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Original article

Synthesis of novel 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-thiones and evaluation of their biocidal effects

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ABSTRACT

Novel 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-thiones have been synthesized in high yields by treatment of the corresponding oxo analogs with Lawesson's reagent. The structure has been confirmed by X-ray analysis. The compounds were tested for *in vitro* antifungal activity against *Rhizoctonia bataticola*, *Sclerotium rolfsii*, *Fusarium oxysporum* and *Alternaria porii*. The compounds exhibited moderate to good activity against all pathogens. Insecticidal activity of these compounds against *Spodoptera litura* was observed to be comparable to commercial pyrethroid insecticide, cypermethrin. The urease inhibitory activity has also been studied.

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1. Introduction

Xanthene derivatives have a wide utility range in laser technology [1], dyes [2], pH sensitive fluorescent materials [3], and are also reported to exhibit a broad spectrum of pharmaceutical activities [4–6]. Further, thio analogs of xanthones and related systems have received considerable attention due to the importance of such structural motifs in biology and photochemistry [7]. Also, it can be indubitably stated that thiocarbonyl compounds are valued not only for their rich and varied chemistry but also for their usefulness in pharmaceutical, polymer, pesticide and herbicide industries [8]. Several bioactive thio compounds, have already been reported for their antifungal activity [9] and insecticidal activity [10]. Therefore, the objective of the present work was to prepare new thio derivatives of xanthenes and to study their biological activity. Recently, we have reported the synthesis of a series of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-ones by the condensation of β-naphthol and aromatic aldehydes with cyclic 1,3-dicarbonyl compounds in presence of pTSA under neat conditions and also in ionic liquid [11]. We have endeavored to develop new and efficient synthetic routes for scaffold manipulation of bioactive compounds [12]. In view of the importance of thioxanthene derivatives, we decided to explore the possibility of synthesizing thio analogs of the reported xanthene polycycles [11] by replacing the cyclohexenone moiety by the corresponding cyclohexenethione and evaluate their antifungal, insecticidal, insect growth regulatory and urease inhibitory activities to develop broad spectrum pesticidal molecules.

2. Results and discussion

2.1. Chemistry

The starting compounds, 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-ones were synthesized as outlined in Scheme 1. The transformation of carbonyl compounds to their thio analogs can be achieved by application of many reagents [13]. The thionation of synthesized xanthene-11-ones was attempted with P_4S_{10} and Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide) using 12-(4-chloro-phenyl)-9,9-dimethyl-8,9,10,12-tetrahydro-benzo[*a*]xanthen-11-one as the model substrate. A series of experiments established that 2.2 mol of Lawesson's reagent per mole of the xanthene-11-one (**1a**) was

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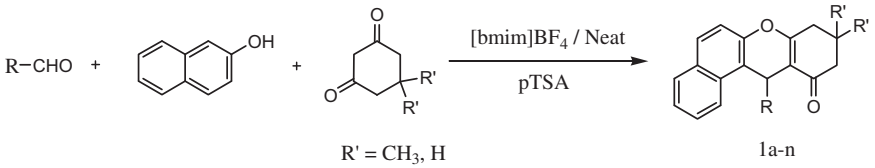


Scheme 1.

required to obtain the optimum yield (85%) of the desired 12-(4-chlorophenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-thione in dry toluene under reflux conditions. However, employing P_4S_{10} to synthesize the target compound did not lead to satisfactory results despite several manipulations involving molar ratios, solvents and temperature. Using the optimized reaction conditions, thionation of a series of xanthene-11-ones (**1a**–**n**) reflecting structural variation was examined.

