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Full Length Research Paper

Antifungal activity of naphthothiazoles derived from Lawsone (*Lawsonia inermis*)

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A series of Naphtho [2,3-d] thiazole-4, 9-diones was prepared by the condensation of bromolawsone with thiosemicarbazones derived from the aldehydes and ketones in dry dimethyl formamide (DMF). The products are also obtained by the cyclization of the intermediate 2-chlorobenzaldehyde thiosemicarbazone of 1,4-napthoquinone in ethanol containing K_2CO_3 obtained from 2,3-dichloro naphthoquinone. These compounds showed that maximum fungicidal activity varied with substituent on the compounds of Lawsone.

Key words: *Lawsonia inermis*, 2,3-dichloronaphthoquinones, thiosemicarbazones, naphthothiazoles, fungicidal activity, *Fusarium oxysporum*, *Curvularia lunata*.

INTRODUCTION

Lawsonia inermis or *L. abla* (Lythraceace) is an extensively branched glabrous shrub and a habitat of North Africa and South West Asia. Now the plant is widely cultivated throughout the tropics for its leaves although stem bark, roots, flowers and seeds have been used in traditional medicine and dyeing purposes (Kirkland and Marzine, 2003). The pigment is used not only for dyeing hair but also for staining the hands and feet. Henna can be found on the nails of Egyptian mummies and is one of the oldest cosmetics still in use. Lawsone is reported to have an antidiabetic immunomodulatory effect (Dikshit et al., 2000). It is also hepato protective (Sanni et al., 2010), and has antioxidant (Anis et al., 2011), antibacterial (Arun et al., 2010), antifungal (Sharma and Sharma, 2011), antiviral (Wurochekke et al., 2004), antidermatophytic (Sharma et al., 2011), tuberculostatic (Sharma, 1990), cytotoxic (Endrini et al., 2007), enzymes inhibitory (Yogisha et al., 2002), nematicidal (Korayem and Osman, 1992), anticoagulant (Kumar et al., 1985) and wound healing effect (Nithya and Anush, 2011). The present attempt is to compile updated information on various heterocycles which were built on *Lawsonia inermis*.

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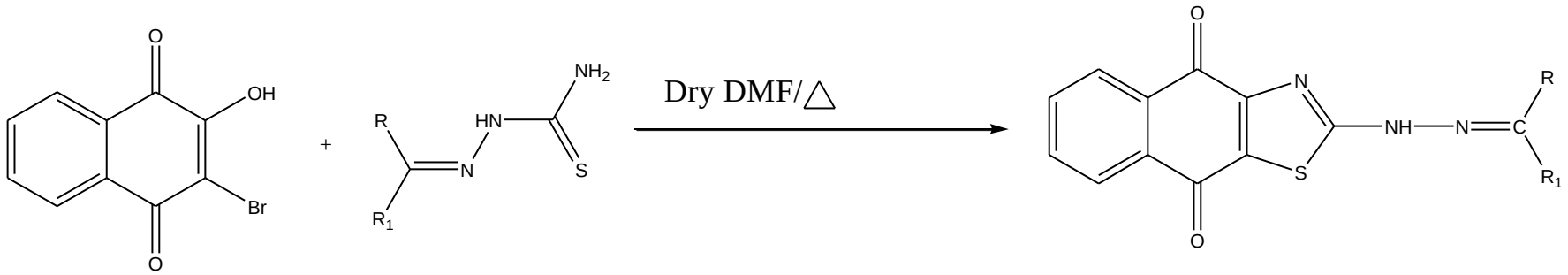
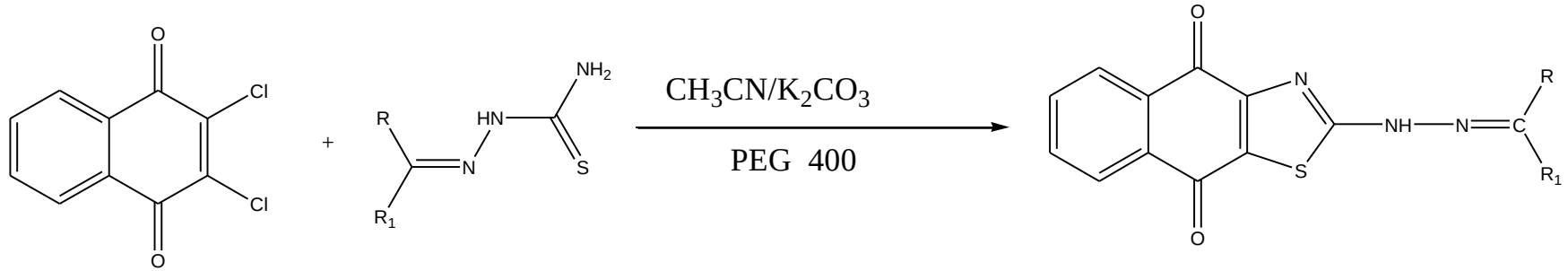
MATERIALS AND METHODS

