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SEARCH FOR NEW PHARMACOPHORE AS ANTIMALARIAL AGENT: SYNTHESIS AND ANTIMALARIAL ACTIVITY OF SOME 2(3*H*)-FURANONES BEARING QUINOLINE MOIETY†

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Abstract: A series of substituted 3-[(substituted-2-chloroquinolin-3-yl)methylene]-5-(substituted-phenyl)-furan-2(3*H*)-ones (**4a-p**) have been synthesized and evaluated for their *in vitro* antimalarial activity against *P. falciparum*. The title compounds were synthesized by condensing 3-(substituted-benzoyl)propionic acids (**3a-d**) with substituted 2-chloroquinoline-3-carbaldehydes (**2a-d**) following modified Perkin's reaction. Compounds 3-[2-chloro-6-methylquinolin-3-yl)methylene]-5-(2,4-dimethyl-phenyl)-furan-2(3*H*)-one (**4n**) and 3-[2-chloro-6-methoxyquinolin-3-yl)methylene]-5-(2,4-dimethyl-phenyl)-furan-2(3*H*)-one (**4p**) showed promising antimalarial activity with MIC of 10 μg/mL.

Keywords: Quinoline, furanones, antimalarial

Malaria, the world's most devastating human parasitic infection, affects over 40% of the world's population. Of the four *Plasmodium* species viz. *P. falciparum, P. vivax, P. malariae* and *P. ovale*, *P. falciparum* is the major cause of fatalities. World Health Organization estimates that there are 350–500 million cases of malaria worldwide, of which 270–400 million are falciparum malaria (1, 2). The parasite's resistance to current antimalarial therapeutics has generated the need for constant research for new antimalarial regimens (3).

Studies on various ring systems as well as knowledge of selective plasmodial targets are in process to develop agents for the treatment of malaria, which would have considerable level of activity and a minimum level of toxicity (3). Quinoline and its derivatives are an important class of pharmaceutical agents known to occur in several natural compounds and found to possess antibacterial (4, 5), antifungal (6), anthelmintic (7), anticonvulsant (8), antiviral (9), anti-inflammatory (10), analgesic (11), cardiovascular (12) and antimalarial (13) activities. Similarly, furan and its derivatives possess good anti-infective properties like antimalarial (14), antifungal (15, 16), antibacterial (17–19), anti-inflammatory (18, 19), analgesic (19) and antiviral (20) in addition to other properties like antioxidant (21), cardiotonic (22), etc.

In view of these observations and as a part of our ongoing research program on development of newer anti-infective agents (19, 23, 24) we herein report the synthesis and antimalarial activity of a series of 2(3*H*) furanones fused with quinoline moiety.

EXPERIMENTAL

Chemicals used were procured from Merck and Sigma-Aldrich. Melting points referred to complete melting were determined by open tube capillary method and are uncorrected. Purity of the compounds was checked by thin layer chromatography (TLC) on silica gel G plates (Merck No. 5544) using toluene : ethyl acetate : formic acid (5:4:1, v/v/v) as solvent system and the spots were located either under UV light or through exposure to iodine vapors. The IR spectra were measured using a Perkin-Elmer 1725X spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance apparatus at 400 and 100 MHz, respectively, in $CDCl_3$ or DMSO with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ)

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are reported in parts per million (ppm) downfield from TMS. The mass spectra were recorded on a Jeol JMS-D 300 instrument fitted with a JMS 2000 data system at 70 eV. Elemental analyses were performed on a Perkin-Elmer model 240 analyzer (C, H, N) and found within ± 0.4% range of theoretical values. Compounds (**2a-d**) and (**3a-d**) were synthesized by reported method (25, 26).