Variously substituted xanthene-11ones (**1a**–**n**) reacted smoothly with Lawesson's reagent in boiling toluene to give the corresponding novel xanthenes-11-thiones (**2a**–**n**) in good to excellent yields in short reaction time (Scheme 2). The results are summarized in Table 1. Compounds **2a**–**n** are stable solids whose structures were established by IR, ^{1}H, and ^{13}C NMR spectroscopies, mass spectrometry and elemental analysis. The structure of **2j** has also been confirmed by a single crystal X-ray analysis [14] (Fig. 1). The thiocarbonyl double bond of compound **2j** has been assigned based on spectral data. IR spectrum of thioxanthene (**2j**) showed C═S stretch at 1581 cm^{-1} while the C═O stretch of the corresponding xanthene (**1j**) appeared at 1651 cm^{-1}. In ^{13}C NMR spectrum of compound **1j**, carbon of carbonyl functionality appeared at δ 196.8 while in corresponding thioxanthene (**2j**) disappearance of carbon of carbonyl functionality occurred and carbon of thiocarbonyl functionality appeared at δ 230. X-ray data of compound **2j** reveals important information about the thiocarbonyl double bond as the bond length of the carbonyl double bond of xanthene was 1.223 Å while the observed bond length of the thiocarbonyl double bond of **2j** was 1.634 Å.

2.2. Biology

These thiones (**2a**–**2n**) were then tested for antifungal, insecticidal, insect growth regulatory and urease inhibitory activities.

2.3. In vitro antifungal activity

All the synthesized compounds were screened for antifungal activity against four soil borne fungi, namely, *Rhizoctonia bataticola* (RB), *Sclerotium rolfsii* (SR), *Fusarium oxysporum* (FO), *and Alternaria porii* (AP) by the poisoned food technique [15] and their calculated ED_{50} values are reported in Table 2. All the compounds showed low to moderate activity against all pathogens (Fig. 2). Maximum activity was observed against *A. porii* (ED_{50} ranges from 135 to 670 μg/mL). Compounds with 2-bromo and 2-naphthyl substitutions showed better antifungal activity than rest of the compounds.

2.4. Insecticidal and insect growth regulatory activity

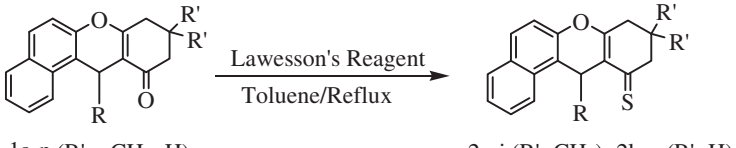
Compounds **2a**–**n** were also evaluated for insecticidal activity as well as insect growth regulatory activity against lepidopteran insect pest namely, *Spodoptera litura* (third instar larvae) at 0.1% dose by both contact and feeding method (Tables 3 and 4) [16] (Figs. 3 and 4). Most of the compounds showed moderate to good insecticidal activity with feeding method whereas low mortality was observed when treated through topical method (i.e. through direct penetration on the insects). The insecticidal activity of few compounds was comparable to that of cypermethrin, a commercial pyrethroid insecticide when tested at a 0.1% dose. The compound with R = 3-BrC_6H_4 was more active in comparison to the compounds having R = H as insecticidal agent. Most of the compounds revealed high activity as insect growth regulator. Compound with 3-bromo substitution was found to be most effective with 100% growth inhibition index at 0.1% dose. Compound with 4-NO_2 and without substitution (compounds **2n** and **2d**) also revealed higher activity (% growth inhibition index = 80 and 75). The percentage of larvae that reached to pupa or adult stage decreased considerably as life cycle progresses. Some of them resulted in abnormal pupae or adults.

2.5. Urease inhibitory activity

All the compounds were tested for urease *inhibitory* activity at 1% dose. The urease inhibitory activity observed with the test compounds was ranged from −8 to 47% during 9–27 h of incubation. The best performer was compound **2k** (R = H) with 47 and 22% urease inhibition (Fig. 5). A perusal of activity data along with SAR revealed that better activity was observed with compounds substituted with aryl group having electron donating groups especially at para position, compounds, **2a** and **2e**. Increase in the aryl ring did not result in any significant change in the urease inhibitory activity. Results for the soil incubation study are reported in Table 5.