Synthesis of compound

The principal coloring matter of henna is Lawsone (2-Hydroxy, 1,4-naphthoquinone) ($C_{10}H_6O_3$, m.p. 190°C decomposes). The Lawsone was synthesized from the extraction of the leaves of *L. inermis*. The structure of Lawsone was established by the formation of acetate and Lawsone leucotriacetate and by oxidation to phthalic acid. Lawsone was prepared by hydrolysis and oxidation of leucotriacetate obtained by thiele acetylation of 1,4-naphtho quinone or by the auto oxidation of alpha-tetralone, 1,2 or 1,3-dihydroxyl naphthalene in a basic medium. The naphthothiazole compounds are synthesized from Lawsone in two steps. In the first step, Lawsone was brominated to get bromolawsone under photo chemical conditions by treating the Lawsone with N-bromo succinimide (NBS) in dry carbon tetra chloride (CCl_4). The reaction mixture was refluxed over a 300 W tungsten lamp while using benzoyl peroxide as a radical initiator. In the second step, the naphthothiazole compounds were prepared by the condensation of bromolawsone with thiosemicarbazones derived from aldehydes and ketones in dry dimethylformamide (DMF) (Figure 1, scheme 1).



Scheme 1



Scheme 2

Figure 1. Naphthothiazole compounds. Scheme 1, naphthothiazole compounds prepared by the condensation of bromolawsone with thiosemicarbazones derived from aldehydes and ketones in dry dimethylformamide. Scheme 2, Naphthothiazole compounds obtained by the reaction of 2, 3- dichloro naphthoquinone with acetonitrile having 5% K_2CO_3 and polyethylene glycol (PEG) 4000 under refluxing using phase transfer catalysis conditions.

The same compounds were also obtained by the reaction of 2,3-dichloro naphthoquinone with acetonitrile having 5% K_2CO_3 and polyethylene glycol (PEG) 4000 under refluxing using phase transfer catalysis conditions (Figure 1, scheme 2).

Spectral data for the synthesized compounds

Serial number 1 in Table 1 indicate that 3-Chloro-(2-p-N,N-dimethylamino-benzaldehydethio semicarbazone) of naphthoquinone have IR (Nujol $v_{max}cm^{-1}$):1600 and 1630 (C = O), 3400 (NH); PMR(DMSO-d_6 δ ppm): 2.8(6H, s) (NCH_3), 6.7(2H, s) 7.1(1H, s), 7.7 to 8.3 (8H, m); MS: m/z 412.5, 375,373, 146, 105. Also, in serial number 6 in Table 1, it can be seen that Naphtho(2,3-d)-2-(2-p-N,N-dimethylaminobenzalhydrazine thiozole, 4,9-dione have IR (Nujol $v_{max}cm^{-1}$):1600 and 1630 (C = O), 3400 (NH); PMR(DMSO-d_6 δ ppm): 6.2-6.4 (NH broad), 2.8(6H, s), 7.2-7.8 (8H, m); MS: m/z 376, 148(100), 146,134, 105,77.