General procedure for the synthesis of 3-[(substituted-2-chloroquinolin-3-yl)methylene]-5-(substituted-phenyl)-furan-2(3*H*)-ones (**4a-p**)

Compounds (**3a-d**) and (**2a-d**) were fused together in equimolar ratio in the presence of acetic anhydride (5–8 drops) in a round bottom flask for half an hour. To this fused mixture, triethylamine (2 drops) was added and heated on heating mantle for another 1 h. After the completion of reaction a solid mass was obtained, which on crystallization with methanol gave the desired products (**4a-p**).

3-[2-Chloroquinolin-3-yl)methylene]-5-phenyl-furan-2(3*H*)-one (**4a**)

Yield: 52%; m.p. 136°C; R_f 0.72; IR (cm^{-1}): 1740 (lactone C=O), 1560 (ArC=C), 1070 (ArC-N), 864 (ArC-H); ^{1}H-NMR (ppm): 6.84 (s, 1H, βH), 7.22–7.28 (m, 5H, H-2,3,4,5,6, phenyl ring), 7.43 (m, 2H, H-5,7, quinoline ring), 7.68 (t, 1H, *J* = 7.3 Hz, H-6, quinoline ring), 7.92 (m, 1H, H-8, quinoline ring), 8.28 (s, 1H, H-4, quinoline ring), 8.38 (s, 1H, olefinic linkage); ^{13}C-NMR (ppm): 167.36, 164.06, 148.50, 147.46, 136.80, 136.14, 134.08, 132.07, 130.30, 129.80, 129.22, 128.31, 128.15, 127.30, 126.12, 125.44, 122.34, 115.33; MS (*m/z*): 334 (M^+), 336 (M^+ + 2).

3-[2-Chloro-6-methylquinolin-3-yl)methylene]-5-phenyl-furan-2(3*H*)-one (**4b**)

Yield: 64%; m.p. 176°C; R_f: 0.80; IR (cm^{-1}): 1740 (lactone C=O), 1558 (ArC=C), 1062 (ArC-N), 810 (ArC-H); ^{1}H-NMR (ppm): 2.15 (s, 3H, CH_3), 6.88 (s, 1H, βH), 7.18–7.25 (m, 5H, H-2,3,4,5,6, phenyl ring), 7.49 (d, 1H, *J* = 1.6 Hz, H-5, quinoline ring), 7.56 (dd, 1H, *J* = 7.8, 1.6 Hz, H-7, quinoline ring), 7.84 (d, 1H, *J* = 7.8 Hz, H-8, quinoline ring), 8.26 (s, 1H, H-4, quinoline ring), 8.34 (s, 1H, olefinic linkage); MS (*m/z*): 348 (M^+), 350 (M^+ + 2). Analysis: Calcd. for $C_{21}H_{14}ClNO_2$: C, 72.52 ; H, 4.06; N, 4.03%; found: C, 72.53; H, 4.07; N, 4.01%.

3-[2,6-Dichloroquinolin-3-yl)methylene]-5-phenyl-furan-2(3*H*)-one (**4c**)

Yield: 56%; m.p. 184°C; R_f: 0.74; IR (cm^{-1}): 1740 (lactone C=O), 1562 (ArC=C), 1068 (ArC-N), 822 (ArC-H); ^{1}H-NMR (ppm): 6.60 (s, 1H, βH), 7.26–7.34 (m, 5H, H-2,3,4,5,6, phenyl ring), 7.62 (d, 1H, *J* = 1.9 Hz, H-5, quinoline ring), 7.68 (dd, 1H, *J* = 8.6, 1.9 Hz, H-7, quinoline ring), 7.80 (d, 1H, *J* = 8.5 Hz, H-8, quinoline ring), 7.94 (s, 1H, H-4, quinoline ring), 8.24 (s, 1H, olefinic linkage); MS (*m/z*): 368 (M^+), 370 (M^+ + 2). Analysis: Calcd. for $C_{20}H_{11}Cl_2NO_2$: C, 65.24; H, 3.01; N, 3.80%; found: C, 65.12; H, 3.02; N, 3.81%.