3. Conclusion

In summary, we have synthesized a novel series of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-thiones and studied their insecticidal, antifungal and urease activity. The spectroscopic analyses and X-ray analysis confirmed the structures of these compounds. The *in vitro* antifungal activity of these compounds revealed that the 2-bromo and 2-naphthyl derivatives were more active among all the xanthene-11-thiones. Insecticidal activity data



Scheme 2.

Table 1
Synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-thiones.

Compound no.	R	R′	Product	Time (min)	Yield (%)
2a	4-ClC_6H_4	CH_3	**2a**	45	85
2b	3-BrC_6H_4	CH_3	**2b**	45	86
2c	4-FC_6H_4	CH_3	**2c**	45	88
2d	C_6H_5	CH_3	**2d**	45	85
2e	4-$(CH_3)C_6H_4$	CH_3	**2e**	40	80
2f	4-$(OCH_3)C_6H_4$	CH_3	**2f**	40	78
2g	2-$(OCH_3)C_6H_4$	CH_3	**2g**	40	77
2h	3-(OCH_3),4-$(OH)C_6H_3$	CH_3	**2h**	50	82
2i	2-Naphthyl	CH_3	**2i**	60	88
2j	2-Thiophenyl	CH_3	**2j**	35	87
2k	C_6H_5	H	**2k**	60	80
2l	2-BrC_6H_4	H	**2l**	60	78
2m	3-ClC_6H_4	H	**2m**	60	80
2n	4-$(NO_2)C_6H_4$	H	**2n**	90	85

have shown that the synthesized compounds have a significant insecticidal activity against the tested microorganisms.

4. Experimental

4.1. General

All the chemicals used were purchased from Sigma–Aldrich and used as received. Thin layer chromatography was used to monitor reaction progress. Column chromatography was performed using 100–200 mesh silica gel and appropriate mixture of petroleum ether/ethyl acetate for elution. Melting points were determined on a Tropical Labequip apparatus and are uncorrected. IR (KBr) spectra were recorded on Perkin–Elmer FTIR spectrophotometer and the values are expressed as ν_{max} cm^{-1}. Mass spectral data were recorded on a Waters micromass LCT Mass Spectrometer and on JEOL-AccuTOF JMS-T100 mass spectrometer having a DART source. The ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Spectrospin spectrometer and Jeol JNM ECX-400P at 300 MHz and 400 MHz, respectively using TMS as an internal standard. The chemical shift values are recorded on δ scale and the coupling constants (J) are in Hertz.

4.2. General procedure for the synthesis of tetrahydrobenzo[a] xanthene-11-thione derivatives

A mixture of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-one (0.3 g, 0.77 mmol), Lawesson's reagent (0.68 g, 1.69 mmol) and anhydrous toluene (15 mL) was placed in a 100 mL round bottomed flask mounted over a magnetic stirrer. The reaction mixture was refluxed for 30–90 min (Table 1). The progress of the reaction was monitored by TLC using petroleum ether:ethyl acetate (90:10). After completion, the solvent was evaporated under reduced pressure. The residue was purified by silica gel (100–200 mesh) column chromatography eluting with petroleum ether:ethyl acetate (99:1).