Antimicrobial activity

Fungicidal activity of compounds naphthothiazoles of Lawson*e* against *Curvularia lunata* and *Fusarium oxysporum* was evaluated by glass slide-humid chamber technique. Different concentrations of the test compounds (120, 360, 600 and 840 mg/ml) were prepared by dissolving 30 mg of compounds in 10 ml of acetone and diluted subsequently by adding distilled water. The solvent treated in a similar manner without the compound served as control. The spore suspension of test fungi was prepared from 7 days, old fungus and the spore suspension was so adjusted that 20 to 30 spore appeared on average per microscopic field (L.P). The spores were counted by using haemocytometer (Moore et al., 2000). The detail of spore germination was recorded at the end of 12 h, by which time most of the spores showed considerable germination. At least 250 to 300 spores in 10 randomly selected microscopic fields (L.P) were scored to calculate the percentage of inhibition of spore germination

Table 1. Fungicidal effect of substituted 2-thiamido-3-chloro-1, 4-naphthoquinone.

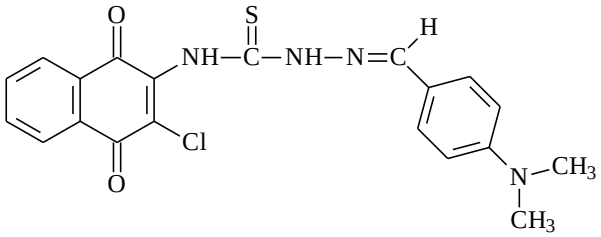
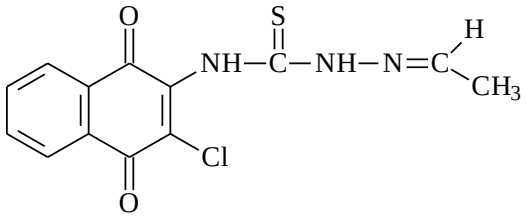
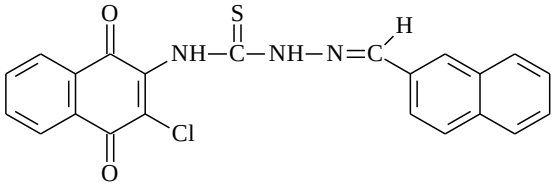
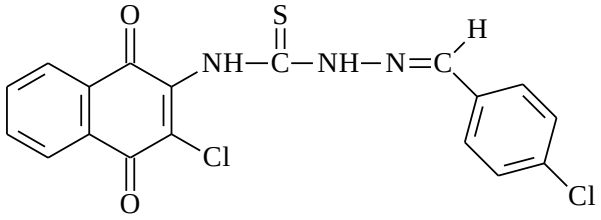
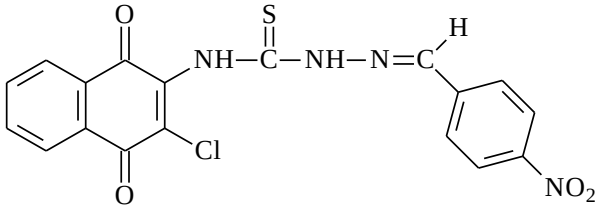
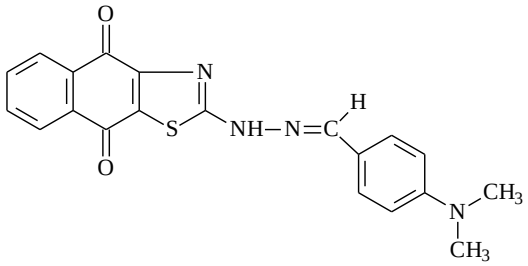
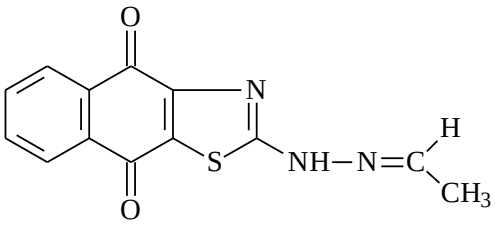
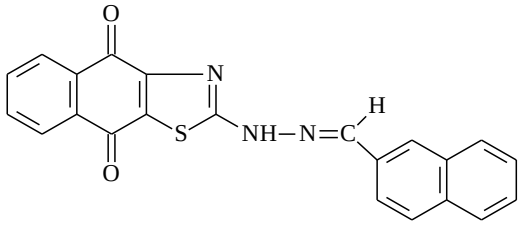
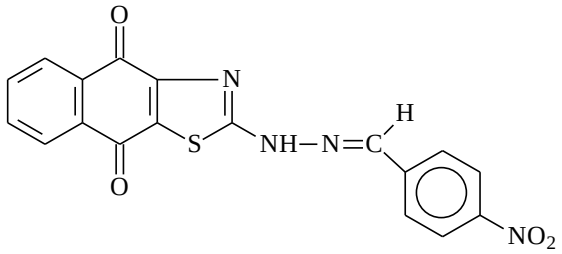
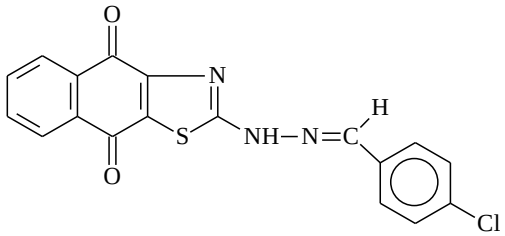
S/N	Compound	Concentration (mg/ml)	Percentage of spore germination	
			C. lunata	*F. oxysporum*
1	 R=H ; R_1 = p-N,N'-dimethylamino	120	85.27	86.35
		360	88.62	90.24
		600	90.73	92.81
		840	93.74	94.36
2	 R_1 = CH_3 ; R=H	120	90.38	92.81
		360	92.56	94.76
		600	96.53	98.24
		840	98.24	100.00
3	 R_1 = Naphthyl; R=H	120	90.36	90.21
		360	90.45	93.46
		600	94.38	95.58
		840	98.36	98.79
4	 R=H; R_1=p-chlorophenyl	120	78.36	82.16
		360	80.25	84.36
		600	84.39	86.13
		840	88.16	90.24
5	 R=H; R_1=p-nitrophenyl	120	78.36	82.16
		360	80.25	84.36
		600	84.39	86.13
		840	88.16	90.24