3-[2-Chloro-6-methoxyquinolin-3-yl)methylene]-5-phenyl-furan-2(3*H*)-one (**4d**)

Yield: 64%; m.p. 154°C; R_f: 0.82; IR (cm^{-1}): 1740 (lactone C=O), 1562 (ArC=C), 1066 (ArC-N), 816 (ArC-H); ^{1}H-NMR (ppm): 3.86 (s, 3H, OCH_3), 6.62 (s, 1H, βH), 7.20–7.26 (m, 5H, H-2,3,4,5,6, phenyl ring), 7.54 (d, 1H, *J* = 1.8 Hz, H-5, quinoline ring), 7.60 (dd, 1H, *J* = 8, 1.8 Hz, H-7, quinoline ring), 7.72 (d, 1H, *J* = 8 Hz, H-8, quinoline ring), 7.92 (s, 1H, H-4, quinoline ring), 8.02 (s, 1H, olefinic linkage); MS (*m/z*): 364 (M^+), 366 (M^+ + 2). Analysis: Calcd. for $C_{21}H_{14}ClNO_3$: C, 69.33; H, 3.88; N, 3.85%; found: C, 69.58; H, 3.87; N, 3.86%.

3-[2-Chloroquinolin-3-yl)methylene]-5-(4-methylphenyl)-furan-2(3*H*)-one (**4e**)

Yield: 34%; m.p. 204°C; R_f: 0.89; IR (cm^{-1}): 1742 (lactone C=O), 1562 (ArC=C), 1066 (ArC-N), 812 (ArC-H); ^{1}H-NMR (ppm): 2.18 (s, 3H, CH_3), 6.84 (s, 1H, βH), 7.20 (d, 2H, *J* = 8.3 Hz, H-3,5, phenyl ring), 7.39 (d, 2H, *J* = 8.2 Hz, H-2,6, phenyl ring), 7.46 (m, 2H, H-5,7, quinoline ring), 7.70 (m, 2H, H-6,8, quinoline ring), 8.18 (s, 1H, H-4, quinoline ring), 8.38 (s, 1H, olefinic linkage); MS (*m/z*): 348 (M^+), 350 (M^+ + 2). Analysis: Calcd. for $C_{21}H_{14}ClNO_2$: C, 72.52; H, 4.06; N, 4.03%; found: C, 72.33; H, 4.05; N, 4.03%.

3-[2-Chloro-6-methylquinolin-3-yl)methylene]-5-(4-methylphenyl)-furan-2(3*H*)-one (**4f**)

Yield: 48%; m.p. 190°C; R_f: 0.81; IR (cm^{-1}): 1795 (lactone C=O), 1558 (ArC=C), 1062 (ArC-N), 820 (ArC-H); ^{1}H-NMR (ppm): 2.24 and 2.26 (s, 6H, 2×CH_3), 6.63 (s, 1H, βH), 7.28 (d, 2H, *J* = 8 Hz, H-3,5, phenyl ring), 7.42 (d, 2H, *J* = 8.1 Hz, H-2,6, phenyl ring), 7.53 (d, 1H, *J* = 1.6 Hz, H-5, quinoline ring), 7.59 (dd, 1H, J = 8.4, 1.6 Hz, H-7, quinoline ring), 7.74 (d, 1H, *J* = 8.4 Hz, H-8, quinoline ring), 7.88 (s, 1H, H-4, quinoline ring), 8.27 (s, 1H, olefinic linkage); MS (*m/z*): 362 (M^+), 364 (M^+ + 2). Analysis: Calcd. for $C_{22}H_{16}ClNO_2$: C, 73.03; H, 4.46; N, 3.87:; found: C, 72.95; H, 4.45; N, 3.85%.

