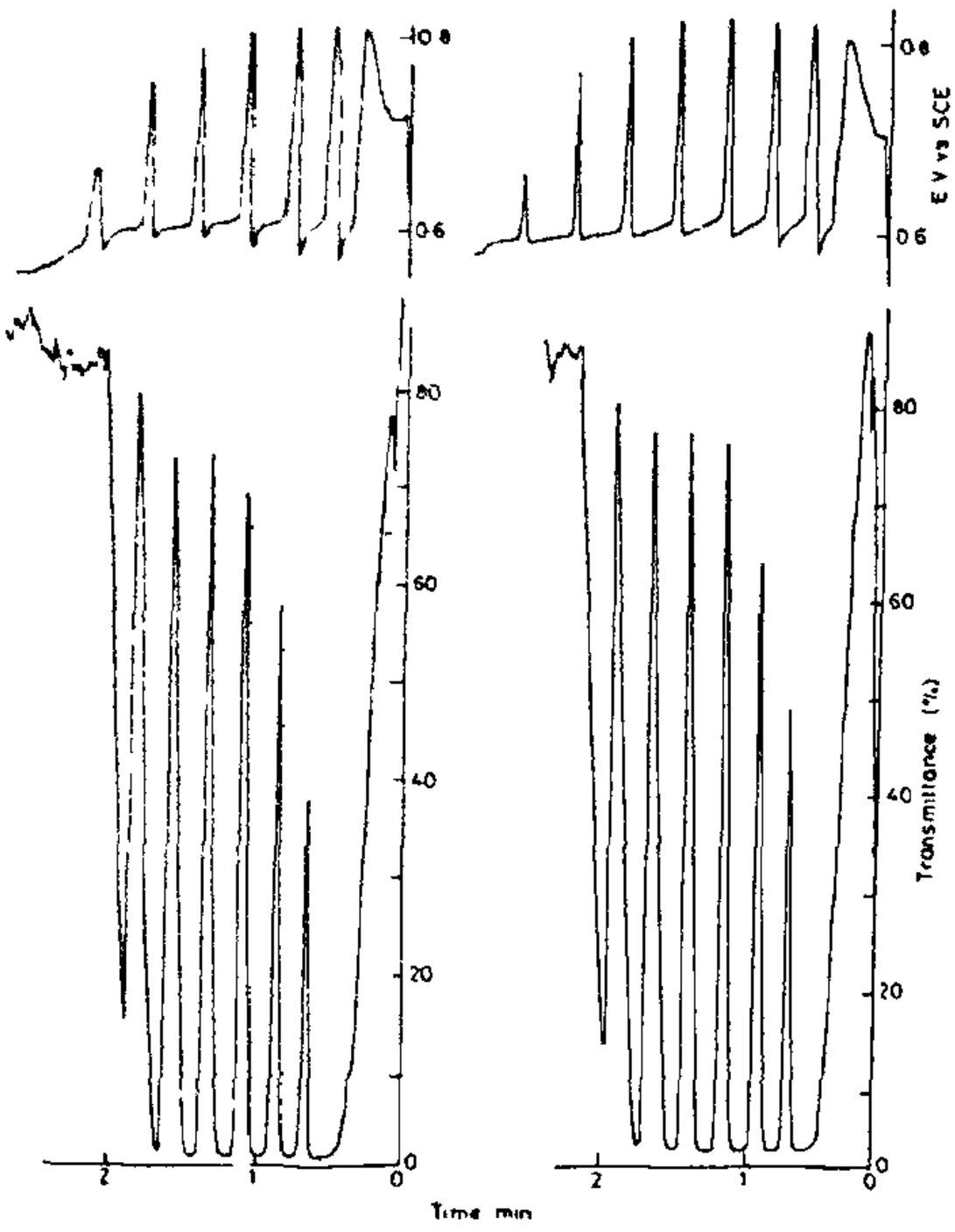

Figure 2. Spectrophotometric ($\lambda = 480\,nm$) and potentiometric (Pt electrode) oscillations in $EAA - Mn^{2+} - H_2SO_4$ – iodate system concentration conditions: $[EAA] = 0.1\,M [Mn^{2+}] = 0.003\,M$ $[H_2SO_4] = 0.1\,M [KIO_3] = 0\,058\,M [H_2O_2]$ $= 0.5\,M$. Temperature 27°C.

