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Synthesis, Characterization Of (3-Chloro-Benzylidene) 4-Phenyl-Thiazol-2-Yl) Amine and Its Antimalarial Activity

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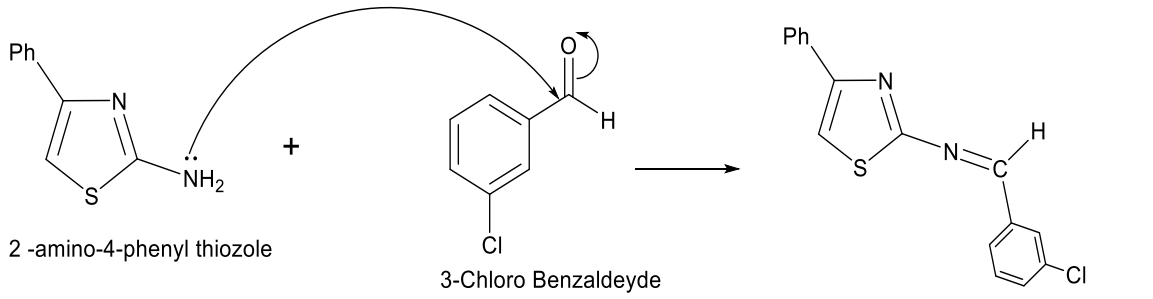
Abstract
In the current study, substituted aromatic aldehydes (2a-c) were combined with 2- amino-4-phenyl thiazole to create a series of 4-phenyl-thiazolyl substituted Schiff bases (3a-c) derivatives. The IR and 1H-NMR of all the produced compounds validated their structures and its antimalarial activity was examined .Emergence of chloroquine (CQ) resistant Plasmodium falciparum strains necessitates discovery of inexpensive antimalarial drugs capable of targeting CQ-resistant strains. Towards this objective, herein we have synthesized and characterized naphthalene-Schiff bases or naphthalene-amine phenols. Among these compounds, 7 demonstrated a significant bioactivity with a half-maximal inhibitory concentration (IC50) of 1.7 M against CQ-resistant Dd2 strains

Keywords: Schiff's base; aromatic aldehydes; 2- amino 4- phenyl thiazole; plasmodium falciparum

Introduction-

In pharmaceutical chemistry, thiazole derivatives have been extremely important. Thiazoles have a wide variety of pharmacological properties, including antimicrobial[1-4], analgesic[6-7], anticonvulsant[8-9], antioxidant[10], hypolipidemic[11], anti HIV-1 [12-13], adenosine receptor antagonist[14-15], and osteoporosis inhibitor[16]. For the creation of antimalarial drugs, Schiff bases have proven to be intriguing moieties[17–18]. As potential antibacterial agents, Schiff bases have been mentioned[19–21]. It is imperative to find and create more powerful antifungal medicines, and several Schiff bases are well-known to be effective ones[22].