3-[2,6-Dichloroquinolin-3-yl)methylene]-5-(4-methylphenyl)-furan-2(3*H*)-one (**4g**)

Yield: 32%; m.p. 264°C; R_f: 0.9; IR (cm^{-1}): 1744 (lactone C=O), 1562 (ArC=C), 1064 (ArC-N), 822 (ArC-H); ^{1}H-NMR (ppm): 2.22 (s, 3H, CH_3), 6.77 (s, 1H, βH), 7.25 (d, 2H, *J* = 8 Hz, H-3,5, phenyl ring), 7.49 (d, 2H, *J* = 8 Hz, H-2,6, phenyl ring), 7.58 (d, 1H, *J* = 2.1 Hz, H-5, quinoline ring), 7.64 (dd, 1H, *J* = 8.6, 2.1 Hz, H-7, quinoline ring), 7.84 (d, 1H, *J* = 8.6Hz, H-8, quinoline ring), 8.02 (s, 1H, H-4, quinoline ring), 8.34 (s, 1H, olefinic linkage); MS (*m/z*): 382 (M^+), 384 (M^+ + 2). Analysis: Calcd. for $C_{21}H_{13}Cl_2NO_2$: C, 65.99; H, 3.43; N, 3.66%; found: C, 65.88; H, 3.42; N, 3.64%.

3-[2-Chloro-6-methoxyquinolin-3-yl)methylene]-5-(4-methylphenyl)-furan-2(3*H*)-one (**4h**)

Yield: 48%; m.p. 242°C; R_f: 0.82; IR (cm^{-1}): 1796 (lactone C=C), 1557 (ArC=C), 1060 (ArC-N), 817 (ArC-H); ^{1}H-NMR (ppm): 2.16 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 6.85 (s, 1H, βH), 7.21 (d, 2H, *J* = 8.2 Hz, H-3,5, phenyl ring), 7.38 (d, 2H, *J* = 8.1 Hz, H-2,6, phenyl ring), 7.32 (d, 1H, *J* = 1.8 Hz, H-5, quinoline ring), 7.68 (s, 1H, H-4, quinoline ring), 7.81 (d, 1H, *J* = 8.1 Hz, H-7, quinoline ring), 8.26 (s, 1H, olefinic linkage); MS (*m/z*): 378 (M^+), 380 (M^+ + 2). Analysis: Calcd. for $C_{22}H_{16}ClNO_3$: C, 69.94; H, 4.27; N, 3.71%; found: C, 70.12; H, 4.28; N, 3.72%.

3-[2-Chloroquinolin-3-yl)methylene]-5-(4-bromophenyl)-furan-2(3*H*)-one (**4i**)

Yield: 30%; m.p. 216°C; R_f: 0.85; IR (cm^{-1}): 1748 (lactone C=O), 1612 (ArC=C), 1062 (ArC-N), 826 (ArC-H); ^{1}H-NMR (ppm): 6.71 (s, 1H, βH), 7.36 (d, 2H, *J* = 8.8 Hz, H-3,5, phenyl ring), 7.48 (d, 2H, *J* = 8.7 Hz, H-2,6, phenyl ring), 7.58–7.68 (m, 4H, H-5,6,7,8, quinoline ring), 8.08 (s, 1H, H-4, quinoline ring), 8.16 (s, 1H, olefinic linkage); MS (*m/z*): 413 (M^+), 415 (M^+ + 2). Analysis: Calcd. for $C_{20}H_{11}ClBrNO_2$: C, 58.21; H, 2.69; N, 3.39%; found: C, 58.38; H, 2.70; N, 3.38%.

3-[2-Chloro-6-methylquinolin-3-yl)methylene]-5-(4-bromophenyl)-furan-2(3*H*)-one (**4j**)

