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Synthesis and characterization of biologically significant 5,5′-(1,4-phenylene)bis(1-N-alkoxyphthalimido-3-aryl-2-pyrazoline) derivatives

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Abstract

A facile synthesis of 5,5′-(1,4-phenylene)bis(3-aryl-2-pyrazolines) **4a-g** has been achieved by the cyclo-addition reaction of hydrazine hydrate with bis-substituted chalcones **3a-g**, which in turn were prepared by the Clasien-Schmidt condensation of *p*-substituted acetophenones **1a-g** with terephthaldehyde. Condensation of **4a-g** with ω-bromoalkoxyphthalimides **5a-b** afforded the titled compounds **6a-n**, some of which exhibited significant antimalarial as well as antimicrobial activity.

Keywords: *Bis-pyrazoline, terephthaldehyde, antimalarial, antimicrobial, ω-bromoalkoxyphthalimide*

Introduction

The pyrazoline nucleus is a ubiquitous feature of pharmacological interest and has been proven to be a fertile source of medicinal agents such as antifungal [1], antibacterial [2], antiamoebic [3], antitumor [4], etc. Many pyrazolines have been found to have activity as analgesic, anti-inflammatory and cyclooxygenase-II (COX-II) [5,6,7] agents. Some new testosterone derivatives with fused substituted pyrazoline ring are recognized as 5-α reductase inhibitors [8]. Pyrazoles are known to possess COX-I, COX-II and human lipooxygenase inhibitory activities [9]. Many pyrazoline derivatives of chalcones have been synthesized [10] and have exhibited antibacterial [11] and cytotoxic [12] activities. Pyrazoles constitute an important group of heterocyclic compounds and some of them possess a wide range of pharmacological properties such as antiproliferative [13], antimicrobial [14], antidepressant [15], antihyperglycemic [16], anticancer [17] etc. Several derivatives of alkoxyphthalimide have been synthesized [18,19] and reported to demonstrate a wide range of pharmacological activities i.e. anticancer [20], antimalarial [21], anticonvulsant [22] etc. In view of these observation and in continuation of our work on pyrazoline based heterocycles, it was considered to synthesize new chemical entities incorporating the two active pharmacophores namely, pyrazoline and alkoxyphthalimide in a single molecular framework using chalcones of teraphthaldehyde and substituted acetophenones as basic building blocks.

Materials and methods

Chemistry

All the melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1800 (FTIR) spectrometer and ^{1}H NMR and ^{13}C NMR spectra ($CDCl_3$) were recorded on a DRX-300 (300 MHz) spectrometer using TMS as internal standard. The mass spectra were recorded on a Jeol SX-102 (FAB) mass spectrometer in which *m*-nitrobenzyl alcohol was used as matrix. The purity of synthesized compounds was

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checked by TLC using silica gel-G and spots were exposed by iodine vapor. All compounds gave satisfactory micro analytical results. In the present investigation the α-β unsaturated carbonyl compounds [23] **3a-g** [3,3′-(1,4-phenylene)bis[1-(phenyl/4-fluorophenyl/4-nitrophenyl/4-chlorophenyl/2,4-dichlorophenyl/4-bromophenyl/4-methoxyphenyl)-prop-2-ene-1-one] and ω-bromoalkoxyphthalimides [24] **5a-b** (phthalimidoxyethyl bromide/phthalimidoxybutyl bromide) were prepared by reported methods.

Synthesis of 5,5′-(1, 4-phenylene)bis(3-phenyl-2-pyrazoline) ***4a***

A mixture of compound 3**a** (0.01 mol) and hydrazine hydrate (0.02 mol) in DMF was refluxed for 5 h. After cooling, the reaction mixture was poured on crushed ice and the separated solid was recrystallised from ethanol. Compounds **4b-g** were similarly prepared using suitable reagents with minor modification of the reaction conditions.