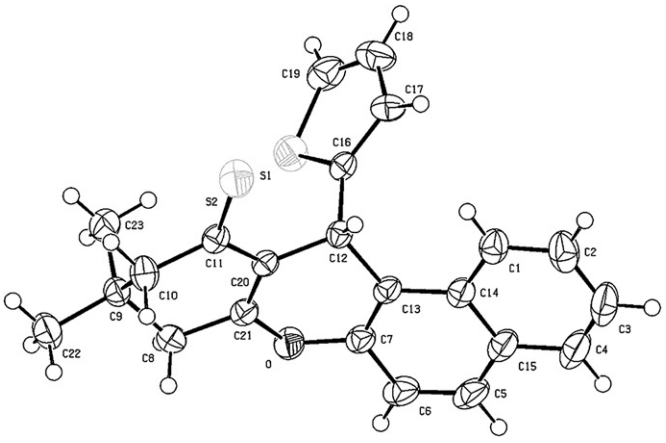


Fig. 1. ORTEP of compound 9,9-dimethyl-12-thiophen-2yl-8,9,10,12-tetrahydro-benzo [*a*]xanthenes-11-thione (**2j**) with atoms represented as 50% thermal probability ellipsoid.

4.3. In vitro antifungal activity

The antifungal activity of the compounds was evaluated *in vitro* using a food poison technique [15].

4.4. In vitro insecticidal activity

The biological assay was conducted against third-instar larvae of *S. litura* (7 ± 1 day old) using the feeding method and topical treatment [16].

4.4.1. Feeding method

The castor leaf was dipped in a 0.1% solution of synthesized compounds for 2 s and then air-dried. Moist filter paper was placed in glass Petri plates (9 cm diameter) on which treated leaf disks were kept. Larvae of *S. litura* prestarved for 4 h were released individually into each Petri plates. Thirty replications were kept for each treatment. Solvent was used as control. Mortality was observed after 24 h.

4.4.2. Topical treatment

The 0.1% stock solution of various compounds was prepared in dichloromethane. 2 μL of each compound was applied on the ventral side of the *S. litura* larvae. Ten treated larvae were released in glass bottles, and fresh tender castor leaves were given as food. Each treatment was kept in triplicate, and solvent was used as control. Mortality was observed after 24 h.

4.5. Insect growth regulatory activity (IGR)

The IGR activity of the above synthesized compounds was evaluated against *S. litura* following the test procedure. Third Instar larvae (*S. litura*) reared on the artificial diet was used for IGR activity. The 0.1% stock solution of test compounds was prepared using appropriate solvent. Newly moulted pre-weighed (30–40 mg) 3rd instar larvae were treated through leaf dip method with different concentrations of the compounds. Individual leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the test solution and allowed to dry. The dishes were infested with ten third-instar larvae. Each treatment was performed in triplicate. Controls were treated with carrier solvent alone. After 24 h treated larvae were observed for larval weight, larval mortality, percentage pupation, deformed pupae, larval–pupal and pupal–adult intermediates, percentage adult emergence and deformed adults and the same were recorded.

4.6. Urease inhibitory activity

The above synthesized compounds were also evaluated for their effect on urease inhibition at a 1% dose according to the following method.

4.6.1. Soil

The soil for *in vitro* incubation experiments was collected from the farm of the Institute. A composite soil sample was collected in bulk from the cultivated fields of known history from a depth of 0–

Table 2
In vitro antifungal activities of **2a**–**2n** thiones.

Compound no.	Antifungal activity							
	RB		SR		FO		AP	
	ED_{50} (μg/mL)	Chi square	ED_{50} (μg/mL)	Chi square	ED_{50} (μg/mL)	Chi square	ED_{50} (μg/mL)	Chi square
2a	334.01	0.44	280.43	3.55	245.46	0.70	310.74	0.42
2b	475.42	4.04	478	1.71	309.57	1.71	320.89	1.44
2c	345.03	2.54	358.22	0.72	260.25	0.72	198.65	2.89
2d	570.39	1.76	525.29	4.32	325.52	4.32	335.72	3.98
2e	489.24	0.47	320.87	4.75	410.45	5.40	385.32	2.54
2f	478.49	3.84	365.40	4.45	278.98	2.11	405.61	2.41
2g	484.26	2.87	324.38	2.37	335.56	3.40	418.48	5.03
2h	566.75	1.66	670.34	2.48	438.39	4.51	432.85	4.03
2i	243.92	4.23	198.75	3.93	188.56	5.33	165.37	4.23
2j	589.64	5.35	456.78	1.87	375.27	5.69	456.20	2.54
2k	437.50	2.96	500.30	2.29	287.20	2.29	209.90	4.00
2l	285.85	1.06	225.46	3.36	148.47	3.36	135.80	3.41
2m	380.35	1.04	425.65	3.59	320.23	5.32	268.20	1.88
2n	554.62	4.69	670.41	2.89	357.60	2.89	212.00	2.65
Hexaconazole	4.36	1.23	12.96	1.01	20.56	1.56	25.54	1.23