Reaction



2 -amino-4-phenyl thiozole

3-Chloro Benzaldeyde

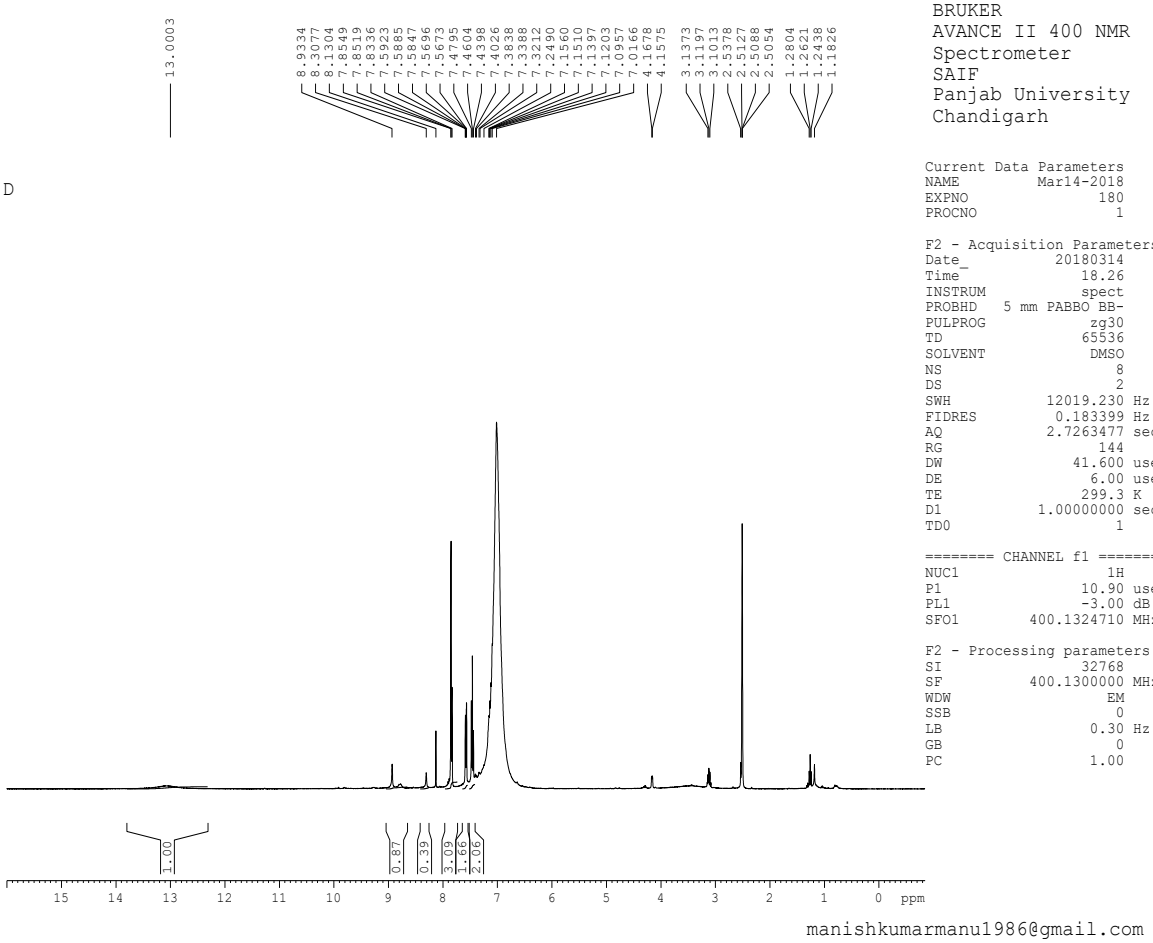
(3-Chloro-benzylidene)-(4-phenyl-thiazol-2-yl)-amine

EXPERIMENTAL SECTION

General Conditions: Melting points were discovered using open capillary tubes and are uncorrected. Iodine spotting and TLC were applied to the silica gel-G surface. Nicolet 5ZDXFT-IR spectrometers in the KBr phase and Brucker WP 200 and 500 SY spectrometers in the 1HNMR phase were used to record the IR spectra. Preparation of [(3-chloro-benzylidiene)-4-phenyl-thiazole-2-yl)-amine: general technique (3a) In the presence of HCl, (0.001mole) 2- amino 4- phenyl thiazole and 0.70gm of 3- chlorobenzaldehyde were refluxed for three to four hours. The product, m.p.-150-1540C, was obtained from the resultant solid after it had been filtered, cleaned, and recrystallized from ethanol. 3a: 1HNMR: 2.6 (s,1H, CH3), 7.2-8.7 (m, 10H, Ar-H), IR (KBr): 1575 cm-1 (C=N)