5,5′-(1,4-phenylene)bis[3-(4-phenyl)-2-pyrazoline] ***4a***. IR (KBr) cm^{-1}: 3048 (C-H str., ArH), 3405 (N—H str.), 1456 (C=C skeleton), 1602 (C=N str.), 1270 (C—N str.), 1124 (N-N str.); ^{1}H NMR ($CDCl_3$) δ: 7.18–7.45 (m, 14H, ArH, *J* (Hz) = 7.62, 7.95), 6.18 (s, 2H, NH), 4.74 (dd, 2H, CH), 3.42 (dd, 2H, C**H$_b$**H$_a$), 2.88 (dd, 2H, CH$_b$**H$_a$**) *J* (Hz) = 7.04, 8.52; ^{13}C NMR δ: 41.33 (CH_2), 71.87 (CH).

5′-(1,4-Phenylene)bis[3-(4-fluorophenyl)-2-pyrazoline] ***4b***. IR (KBr) cm^{-1}: 3076 (C—H str., Ar-H), 3418 (N—H str.), 1544 (C=C skeleton), 1608 (C=N str.), 1275 (C-N str.), 1133 (N—N str.), 1386 (C—F str.); ^{1}H NMR ($CDCl_3$) δ: 6.99–7.21 (m, 12H, Ar—H, *J* (Hz) = 7.95, 9.00, H—F = 7.34), 6.18 (s, 2H, NH), 4.74 (dd, 2H, CH), 3.43 (dd, 2H, C**H$_b$**H$_a$), 2.89 (dd, 2H, CH$_b$**H$_a$**), *J* (Hz) = 7.04, 8.52; ^{13}C NMR δ: 41.33 (CH_2), 71.87 (CH), 166.78 (C—F).

5,5′-(1,4-Phenylene)bis[3-(4-nitrophenyl)-2-pyrazoline] ***4c***. IR (KBr) cm^{-1}: 3067 (C—H str., Ar—H), 3411 (N—H str.), 1328–1540 (N—O str., NO_2), 1280 (C—N str.); ^{1}H NMR ($CDCl_3$) δ: 7.18–8.17 (m,12H, ArH, *J* (Hz) = 7.95, 8.70), 6.18 (s, 2H, NH), 4.74 (dd, 2H, CH), 3.53 (dd, 2H, C**H$_b$**H$_a$), 2.99 (dd, 2H, CH$_b$**H$_a$**), *J* (Hz) = 7.04, 8.52; ^{13}C NMR δ: 40.66 (CH_2), 71.87 (CH), 148.08 (C—F).

5,5′-(1,4-Phenylene)bis[3-(4-chlorophenyl)-2-pyrazoline] ***4d***. IR (KBr) cm^{-1}: 3070 (C—H str., Ar—H), 3413 (N—H str.), 1535 (C=C str.), 744 (C—Cl str.); ^{1}H NMR ($CDCl_3$) δ: 7.18–7.66 (m,12H, ArH, *J* (Hz) = 7.95, 8.32), 6.18 (s, 2H, NH), 3.43 (dd, 2H, C**H$_b$**H$_a$), 2.89 (dd, 2H, CH$_b$**H$_a$**), *J* (Hz) = 7.04, 8.52; ^{13}C NMR δ: 41.09 (CH_2), 71.87 (CH).

5,5′-(1,4-Phenylene)bis[3-(2,4-dichlorophenyl)-2-pyrazoline] ***4e***. IR (KBr) cm^{-1}: 3078 (C—H str., Ar—H), 3421 (N—H str.), 1567 (C=C str.), 748 (C—Cl str.); ^{1}H NMR ($CDCl_3$) δ: 7.18–7.82 (m,10H, ArH, *J* (Hz) = 7.95, 8.50), 6.18 (s, 2H, NH), 3.53 (dd, 2H, C**H$_b$**H$_a$), 2.99 (dd, 2H, CH$_b$**H$_a$**), *J* (Hz) = 7.04, 8.52; ^{13}C NMR δ: 41.30 (CH_2), 71.67 (CH).