RB – *Rhizoctonia bataticola*; SR – *Sclerotium rolfsii*; FO – *Fusarium oxysporium*; AP – *Alternaria porii*; ED_{50} is an average of four replicates and its standard deviation (±) ranged from ±0.44 to ±5.03; Chi square for heterogeneity (tabular value at 0.05 level) = 5.991 (degrees of freedom = 3).

15 cm following a standard sampling procedure. The physical and chemical characteristics of the soil were as follows: sand, 60.8%; clay, 20.5%; and slit, 18.7%; pH 7.9 (soil/water 1:2.5); EC at 25 °C, 0.35 d Sm^{-1}; organic carbon, 0.50%; available N, 55.72 mg kg^{-1} of soil; nitrate-N, 12.9 mg kg^{-1} of soil; nitrite-N, traces; and ammonium-N, 5.6 mg kg^{-1} of soil. It was air-dried at room temperature, ground, and passed through a 2 mm sieve. The soil was thoroughly mixed before use.

4.6.2. Experiment

The experiments were conducted following a completely randomized design (CRD) with three replicates. The test chemicals were tested at a 1% dose of applied urea-N along with a urea alone control. The samples were incubated in 100 mL capacity plastic beakers (50 g of air-dried soil was taken per beaker). A calculated amount of the test chemical (0.1 mg for 1% dose of applied urea-N, respectively) in acetone was added to each beaker and mixed thoroughly. In all of the treatments including control, the same volume of acetone was added. After thorough mixing, 10 mg of urea-N (200 mg of urea-N kg^{-1} of soil) in aqueous solution was added and mixed thoroughly. Distilled water was added to each beaker to maintain the moisture at 50% water-holding capacity of the soil. The controls were similarly processed with urea alone at 200 mg kg^{-1} urea-N level without adding any test inhibitor. All of the beakers were accurately weighed, labeled, and kept at 25 ± 1 °C with 98% relative humidity in an incubator. Soil moisture was maintained by adding distilled water every day after taking the difference of weight if necessary.

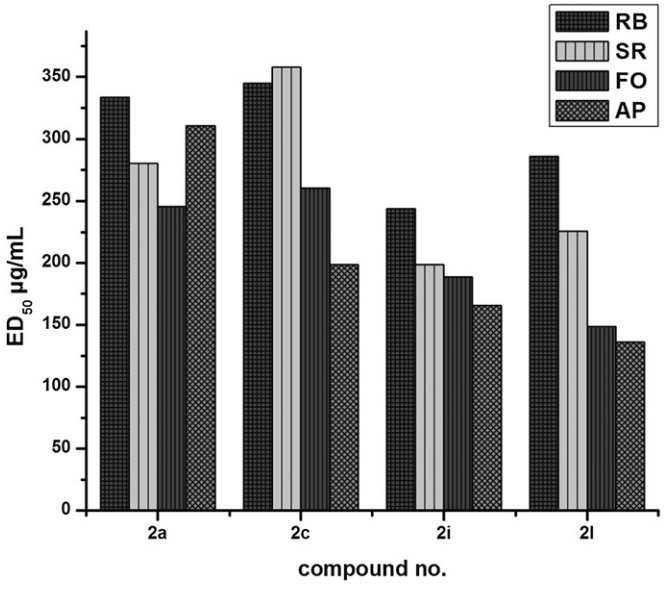


Fig. 2. *In vitro* antifungal activities of selected compounds. Columns represent ED_{50} μg/mL of selected compounds against RB – *Rhizoctonia bataticola*; SR – *Sclerotium rolfsii*; FO – *Fusarium oxysporium*; AP – *Alternaria porii*.