Yield: 42%; m.p. 174°C; R_f: 0.83; IR (cm^{-1}): 1748 (lactone C=O), 1602 (ArC=C), 1066 (ArC-N), 810 (ArC-H); ^{1}H-NMR (ppm): 2.20 (s, 1H, CH_3), 6.60 (s, 1H, βH), 7.34 (d, 2H, *J* = 8.6 Hz, H-3,5, phenyl ring), 7.44 (d, 2H, *J* = 8.6 Hz, H-2,6, phenyl ring), 7.50 (d, 1H, *J* =1.9 Hz, H-5, quinoline ring), 7.60 (dd, 1H, *J* = 8.3, 1.9 Hz, H-7, quinoline ring), 7.78 (d, 1H, *J* = 8.4 Hz, H-8, quinoline ring), 7.96 (s, 1H, H-4, quinoline ring), 8.21 (s, 1H, olefinic linkage); MS (*m/z*): 427 (M^+), 429 (M^+ + 2). Analysis: Calcd. for $C_{21}H_{13}ClBrNO_2$: C, 59.11; H, 3.07; N, 3.28%; found: C, 58.96; H, 3.08; N, 3.29%.

3-[2,6-Dichloroquinolin-3-yl)methylene]-5-(4-bromophenyl)-furan-2(3*H*)-one (**4k**)

Yield: 32%; m.p. 156°C; R_f: 0.86; IR (cm^{-1}): 1750 (lactone C=O), 1580 (ArC=C), 1060 (ArC-N), 818 (ArC-H); ^{1}H-NMR (ppm): 6.60 (s, 1H, βH), 7.35–7.66 (m, 7H, H-5,7,8 of quinoline ring merged with H-2,3,5,6 of phenyl ring), 8.04 (s, 1H, H-4, quinoline ring), 8.21 (s, 1H, olefinic linkage); MS (*m/z*): 447 (M^+), 449 (M^+ + 2). Analysis: Calcd. for $C_{20}H_{10}Cl_2BrNO_2$: C, 53.73; H, 2.25; N, 3.13%; found: C, 53.62; H, 2.23; N, 3.12%.

3-[2-Chloro-6-methoxyquinolin-3-yl)methylene]-5-(4-bromophenyl)-furan-2(3*H*)-one (**4l**)

Yield: 38%; m.p. 264°C; R_f: 0.89; IR (cm^{-1}): 1748 (lactone C=O), 1612 (ArC=C), 1064 (ArC-N), 812 (ArC-H); ^{1}H-NMR (ppm): 3.78 (s, 1H, OCH_3), 6.64 (s, 1H, βH), 7.34–7.58 (m, 7H, H-5,7,8 of quinoline ring merged with H-2,3,5,6 of phenyl ring), 7.94 (s, 1H, H-4, quinoline ring), 8.08 (s, 1H, olefinic linkage); MS (*m/z*): 443 (M^+), 445 (M^+ + 2). Analysis: Calcd. for $C_{21}H_{13}ClBrNO_3$: C, 56.98; H, 2.96; N, 3.16%; found: C, 56.83; H, 2.97; N, 3.17%.

3-[2-Chloroquinolin-3-yl)methylene]-5-(2,4-dimethylphenyl)-furan-2(3*H*)-one (**4m**)

Yield: 36%; m.p. 138°C; R_f: 0.92; IR (cm^{-1}): 1741 (lactone C=O), 1560 (ArC=C), 1064 (ArC-N), 824 (ArC-H); ^{1}H-NMR (ppm): 2.18 and 2.22 (s, 6H, 2×CH_3), 6.61 (s, 1H, βH), 7.11–7.18 (m, 3H, H-3,5,6, phenyl ring), 7.42–7.76 (m, 5H, H-4,5,6,7,8, quinoline ring), 8.25 (s, 1H, olefinic linkage); MS (*m/z*): 362 (M^+), 364 (M^+ + 2). Analysis: Calcd. for $C_{22}H_{16}ClNO_2$: C, 73.03; H, 4.46; N, 3.87%; found: C, 73.18; H, 4.45; N, 3.86%.