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SYNTHESIS OF 2-METHYL 4-[2'-((MERCAPTOACETOXY)BENZIMIDAZOLYL /BENZOXAZOLYL]-6-or 7-SUBSTITUTED QUINOLINES AS POTENT ANTIMALARIALS

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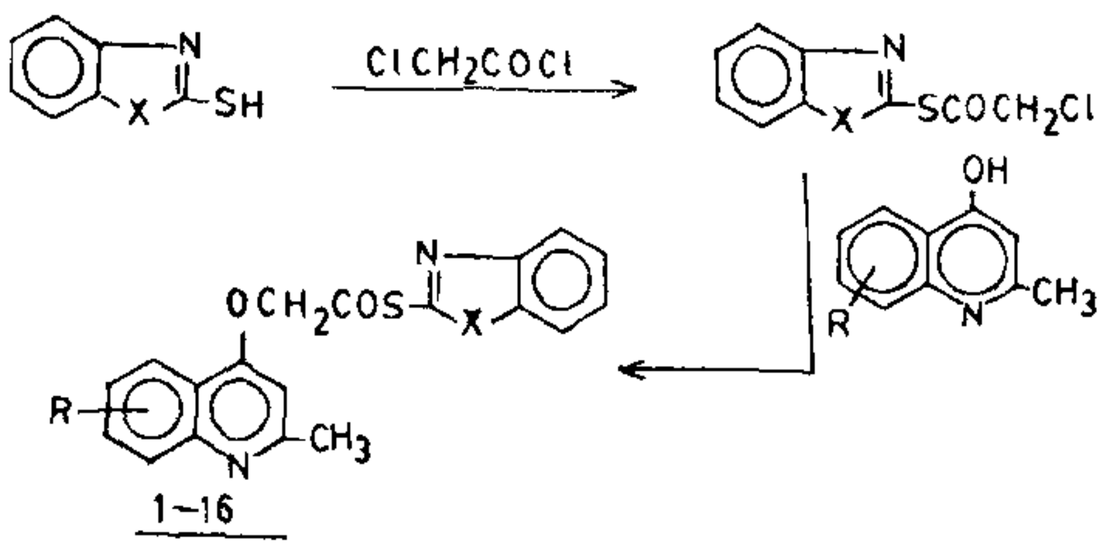
DRUGS of quinoline[1–4] type are known for their activity against erythrocytic stages of the malarial parasite. Benzimidazoles[5,6] and benzoxazoles[7,8] are also well established as biologically active agents. An attempt has been made to develop new agents that would structurally include systems related to quinoline along with benzimidazole/benzoxazole and hopefully this may result in compounds having better antimalarial activity.

2-Mercapto-benzimidazole/benzoxazole on chloroacetylation gave 2-chloroacetylmercapto-benzimidazole/benzoxazole which on condensation with 2-methyl-6 or 7-substituted quinolines, yielded 2-methyl-4-[2'-(mercapto acetoxy)benzimidazolyl/benzoxazolyl)-6 or 7-substituted quinolines.



Scheme-1

All m.ps were recorded in an open capillary and are uncorrected. The IR spectra of the compounds were taken in Perkin-Elmer 137 and 177 spectrophotometer in KBr pellets (ν_{max} in cm^{-1}) and PMR on varian A-60D and Perkin Elmer R-32 spectrometer, using TMS as internal reference. The mass spectra of the compounds were taken in Jeol-JMS-D-300 instrument.