5,5′-(1,4-Phenylene)bis[3-(4-bromophenyl)-2-pyrazoline] ***4f***. IR (KBr) cm^{-1}: 3063 (C—H str., Ar—H), 3407 (N—H str.), 1524 (C=C str.), 576 (C—Br str.); ^{1}H NMR ($CDCl_3$) δ: 7.18–7.47 (m, 12H, ArH, *J* (Hz) = 7.95, 8.50), 6.18 (s, 2H, NH), 3.45 (dd, 2H, C**H$_b$**H$_a$), 2.91 (dd, 2H, CH$_b$**H$_a$**), *J* (Hz) = 7.04, 8.52; ^{13}C NMR δ: 41.91 (CH_2), 71.87 (CH), 123.79 (C-Br).

5,5′-(1,4-Phenylene)bis[3-(4-methoxyphenyl)-2-pyrazoline] ***4g***. IR (KBr) cm^{-1}: 3053 (C—H str., Ar—H), 3410 (N—H str.), 1028 (C—O str.); ^{1}H NMR ($CDCl_3$) δ: 7.18–7.49 (m, 12H, ArH, *J* (Hz) = 7.95, 8.74), 6.18 (s, 2H, NH), 3.45 (dd, 2H, C**H$_b$**H$_a$), 2.92 (dd, 2H, CH$_b$**H$_a$**), *J* (Hz) = 7.04, 8.52; ^{13}C NMR δ: 41.12 (CH_2), 71.87 (CH), 160.80 (C—O), 55.20 (O-CH_3).

Synthesis of 5,5′-(1,4-phenylene)bis(1-N-ethoxyphthalimido-3-phenyl-2-pyrazoline) ***6a***. Compound **4a** (0.01 mol) was dissolved in DMF and sodium hydride (0.02 mol) was added to it portionwise with constant stirring at 5°C for 1 h. ω-Bromoethoxyphthalimide **5a** (0.02 mol) was then added to the above mixture with constant stirring on a magnetic stirrer for 1–2 h and further stirred for 4–6 h. Excess of solvent was removed *in vacuo*. After cooling, a brownish coloured solid was obtained which was recrystallised from ethanol. Compounds **6b-n** were similarly prepared using appropriate reactants with an appropriate reflux time. Physical and analytical data for **6a–6n** are given in Table I.

6a. IR (KBr) cm^{-1}: 3040 (C—H str., Ar—H), 1728 (C=O str., CO—N—CO), 1616 (C=N str.), 1220 (C—N str.), 1107 (N—N str.), 1370 (N—O str.), 2830 (C—H str., CH_2); ^{1}H NMR ($CDCl_3$) δ: 7.08–7.81 (m, 22H, ArH, *J* (Hz) = 6.63, 7.95, 8.32), 4.20 (dd, 2H, CH), 3.48 (dd, 2H, **CH$_b$**CH$_a$), 2.90 (dd, 2H, CH$_b$**CH$_a$**), (*J* (Hz) = 11.75, 14.00), 4.51 (t, 4H, OCH_2, *J* (Hz) = 12.00), 3.08 (t, 4H, NCH_2, *J* (Hz) = 15.00), ^{13}C NMR δ: 166.00 (C=O), 67.30 (CH), 70.77 (OCH_2), 55.48 (NCH_2), 45.60 (CH_2); MS m/z: 744 $[M]^+$, 667, 598, 590, 570, 452, 396, 348, 292, 174, 77.

5,5′-(1,4-Phenylene)bis[1-N-ethoxyphthalimido-3-(4-fluorophenyl)-2-pyrazoline] ***6c***. IR (KBr) cm^{-1}: 3073 (C—H str., Ar—H), 1734 (C=O str., CO—N—CO), 1621 (C=N str.), 1223 (C—N str.), 1115 (N—N str.), 1381 (N—O str.), 2842 (C—H str., CH_2), 1387 (C—F str.); ^{1}H NMR ($CDCl_3$) δ: 6.96–7.81 (m, 20H, ArH,

Table I. Physical and Analytical data for compounds **6a-n**.