3-[2-Chloro-6-methylquinolin-3-yl)methylene]-5-(2,4-dimethylphenyl)-furan-2(3*H*)-one (**4n**)

Yield: 32%; m.p. 174°C; R_f: 0.91; IR (cm^{-1}): 1755 (lactone C=O), 1610 (ArC=C), 1068 (ArC-N), 824 (ArC-H); ^{1}H-NMR (ppm): 2.20, 2.24 and 2.30 (s, 9H, 2×CH_3), 6.60 (s, 1H, βH), 7.15–7.22 (m, 3H, H-3,5,6, phenyl ring), 7.48 (d, 1H, *J* = 1.7 Hz, H-5, quinoline ring), 7.56 (dd, 1H, *J* = 7.8, 1.7 Hz, H-7, quinoline ring), 7.68 (d, 1H, *J* = 7.7 Hz, H-8, quinoline ring), 7.78 (s, 1H, H-4, quinoline ring), 8.28 (s, 1H, olefinic linkage); MS (*m/z*): 376 (M^+), 378 (M^+ + 2). Analysis: Calcd. for $C_{23}H_{18}ClNO_2$: C, 73.50; H, 4.83; N, 3.73%; found: C, 73.53; H, 4.82; N, 3.72%.

3-[2,6-Dichloroquinolin-3-yl)methylene]-5-(2,4-dimethylphenyl)-furan-2(3*H*)-one (**4o**)

Yield: 42%; m.p. 184°C; R_f: 0.87; IR (cm^{-1}): 1742 (lactone C=O), 1562 (ArC=C), 1062 (ArC-N), 821

(ArC-H); ^{1}H-NMR (ppm): 2.28 and 2.32 (s, 6H, 2×CH_3), 6.60 (s, 1H, βH), 7.06 (d, 1H, *J* = 1.5 Hz, H-3, phenyl ring), 7.14 (dd, 1H, *J* = 7.2, 1.5 Hz, H-5, phenyl ring), 7.32(d, 1H, *J* = 7.2 Hz, H-6, phenyl ring), 7.56 (d, 1H, *J* = 1.7 Hz, H-5, quinoline ring), 7.62 (dd, 1H, *J* = 7.4, 1.7 Hz, H-7, quinoline ring), 7.80 (d, 1H, *J* = 7.4 Hz, H-8, quinoline ring), 8.10 (s, 1H, H-4, quinoline ring), 8.28 (s, 1H, olefinic linkage); MS (*m/z*): 396 (M^+), 398 (M^+ + 2). Analysis: Calcd. for $C_{22}H_{15}Cl_2NO_2$: C, 66.68; H, 3.82; N, 3.53%; found: C, 66.72; H, 3.80; N, 3.54%.

3-[2-Chloro-6-methoxyquinolin-3-yl)methylene]-5-(2,4-dimethylphenyl)-furan-2(3*H*)-one (**4p**)

Yield: 36%; m.p. 200°C; R_f: 0.92; IR (cm^{-1}): 1756 (lactone C=O), 1612 (ArC=C), 1060 (ArC-N), 818 (ArC-H); ^{1}H-NMR (ppm): 2.28 and 2.34 (s, 6H, 2×CH_3), 3.98 (s, 3H, OCH_3), 6.62 (s, 1H, βH), 6.96 (d, 1H, *J* = 1.6 Hz, H-3, phenyl ring), 7.11 (dd, 1H, *J* = 7.2, 1.6 Hz, H-5, phenyl ring), 7.26 (d, 1H, *J* = 7.2 Hz, H-6, phenyl ring), 7.34 (d, 1H, *J* = 1.8Hz, H-5, quinoline ring), 7.52 (dd, 1H, *J* = 7.7, 1.8 Hz, H-7, quinoline ring), 7.64 (d, 1H, *J* = 7.6 Hz, H-8, quinoline ring), 7.72 (s, 1H, H-4, quinoline ring), 8.26 (s, 1H, olefinic linkage); MS (*m/z*): 392 (M^+), 394 (M^+ + 2). Analysis: Calcd. for $C_{23}H_{18}ClNO_3$: C, 70.50; H, 4.63; N, 3.57%; found: C, 70.66; H, 4.62; N, 3.58%.