4.6.3. Sampling and estimation of urea-N from the soil samples

The soil samples (5 g) were withdrawn after 9 and 27 h of incubation and extracted with 1 M aqueous sodium sulfate (50 mL) solution containing 2.5 mg of phenyl mercuric acetate to stop the urea hydrolysis after extraction. The soil with extracting solution was shaken for an hour on a reciprocal shaker. The soil samples were filtered and estimated for urea-N following the Douglas and Bremner method [17]. The contents of urea-N were obtained from the standard curves and expressed in milligrams per kilogram.

Table 3
Insecticidal activities against *Spodoptera litura* at 0.1% through both contact and feeding technique.

Compound no.	Insect mortality (*S. litura*)	
	Contact	Stomach
2a	30	40
2b	30	10
2c	10	40
2d	20	20
2e	10	20
2f	0	10
2g	15	30
2h	0	10
2i	0	80
2j	0	10
2k	10	30
2l	50	90
2m	30	60
2n	0	70
Cypermethrin	100	–[a]
Aza	–[a]	100

[a] Not applicable.

Table 4
IGR (insect growth regulator) activities of **2a**–**2n** thiones against *Spodoptera litura* at 0.1%.

Compound no.	% Mortality	% Abnormal larva/dead larva	% Abnormal pupa/dead pupa	% Normal adult	% Growth inhibition index
2a	40	10	20	30	70
2b	50	50	0	0	100
2c	0	50	0	50	50
2d	50	0	15	35	75
2e	30	10	10	50	50
2f	10	10	20	60	40
2g	30	20	10	40	60
2h	10	0	20	70	30
2i	0	20	10	70	30
2j	15	0	20	65	35
2k	40	0	10	50	50
2l	0	20	5	75	25
2m	30	20	10	40	60
2n	50	10	20	20	80

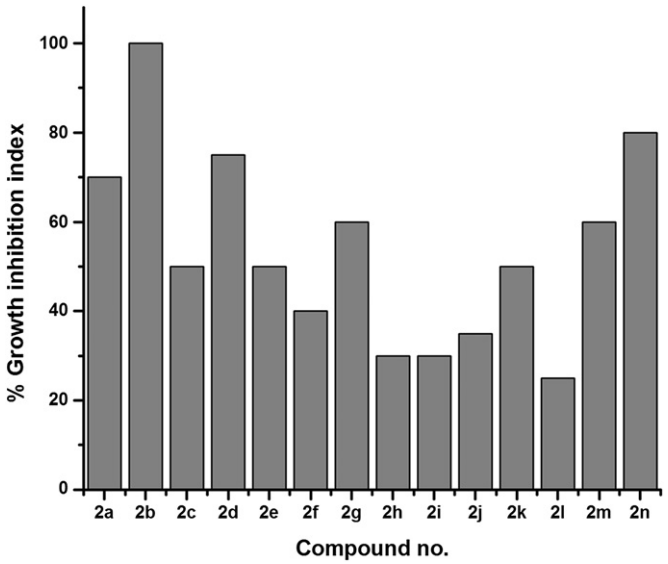


Fig. 4. IGR (insect growth regulator) activities of **2a**–**2n** thiones. Columns represent the % growth inhibition index of **2a**–**2n** against *Spodoptera litura* at 0.1%.