Cpd.	Ar	N	Mol. Formula	m.wt	Yield %	m.p.(c)	Analysis (%) found (calcd)		
							C	N	H
6a	C_6H_5-	2	$C_{44}H_{36}N_6O_6$	744	76	130	70.88 (70.96)	11.14 (11.29)	4.72 (4.8)
6b	C_6H_5-	4	$C_{48}H_{44}N_6O_6$	800	65	120	71.64 (72.00)	10.41 (10.50)	4.48 (5.5)
6c	4-F.C_6H_4-	2	$C_{44}H_{34}N_6O_6F_2$	780	59	112	67.61 (67.69)	10.65 (10.76)	4.29 (4.35)
6d	4-F.C_6H_4-	4	$C_{48}H_{44}N_6O_6F_2$	836	62	108	68.80 (68.89)	9.82 (10.04)	5.18 (5.26)
6e	4-NO_2.C_6H_4-	2	$C_{44}H_{34}N_8O_{10}$	834	51	132	63.18 (63.30)	13.36 (13.42)	4.02 (4.07)
6f	4-NO_2.C_6H_4-	4	$C_{48}H_{42}N_8O_{10}$	890	72	123	64.60 (64.71)	12.53 (12.58)	4.67 (4.71)
6g	4-Cl.C_6H_4-	2	$C_{44}H_{34}N_6O_6C_{l2}$	813	67	109	64.81 (64.94)	10.23 (10.33)	4.16 (4.18)
6h	4-Cl.C_6H_4-	4	$C_{48}H_{42}N_6O_6C_{l2}$	869	76	96	66.17 (66.28)	9.51 (9.66)	4.75 (4.83)
6i	2, 4-Cl_2.C_6H_3-	2	$C_{44}H_{32}N_6O_6Cl_4$	882	42	116	59.81 (59.86)	9.46 (9.52)	3.48 (3.62)
6j	2, 4-Cl_2.C_6H_3-	4	$C_{48}H_{40}N_6O_6Cl_4$	938	47	101	60.34 (61.40)	8.86 (8.95)	4.13 (4.26)
6k	4-Br.C_6H_4	2	$C_{44}H_{34}N_6O_6Br_2$	902	67	104	58.45 (58.53)	9.22 (9.31)	3.69 (3.76)
6l	4-Br.C_6H_4	4	$C_{48}H_{42}N_6O_6Br_2$	958	56	95	59.94 (60.12)	8.63 (8.76)	4.31 (4.38)
6m	4-OCH_3.C_6H_4	2	$C_{46}H_{40}N_6O_8$	804	61	119	68.46 (68.56)	10.29 (10.44)	4.93 (4.97)
6n	4-OCH_3.C_6H_4	4	$C_{50}H_{48}N_6O_8$	860	60	103	69.70 (69.76)	9.55 (9.76)	5.50 (5.58)

J (Hz) = 7.95, 9.00, H—F = 8.66), 4.20 (dd, 2H, CH), 3.48 (dd, 2H, $\mathbf{CH_b}CH_a$), 2.90 (dd, 2H, $CH_b\mathbf{CH_a}$), (*J* (Hz) = 11.75, 14.00), 4.51 (t, 4H, OCH_2, *J* (Hz) = 12.00), 3.08 (t, 4H, NCH_2, *J* (Hz) = 15.00), ^{13}C NMR δ: 166.74 (C—F), 166.00(C═O), 67.30 (CH), 70.77 (OCH_2), 55.48 (NCH_2), 45.80 (CH_2); MS m/z: 780 $[M]^+$, 685, 634, 606, 590, 488, 432, 348, 292, 190, 174, 146, 95.