Table 2. Fungicidal effect of naphtha [2,3-d] thiazole 4,9-diones.

S/N	Compound	Concentration (mg/ml)	Percentage of spore germination	
			C. lunata	*F.oxysporum*
6	 R=H;R_1=p-N,N-dimethylaminophenyl	120	87.65	89.28
		360	90.26	91.26
		600	93.25	94.75
		840	95.38	96.38
7	 R=H; R_1=CH_3	120	92.76	93.36
		360	94.52	95.76
		600	96.38	98.34
		840	98.84	99.21
8	 R= H; R_1= naphthyl	120	88.61	92.35
		360	90.26	94.68
		600	95.21	98.00
		840	98.31	100.00
9	 R=H; R_1=p-nitrophenyl	120	92.00	95.00
		360	95.20	97.28
		600	98.12	100.00
		840	100.00	100.00
10	 R=H; R1=p-chlorophenyl	120	80.82	85.38
		360	83.46	89.35
		600	85.70	91.24
		840	88.32	93.54

by using the formula:

$$\text{Percentage of inhibition of spores germination} = \frac{\text{Percentage of germination in treatment}}{\text{Percentage of germination in control}} \times 100$$

RESULTS AND DISCUSSION

From the obtained results, it is evident that most of the compounds like 8, 9 and 10 possessed very good activity against fungi like *Curvularia lunata* and *Fusarium oxysporum* and the remaining compounds showed moderate activity against the fungi tested. In the uncyclized intermediates (Table 1) 2-thiamido-3-chloro-1.4-naphthoquinones, the substituent R was different. In 1 and 2 compounds, the substituent was N, N-dimethyl Aniline and methyl groups. These two are electron releasing groups. So, the electron density in the ring increased which in turn increased the rate of reaction that is, inhibition of the percentage of spore germination was high even at minimum concentration that is, 120 mg/ml whereas in the compound number 3 since the naphthyl ring is stabilized by resonance, it facilitated and increased the inhibition of the percentage of spore germination. Even though the intermediates 4, 5 were active, it was somewhat less. This may be due to the presence of electron with drawing nitro group and inductive effect of chlorine.

In cyclized molecules, the compound (Table 2), 8-naphthyl substituent increased the rate of reaction due to resonance whereas in compound number 9, electrons with drawing effect of NO_2 group on benzene ring was predominant over the effects caused by N, N- dimethyl Aniline, methyl and chloro group. Hence, it was more reactive and the percentage of inhibition of spore germination was more when compared with other substituent. In conclusion, it is the inhibition of spore germination that varied with different substituent.

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