T. Zhao, H. Gong, H. Zhu. *Bioorg. Med. Chem. Lett*., **22**, 3589 (2012).
10. M. Abdel-Aziz, G-D. Abuo-Rahma, A.A. Hassan. *Eur. J. Med. Chem*., **44**, 3480 (2009).
11. O. Ruhoğlu, Z. Ozdemir, U. Caliş, B. Gümüşel, A.A Bilgin. *Arzneimittel forschung*., **55**, 431 (2005).
12. B. Cottineau, P. Toto, C. Marot, A. Pipaud, J. Chenault. *Bioorg. Med. Chem. Lett*., **19**, 2105 (2002).
13. D. Wu, F. Jin, W. Lu, J. Zhu, C. Li, W. Wang, Y. Tang, H. Jiang, J. Huang, G. Liu, J. Li. *Chem. Biol. Drug Des*., **79**, 897 (2012).
14. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails
15. S. Bawa, H. Kumar. *Indian J. Heterocyl. Chem*., **14**, 249 (2005).
16. S. Bawa, S. Kumar, S. Drabu, B.P. Panda, R. Kumar. *J. Pharm. Bioall. Sci*., **01**, 32 (2009)
17. Kumar S, Bawa S, Kaushik D, Panda BP. *Arch Pharm Chem Life Sci* ., **344**, 474 (2011).

ЕДНОСТАДИЙНА СИНТЕЗА НА 4- (ЗАМЕСТЕН-АНИЛИНОМЕТИЛ-3- (6-МЕТОКСИ-2-НАФТИЛ) -1-ФЕНИЛ-1*H*-ПИРАЗОЛИ ПОСРЕДСТВОМ $NaBH_4$ / I_2 И ТЯХНАТА АНТИМИКРОБНА ОЦЕНКА

Н. Гоел [1], С. Кумар[2], С. Бава[2]*

[1] Институт по фармация „Махараджа Сураджмал“, (филиал на университет GGSIP, Ню Делхи) С-4, Джанакпури, Ню Делхи

[2] Катедра по фармацевтична химия, Фармацевтичен факултет, Джамия Хамдард, Ню Делхи

Получена на 6 януари 2014 г.; Ревизирана на 4 март 2014г.

(Резюме)

Серия от съединения (Va-Vl) бяха синтезирани чрез директно редуктивно аминиране на 3- (нафтален-2-ил) -1-фенил-1 H-пиразол-4-карбалдехид с различни заместени ароматни амини, използвайки $NaBH_4$ в присъствието на I_2 като редуциращ агент. Реакцията се извършва в безводен метанол при неутрални условия и стайна температура. Структурите на синтезираните съединения (Va-VI), са определени въз основа на IR, ^{1}H и ^{13}C-ЯМР и мас спектрални данни. Всички 4- (заместен-анилинометил-3- (2-нафтил) -1-фенил-1H-пиразолови производни (Va-Vl) бяха тествани ин витро за противогъбична и антибактериална активност срещу различни гъбични и бактериални щамове. Повечето от съединенията показват значителна противогъбична активност, но лоша антибактериална активност срещу тестваните щамове. Съединенията V_g, V_j и V_k, показват отлична противогъбична активност срещу гъбичните щам *Aspergillus Niger* MTCC 281 и *Aspergillus flavus* MTCC 277 (% инхибиране в обхвата от 47.7-52.8).