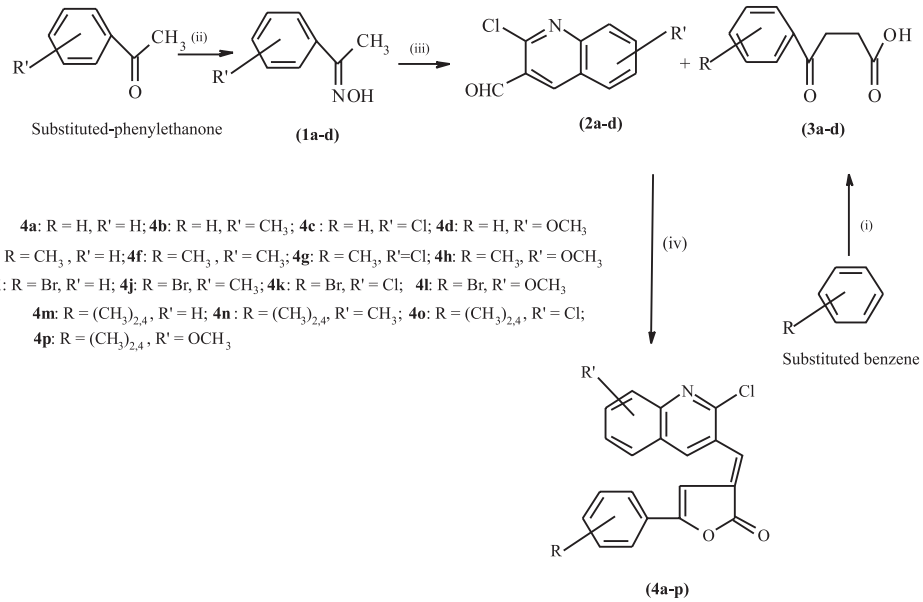
Antimalarial activity

The *in vitro* antimalarial activity was carried out according to the microassay protocol of Rieckmann et al. (27) with minor modifications. The cultures of *P. falciparum* 3D7 strain are routinely maintained in medium RPNI supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum (28). The asynchronous parasite of *P. falciparum* was synchronized after 5% D-sorbitol treatment to obtain parasitized cells harboring only the ring stage (29). For carrying out the assay, an initial ring stage parasitemia of 1.2 to 1.5% at 3% hematocrit in total volume of 200 µL of medium RPMI-1640 was uniformly maintained. A stock of 5 mg/mL concentrate of the given test samples was prepared in DMSO and subsequent dilutions were prepared in the range of 2 µg/mL to 200 µg/mL. The culture plates were incubated at 37°C in a candle jar. After 36–40 h of incubation, the blood smears from each well were prepared and stained with Giemsa stain. The slides were microscopically observed to record maturation of ring stage parasites into trophozoites and schizonts in the presence of different concentrations of the test compounds. The test concentration which inhibits the complete maturation into schizonts, was recorded as the minimum inhibitory concentration (MIC). Chloroquine was used as the standard reference drug. Activity of all the tested compounds is shown in Table 1.

RESULTS AND DISCUSSION

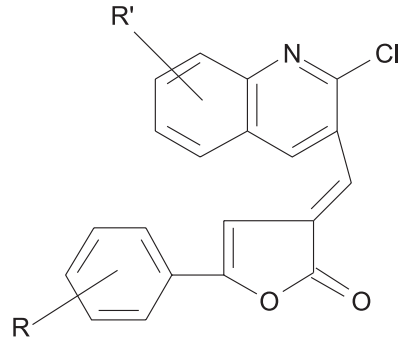
Chemistry

The title compounds (**4a-p**) were successfully synthesized by following modified Perkin reaction (Scheme 1). Calculation of δ-values using incre-



Scheme 1. Synthesis of title compounds. Reagents and conditions: (i) anhydrous $AlCl_3$, succinic anhydride; (ii) hydroxylamine hydrochloride, sodium acetate, (iii) N,N-dimethylformamide, $POCl_3$; (iv) acetic anhydride, triethylamine

Table 1. Antimalarial *in vitro* activity of (**4a-p**) against *P. falciparum*.