5. Spectral data

*5.1. 12-(4-Chloro-phenyl)-9,9-dimethyl-8,9,10,12-tetrahydro-benzo[a]xanthene-11-thione (**2a**)*

Pink solid, yield: 85%, m.p.: 184–186 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.83 (s, 3H, CMe), 1.03 (s, 3H, CMe), 2.67 (d, 1H, J = 16.8 Hz, CH_2CO), 2.75 (d, 1H, J = 16.8 Hz, CH_2CO), 2.82 and 2.84 (AB system, 2H, J = 16.8 Hz, $CH_a.CH_bCMe_2$), 6.12 (s, 1H, Ar*CH*), 7.18 (d, 2H, J = 8.8 Hz, Ar–H), 7.33 (d, 2H, J = 8.8 Hz, Ar–H), 7.41–7.54 (m, 3H, Ar–H), 7.90 (d, 2H, J = 8.8 Hz, Ar–H), 8.11 (d, 1H, J = 8 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.25, 28.86, 33.02, 37.12, 42.87, 60.95, 116.96, 123.39, 125.27, 127.27, 128.20, 128.69, 129.04, 130.71, 142.95, 146.28, 162.69, 231.5 (C=S); IR (KBr, cm^{-1}) ν_{max} = 2920.38, 1579.42, 1369.40, 1221.22, 1186.88; MS (ESI): m/z = $[M + H]^+$ 405, 407 $[M + 2]^+$.

*5.2. 12-(3-Bromo-phenyl)-9,9-dimethyl-8,9,10,12-tetrahydro-benzo[a]xanthene-11-thione (**2b**)*

Pink solid, yield: 86%, m.p.: 140 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.81 (s, 3H, CMe), 0.99 (s, 3H, CMe), 2.68 (s, 2H, CH_2), 2.76 (d, 1H, J = 16.8 Hz, CH_2CO), 2.83 (d, 1H, J = 16.8 Hz, CH_2CO), 6.10 (s, 1H, Ar*CH*), 7.02–7.08 (m, 1H, Ar–H), 7.15 (d, 1H, J = 8.1 Hz, Ar–H), 7.26 (d, 1H, J = 8 Hz, Ar–H), 7.36–7.44 (m, 3H, Ar–H), 7.48–7.53 (m, 1H, Ar–H), 7.84–7.87 (d, 2H, J = 8.7 Hz, Ar–H), 8.08 (d, 1H, J = 8.4 Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.43, 28.81, 33.19, 37.49, 42.94, 61.01, 116.93, 117.78, 122.16, 123.30, 123.51, 125.19, 127.24, 128.12, 128.60, 129.05, 129.41, 130.98, 131.63, 132.12, 146.31, 146.86, 161.53, 230.36 (C=S); IR (KBr, cm^{-1}) ν_{max} = 2958.31, 1585.75, 1368.93, 1219.12, 1187.01; MS (FAB): m/z = $[M]^+$ 449, 451 $[M + 2]^+$.

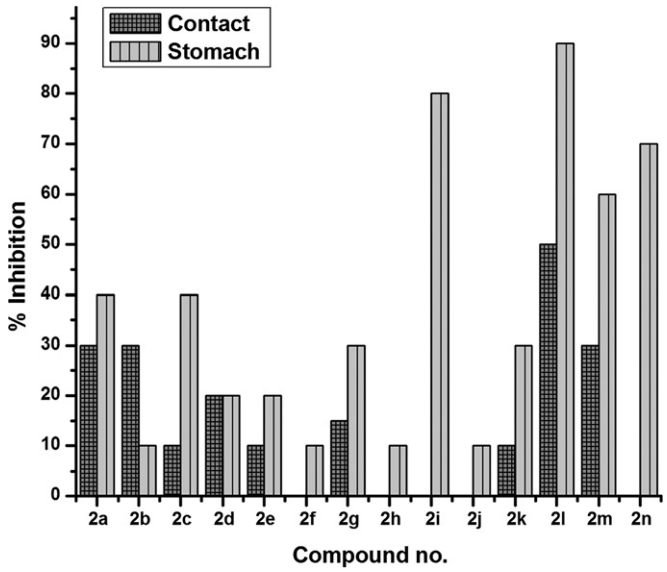


Fig. 3. Insecticidal activities of compounds **2a**–**2n**. Columns represent the % inhibition of compounds **2a**–**2n** against *Spodoptera litura* at 0.1% through both contact and feeding technique.