5,5′-(1,4-Phenylene)bis[1-N-ethoxyphthalimido-3-(4-nitrophenyl)-2-pyrazoline] ***6e***. IR (KBr) cm^{-1}: 3069 (C—H str., Ar—H), 1732 (C═O str., CO—N—CO), 1332-1546 (N—O str., NO_2), 2840 (C—H str., CH_2), 1221 (C—N str.); ^{1}H NMR ($CDCl_3$) δ: 7.32–8.18 (m, 20H, ArH, *J* (Hz) = 6.63, 7.95, 8.70), 4.20 (dd, 2H, CH), 3.48 (dd, 2H, $\mathbf{CH_b}CH_a$), 2.90 (dd, 2H, $CH_b\mathbf{CH_a}$), (*J* (Hz) = 11.75, 14.00), 4.51 (t, 4H, OCH_2, *J* (Hz) = 12.00), 2.97 (t, 4H, NCH_2, *J* (Hz) = 15.00), ^{13}C NMR δ: 166.00 (C═O), 67.30 (CH), 70.77 (OCH_2), 55.48 (NCH_2), 45.13 (CH_2); MS m/z: 834 $[M]^+$, 712, 688, 660, 590, 542, 486, 348, 292, 244, 146, 122.

5,5′-(1,4-Phenylene)bis[1-N-ethoxyphthalimido-3-(4-chlorophenyl)-2-pyrazoline] ***6g***. IR (KBr) cm^{-1}: 3067 (C—H str., Ar—H), 1733 (C═O str., CO—N—CO), 2840 (C—H str., CH_2), 1379 (N—O str.), 744 (C—Cl str.); ^{1}H NMR ($CDCl_3$) δ: 7.10–7.80 (m, 20H, ArH, *J* (Hz) = 7.95, 8.32), 4.20 (dd, 2H, CH), 3.48 (dd, 2H, $\mathbf{CH_b}CH_a$), 2.90 (dd, 2H, $CH_b\mathbf{CH_a}$), (*J* (Hz) = 11.75, 14.00), 4.52 (t, 4H, OCH_2, *J* (Hz)= 12.00), 3.08 (t, 4H, NCH_2, *J* (Hz) = 15.00), ^{13}C NMR δ: 166.00 (C═O), 67.30 (CH), 70.77 (OCH_2), 55.48 (NCH_2), 45.56 (CH_2); MS m/z: 817 $[M + 4]^+$, 813 $[M]^+$, 704, 702, 667, 639, 591, 521, 348, 292, 226, 222, 174, 146, 113, 111.

5,5′-(1,4-Phenylene)bis[1-N-butoxyphthalimido-3-(2,4-dichlorophenyl)-2-pyrazoline] ***6j***. IR(KBr) cm^{-1}: 3076 (C—H str., Ar-H), 1736 (C═O str., CO—N—CO), 1381 (N—O str.), 749 (C—Cl str.); ^{1}H NMR ($CDCl_3$) δ:7.18–7.86 (m,18H, ArH, *J* (Hz) =6.63, 7.95, 8.50), 4.20 (dd, 2H, CH), 3.48 (dd, 2H, $\mathbf{CH_b}CH_a$), 2.90 (dd, 2H, $CH_b\mathbf{CH_a}$), (*J* (Hz) = 11.75, 14.00), 4.56 (t, 4H, OCH_2, *J* (Hz) = 10.30), 1.77–1.80 (m, 8H, $NCH_2\mathbf{(CH_2)_2}CH_2O$, *J*(Hz) = 6.00), 3.25 (t, 4H, NCH_2, *J* (Hz) = 14.00), ^{13}C NMR δ: 165.30 (C═O), 67.30 (CH), 70.77 (OCH_2), 55.48 (NCH_2), 45.13 (CH_2), 26.78 ($NCH_2\mathbf{CH_2}$), 28.11 ($OCH_2\mathbf{CH_2}$); MS m/z: 946 $[M + 8]^+$, 938 $[M]^+$, 797, 792, 793, 736, 648, 646, 534, 404, 298, 292, 290, 202, 149, 146, 145.