3-[2-Cloroquinolin-3-yl)methylene]-5-aryl-furan-2(3*H*)-one **(4a-p)**

Compound	R	R'	MIC (µg/mL)
4a	H	H	>100
4b	H	CH_3	50
4c	H	Cl	>100
4d	H	OCH_3	>100
4e	CH_3	H	>100
4f	CH_3	CH_3	50
4g	CH_3	Cl	>100
4h	CH_3	OCH_3	50
4i	Br	H	>100
4j	Br	CH_3	>100
4k	Br	Cl	>100
4l	Br	OCH_3	>100
4m	$(CH_3)_{2,4}$	H	50
4n	$(CH_3)_{2,4}$	CH_3	10
4o	$(CH_3)_{2,4}$	Cl	>100
4p	$(CH_3)_{2,4}$	OCH_3	10

MIC = Minimum inhibitory concentration for the development of ring stage parasite into the schizont stage during 40 h incubation. Standard drug – chloroquine, MIC 0.032 µg/mL

mental parameters for the hydrogen (semicyclic double bond) suggest (*E*)-configuration. All the synthesized compounds were characterized by spectroscopic data as IR, ^{1}H-NMR, ^{13}C-NMR, mass and elemental analysis.

In general, the infrared spectra of the furanones (**4a-p**) revealed stretchings at 1790–1740cm^{-1} corresponding to lactone C=O. In the ^{1}H-NMR spectral data, the presence of two singlets of one proton each between ä 6.60–6.88 and 8.02–8.34 ppm, due to ring βH and the olefinic hydrogen of the arylidene substituent were taken as conformation of cyclization to furanone.

Antimalarial activity

All the synthesized compounds (**4a-p**) were tested for antimalarial activity. Compounds **4n** and **4p** showed MIC of 10 µg/mL, while four compounds have shown MIC of 50 µg/mL. Compounds having methyl group on the phenyl ring and methyl (**4f**) and methoxyl group (**4h**) on quinoline moiety showed a MIC of 50 µg/mL. An increase in the number of methyl groups on phenyl ring (**4n** and **4p**) and placing the same substituents on quinoline ring decreases the MIC from 50 to 10 µg/mL. However, the antimalarial activity decreases in compounds (**4i-l**) having bromo substituent on phenyl ring. Biological evaluation data showed that the compounds are promising antimalarial agents. The two synthesized compounds **4n** and **4p** emerged as lead compounds. It is conceivable that these derivatives could be further modified to develop potent antimalarial agents. The furanone derivatives discov-

ered in this study may provide valuable therapeutic intervention for the treatment of malaria.

Structure activity relationship

On the basis of analysis of antimalarial activity data a structure activity relationship can be established, according to which:

The presence of methyl and methoxy group on quinoline moiety enhanced antimalarial activity.
A further increase in activity was observed with an increase in number of electropositive group(s) on phenyl moiety (**4f** = 50 μg/mL; **4n** = 10 μg/mL).

The presence of electronegative group(s) on phenyl ring has lowered activity as compared to electropositive group(s) (**4j** = > 100 μg/mL; **4f** = 50 μg/mL).

An increase in electropositive nature on phenyl ring increases the potency of compounds (**4f** = 50 μg/mL; **4n** = 10 μg/mL).

CONCLUSION

Preliminary *in vitro* testing showed that 2(3*H*)furanones linked with quinoline moiety demonstrated antimalarial activity in the micromolar range. The activity in this range in a new class of drugs has the potential to represent an important advancement in the treatment of malaria.

These promising *in vitro* results from our first series of antimalarial compounds showed a new structural class of antimalarial agents, which could have potential therapeutic utility in this devastating disease.

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