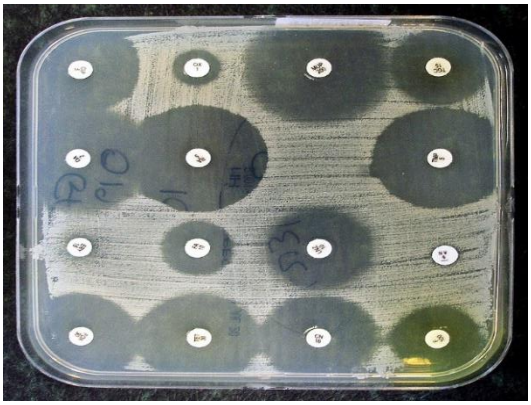
IR Data

Sr. No.	Frequency in cm^{-1}	Assignment	Literature value cm^{-1}
1	3194.26	Ar -H	3300-2900
2	1608.70	C=N stretching	1640-1690
3	1473.68	C=C stretching	1400-1500



BIOASSAY

Plasmodium culture



By using the Trager and Jensen method, two Plasmodium falciparum lines—chloroquine-sensitive (HB3) and chloroquine-resistant (Dd2)—were produced in intraerythrocytic culture [23]. Human serum and erythrocytes were used to maintain cultures at 2% haematocrit and 5% parasitaemia in a 3% oxygen/3% carbon dioxide environment. Sorbitol therapy led to the synchronisation of developmental stage [24]. By monitoring the incorporation of 3 hypoxanthine, it was possible to calculate the half-maximal inhibitory concentration values

(IC50) and stop parasite growth [21]. The medicine was administered to the parasites starting at the late ring stage and continued for 4 hours at the mid-trophozoite stage before the parasites were harvested and tested for radioactivity. At escalating concentrations, compounds 1 through 7 were added as 1:1000 dilutions of a stock solution of 10 mM dimethyl sulfoxide (DMSO). Vehicle did not affect 3 H on its own.

RESULTS AND DISCUSSION

Several five member aromatic systems having three hetero atoms at symmetrical position 1,3,4-thiadiazole had been studied because of their interesting physiological properties. Specifically substituted benzaldehyde or naphthaldehyde were combined with 2-amino-5-diethylamino-pentane in an equal amount of methanol to produce the desired Schiff-base phenols or Schiff base naphthalene ligands for evaluation [19]. Furthermore, by reducing their corresponding Schiff-base counterparts with KBH4 at 80°C for 3 hours, substituted amine phenol or amine naphthalene ligands were also produced [20]. All compounds underwent standard analytical procedure purification and characterization. The spectral and analytical data for digits 1 through 7 agreed with the suggested formulation. By measuring the incorporation of 3 H hypoxanthine, we assessed 1-7's capacity to prevent the formation of trophozoites in intraerythrocytic culture [21]. A more accurate way to quantify parasite development is through the inhibition of hypoxanthine incorporation, which correlates well with direct blood smear counts. Unfortunately, neither the CQ-sensitive (HB3) nor the CQ-resistant (Dd2) strains were significantly affected by compounds 1, 2, 3, 4, and 6. The moderate half-maximal inhibitory concentration (IC50) values for the active compounds 5 and 7 against CQ-sensitive lines, respectively, were 5.53 and 6.38 M. However, compound 7 was found to be twice as effective as compound 5 against CQ-resistant Dd2 lines (IC50, 3.5 M for compound 5; 1.7 M for compound 7). The structural differences of compounds 5 and 7 may be responsible for their varied biological actions. The quinoline ring of the CQ, which lacks chlorine at position 7 and the quinonyl basic nitrogen, has a simple substituted aromatic ring in position 5, but the quinoline ring of the 7 contains a naphthalene ring. Furthermore, it has been demonstrated previously that nitrogen atoms of side chain in chloroquine and aromatic ring assist in accumulation of the drug within the digestive vacuole of the parasite (Vydac) employing an eluent mixture of methanol and water (100% water for first 5 minutes, followed by a change to 50 : 50 (Water : MeOH) for the next 5-20 minutes, and finally 100% MeOH for the next 20-25 minutes). The retention times (Rt) are given for selected compounds.

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