5,5′-(1,4-Phenylene)bis[1-N-butoxyphthalimido-3-(4-bromophenyl)-2-pyrazoline] ***6l***. IR (KBr) cm^{-1}: 3063 (C—H str., Ar-H), 1731 (C═O str., CO—N—CO), 1379 (N—O str.), 574 (C—Br str.); ^{1}H NMR ($CDCl_3$) δ:7.18–7.86 (m, 20H, ArH, *J* (Hz) = 7.95, 8.50), 4.20 (dd, 2H, CH), 3.48 (dd, 2H, $\mathbf{CH_b}CH_a$), 2.90 (dd, 2H, $CH_b\mathbf{CH_a}$), (*J* (Hz) = 11.75, 14.00), 4.56 (t, 4H, OCH_2, *J* (Hz) = 10.30), 1.76–7.80 (m, 8H, $NCH_2\mathbf{(CH_2)_2}CH_2O$, *J* (Hz) = 6.00), 3.24 (t, 4H, NCH_2, *J* (Hz) = 14.00), ^{13}C NMR δ: 165.35 (C═O), 69.88 (CH), 75.60 (OCH_2), 57.00 (NCH_2), 43.25 (CH_2), 26.78 ($NCH_2\mathbf{CH_2}$), 28.11 ($OCH_2\mathbf{CH_2}$); MS m/z: 960$[M + 2]^+$, 958 $[M]^+$, 812, 804, 803, 756, 666, 648, 554, 404, 312, 310, 292, 202, 156, 155, 146.

5,5′-(1,4-Phenylene)bis[1-N-butoxyphthalimido-3-(4-methoxyphenyl)-2-pyrazoline] ***6n***. IR (KBr) cm^{-1}: 3065 (C—H str., Ar—H), 1728 (C═O str., CO—N—CO), 1375 (N—O str.), 1060 (O—CH_3 str.); ^{1}H NMR ($CDCl_3$) δ:6.94–7.83 (m, 20H, ArH, *J* (Hz) = 6.63, 7.95, 8.74), 4.20 (dd, 2H, CH), 3.48 (dd, 2H, $\mathbf{CH_b}CH_a$), 2.90 (dd, 2H, $CH_b\mathbf{CH_a}$), (*J* (Hz) = 11.75, 14.00), 4.56 (t, 4H, OCH_2, *J* (Hz) = 10.30), 1.77-7.80 (m, 8H, $NCH_2\mathbf{(CH_2)_2}CH_2O$, *J* (Hz) = 6.00), 3.30 (t, 4H, NCH_2, *J* (Hz) = 14.00), ^{13}C NMR δ: 165.00 (C═O), 69.87 (CH), 74.60 (OCH_2), 57.00 (NCH_2), 43.25 (CH_2),