2-Chloroacetylmercaptobenzimidazole and 2-chloroacetylmercaptobenzoxazole were prepared according to the methods reported earlier[9]. 2-Methyl-4-hydroxy 6- or 7-substituted quinolines were also prepared as described in literature[10]. 2-Chloro-acetyl mercapto-benzimidazole (2.26 g; 0.01 mol) and 2-methyl 4-hydroxyquinoline (1.6 g; 0.01 mol) were refluxed in 15 ml pyridine for 4 hr. The residue after distilling pyridine was poured in a mixture of conc. HCl and ice. The solid separated was filtered and recrystallized with methanol. m.p. 134°C; yield: 2.16 g (62.6%), Anal. for $C_{19}H_{15}N_3O_2S$, Calc.: N, 12.1%; C, 65.3% & H, 4.3%; found N, 11.8%; C, 65.0% and H, 3.1%; IR (KBr) cm^{-1} 1610 (C=N), 1620 (C=O), 3250–3300 (NH), 1235 (C—O—C), 650 (C—S); PMR ($CDCl_3$); δ2.5 (s, 3H, CH_3), 3.82 (s, 2H, OCH_2) 8.0–8.4 (br, 1, NH), 6.7–7.34 (m, Ar-H); Mass: M^+ at m/e 349.

Other compounds of the series were prepared similarly and the results are shown in table 1.

Table 1 *Physical data of 2-methyl 4[2'-(mercaptoacetoxy)benzimidazolyl/benzoxazolyl] 6- or 7-substituted quinolines*

Compd.*	X	R	m p °C	Molecular formula	% of N		Biological activity	
					Calc.	Found	ED_{50}	ED_{90}
1	NH	H	134	$C_{19}H_{15}N_3O_2S$	12.1	12.0	~80	~185
2	NH	6-CH_3	152–54	$C_{20}H_{17}N_3O_2S$	11.6	11 8	95	~220
3	NH	7-CH_3	164–65	$C_{20}H_{17}N_3O_2S$	11 6	11.4	125	400
4	NH	6-OCH_3	186–88	$C_{20}H_{17}N_3O_3S$	11.1	11 0	30	~555
5	NH	7-OCH_3	172–73	$C_{20}H_{17}N_3O_3S$	11.1	11.0	~40	90
6	NH	6-NO_2	158	$C_{19}H_{14}N_4O_4S$	14 3	14 1	90	200
7	NH	7-NO_2	143–45	$C_{19}H_{14}N_4O_4S$	14 3	14 2	180	~400
8**	NH	7-Cl	160	$C_{19}H_{14}ClN_3O_2S$	11 0	10.5	~200	300
9	O	H	123–24	$C_{19}H_{14}N_2O_3S$	8 0	8 2	85	250
10	O	6-CH_3	248–52	$C_{20}H_{16}N_2O_3S$	7.7	7.2	105	250
11	O	7-CH_3	127	$C_{20}H_{16}N_2O_3S$	7.7	7 4	~150	~300
12	O	6-OCH_3	180–83	$C_{20}H_{16}N_2O_4S$	7.4	7.1	Inactive	Inactive
13	O	7-OCH_3	118–20	$C_{20}H_{16}N_2O_4S$	7 4	7.6	~115	~300
14	O	6-NO_2	150	$C_{19}H_{13}N_3O_5S$	10.6	10.5	~200	~300
15	O	7-NO_2	117	$C_{19}H_{13}N_3O_5S$	10 6	10.3	~250	>400
16	O	7-Cl	98	$C_{19}H_{13}ClN_2O_3S$	7.3	7.3	~60	>100

* Compounds were obtained in 42–63 % yields C & H analysis were within a range of ±0 5 %.
** PMR (DMSO-d_6). δ1.8 (s, 3H, CH_3), δ3.4 (s, 2H, OCH_2), δ8.3–8 6 (br, 1, NH), δ6.7–7 4 (m, Ar-H).

Antimalarial activity: All biological studies were carried out on albino mice of either sex weighing 20 ± 2 g. The number of each group was 5–10. Recipient mice received a single inoculum of approximately 10^7 infected red cells.

Four day suppressive test of blood Schizontocidal action against *P. yoelli nigeriensis* in mice[11]: Oral treatment with the compound in suspension was followed 2 hr after infection. Various doses in different groups of infected mice were given once every day for 4 consecutive days. Regular blood microscopical examinations were carried out 4 days after the infection for 10-day post infection. A range of values of doses and percentage activity are plotted to obtain a dose activity curve for calculation of 50 % and 90 % effective doses (table 1).

All the compounds were tested for antimalarial activity against *P. yoelli nigeriensis* in mice. Results in table 1 indicate that compounds 1, 4, 7, 9 and 16 exhibit considerable antimalarial activity.

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