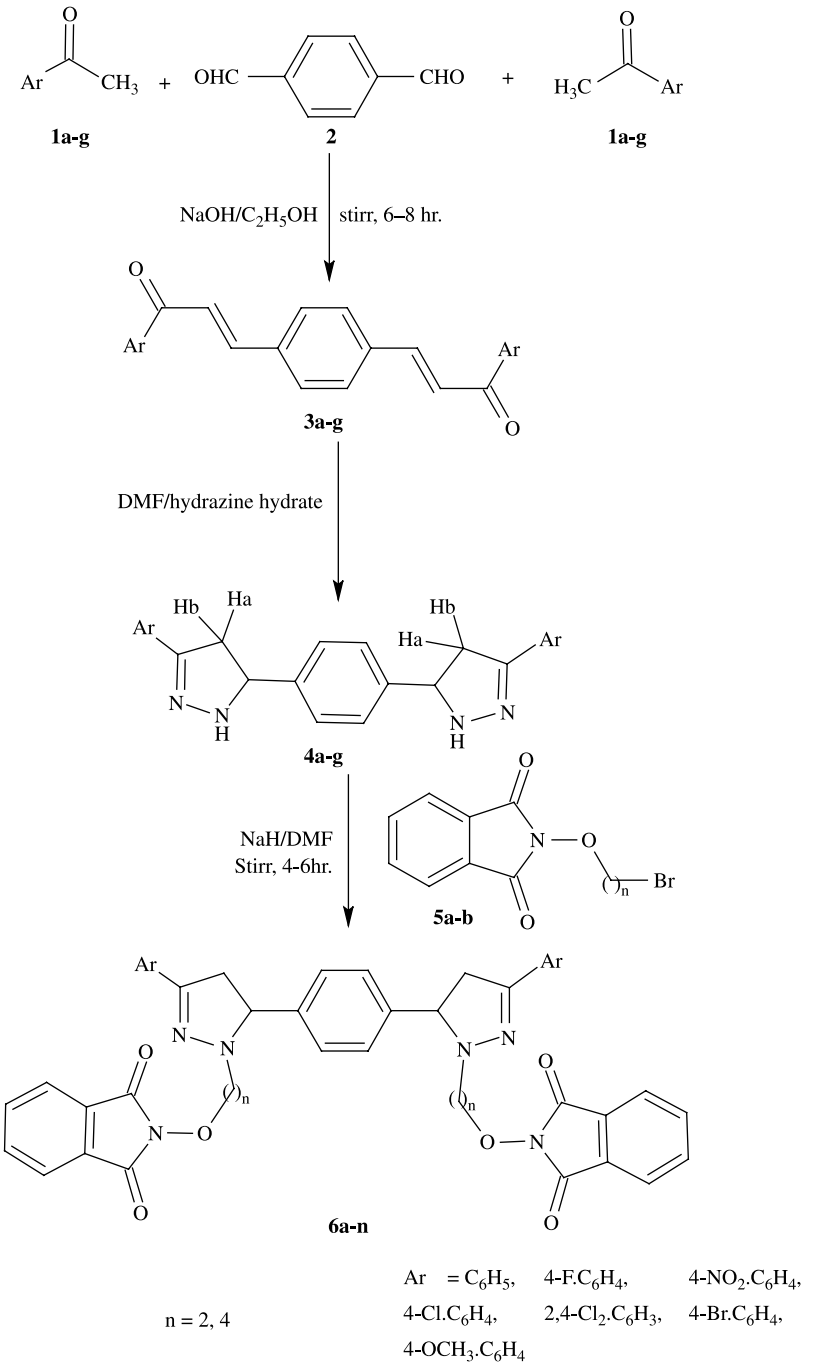
26.78 ($NCH_2\mathbf{CH_2}$), 28.11 ($OCH_2\mathbf{CH_2}$); MS m/z: 860 $[M]^+$, 753, 714, 658, 646, 568, 456, 404, 292, 214, 202, 107.

Antimalarial activity

A simple *in vitro*, one-step, one-pot, microtiter-plate based, high-throughput antimalarial drug screening method [25] was used based on the fact that the red colour of here- PFHRP II (*Plasmodium falciparum* histidine- rich protein II) complex changes to green on dissociation of the bound hence by a candidate antimalarial drug. This method involves the use of a mixture of hence and a recombinantly produced HRP II to which a candidate drug is added and the change in colour following a short incubation period is monitored.

Antimicrobial activity

All the newly synthesized compounds were also tested *in vitro* for their ability to inhibit the growth of four bacterial strains *viz. Klebseilla pneumoniae, Proteus mirabilis, Bacilus subtilis* and *Escherichia coli* using 50 μg/mL concentrations in DMF by the cup or well



Scheme 1. Synthetic route to **6a–n**.

method [26]. Antimicrobial activity was measured as a function of zone of inhibition (mm). Results were compared to the standard ciprofloxacin by measuring zone of inhibition using disc diffusion method [27].

Result and discussion

Chemistry

5,5′-(1,4-Phenylene)bis(3-phenyl-2-pyrazoline) **4a** was prepared by the cyclisation of an α-β unsaturated carbonyl compound **3a** with hydrazine hydrate in DMF (Scheme 1). In order to obtain the titled compound **6a**, ω-bromoethoxyphthalimide **5a** was condensed with **4a,** sodium hydride in DMF being used to replace the acidic hydrogen present on the nitrogen. Confirmations of the formation of **6a** from **4a** were obtained through spectral and analytical data. Disappearance of N—H str. (3405 cm^{-1}) in IR and singlet for N—H proton (δ 6.18) in NMR which were present in **4a** and appearance of carbonyl absorption band at 1728 cm^{-1} of CO—N—CO, N—O str. at 1370 cm^{-1} and two triplets at δ 4.51 and 3.08 for OCH_2 and NCH_2 respectively in the ^1H NMR spectra indicated formation of the titled compound **6a**. Compounds **6c**, **6e**, **6g**, **6i**, **6k** and **6m** were similarly prepared. Compounds **6b, 6d**, **6f**, **6h**, **6j, 6r** and **6n** were synthesized using ω-bromo-butoxyphthalimide.

Antimalarial activity

Using the present assay seven pyrazoline derivatives were tested. It was observed that phthalimidoxy-containing derivatives are more active than the parent pyrazoline analogues (without phthalimidoxy). Unsubstituted aryl derivative were observed to be the least potent, the methoxy and nitro derivatives possess intermediate activity, and the halogenated derivatives to be the most potent; of the four halogen derivatives studied, the 2,4-dichloro and 4-chloro-derivatives seemed to be slightly more effective than the fluoro- and bromo derivatives. Graphical representation of comparative antimalarial activity for the synthesized compounds is depicted in Figure 1.

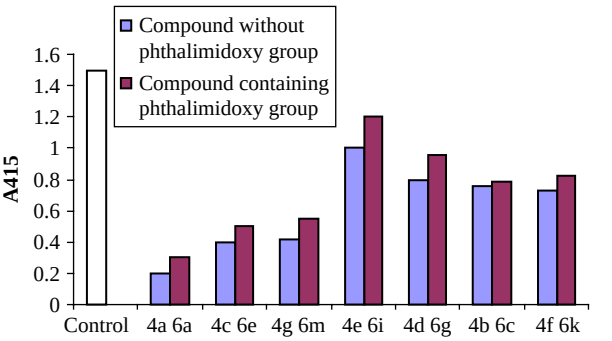


Figure 1. Comparative antimalarial activity of various bis-pyrazolines and their ethoxyphthalimido analogues.

Antimicrobial activity

Most of the compounds were inactive against *Bacilus subtilis*, whereas all the compounds exhibited low to moderate activity against other strains of bacteria as compared to the standard drug (Table II). Compound **(6i)** was found to be highly active against *K. pneumoniae* and the activity of **(6k)** was comparable to that of the standard; others were moderate active. In the case of *E. coli* the compounds were moderate to highly active as compared to the standard ciprofloxacin.

It can be concluded from the above results that the antibacterial activities of the compounds depend on the carbon chain length of the alkoxyphthalimide group and the presence of substitution on the phenyl group. It was observed for many compounds that as the length of alkyl side chain increased, inhibitory activity decreased.

Table II. Antibacterial activity of compounds **6a-n**⋆†.

Compd. No.	*K. pneumoniae*	*P. mirabilis*	*B. subtilis*	*E. coli*
6a	10 (0.55)	12 (0.42)	9 (0.34)	12 (0.54)
6b	11 (0.61)	9 (0.32)	–	14 (0.63)
6c	14 (0.77)	14 (0.5)	13 (0.5)	13 (0.59)
6d	12 (0.66)	13 (0.46)	11 (0.42)	11 (0.5)
6e	16 (0.88)	16 (0.57)	–	19 (0.86)
6f	13 (0.72)	12 (0.42)	–	17 (0.77)
6g	15 (0.83)	18 (0.64)	12 (0.46)	13 (0.59)
6h	13 (0.72)	14 (0.5)	8 (0.30)	15 (0.68)
6I	20 (1.11)	16 (0.57)	9 (0.34)	18 (0.81)
6j	17 (0.94)	17 (0.60)	6 (0.23)	17 (0.77)
6k	18 (1.11)	16 (0.57)	9 (0.34)	16 (0.72)
6l	15 (0.94)	20 (0.71)	10 (0.38)	13 (0.59)
6m	16 (0.88)	18 (0.64)	7 (0.26)	21 (0.95)
6n	14 (0.77)	17 (0.60)	5 (0.19)	20 (0.90)
Ciprofloxacin (standard)	18	28	26	22

⋆ Zone of inhibition in mm; Diameter of disc is 5 mm; † Activity index (in parentheses) = Inhibition zone of the compound / inhibition zone of the standard.

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