*5.3. 12-(4-Fluoro-phenyl)-9,9-dimethyl-8,9,10,12-tetrahydro-benzo[a]xanthene-11-thione (**2c**)*

Pink solid, yield: 88%, m.p.: 140 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.97 (s, 3H, CMe), 1.13 (s, 3H, CMe), 2.69 (d, 1H, J = 18.3 Hz, CH_2CO),

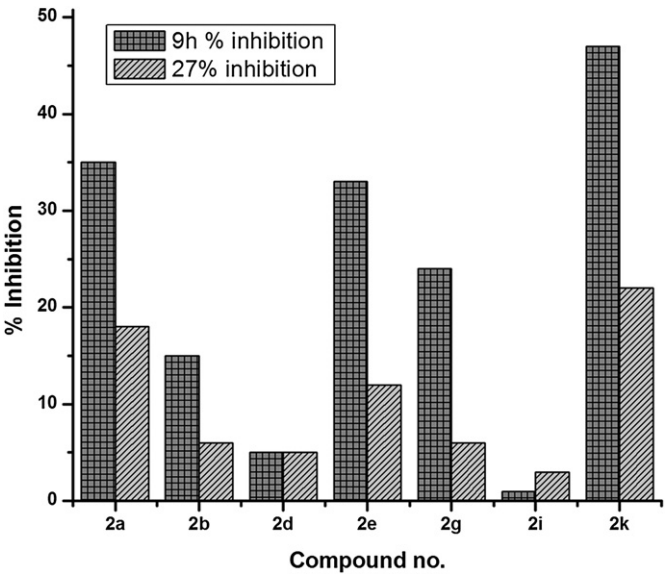


Fig. 5. Urease inhibitory activity of selected compounds. Columns represent the % inhibition of selected compounds during 9–27 h of incubation.

Table 5
Urease inhibitory activity of **2a**–**2n** thiones.

Compound no.	R	R′	9 h % Inhibition	27 h % Inhibition
2a	4-ClC_6H_4	CH_3	35	18
2b	3-BrC_6H_4	CH_3	15	6
2c	4-FC_6H_4	CH_3	−3	0
2d	C_6H_5	CH_3	5	5
2e	4-$(CH_3)C_6H_4$	CH_3	33	12
2f	4-$(OCH_3)C_6H_4$	CH_3	5	−4
2g	2-$(OCH_3)C_6H_4$	CH_3	24	6
2h	3-(OCH_3),4-$(OH)C_6H_3$	CH_3	−6	12
2i	2-Naphthyl	CH_3	1	3
2j	2-Thiophenyl	CH_3	4	−8
2k	C_6H_5	H	47	22
2l	2-BrC_6H_4	H	1	−2
2m	3-ClC_6H_4	H	6	2
2n	4-$(NO_2)C_6H_4$	H	1	−1

2.77 (d, 1H, J = 18 Hz, CH_2CO), 2.85 and 2.87 (AB system, 2H, J = 16.8 Hz, $CH_aCH_bCMe_2$), 6.29 (s, 1H, Ar*CH*), 6.82–6.87 (m, 2H, Ar–H), 7.35–7.54 (m, 5H, Ar–H), 7.76–7.82 (m, 2H, Ar–H), 8.14 (d, 1H, J = 8.4 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.40, 28.39, 32.80, 36.40, 41.76, 60.35, 114.55, 114.83, 116.97, 117.75, 122.92, 125.26, 127.43, 128.72, 129.16, 130.16, 130.53, 130.64, 131.22, 140.21, 146.26, 158.75, 161.97, 162.53, 230.59 (C═S); IR (KBr, cm^{-1}): ν_{max} = 2924.23, 1579.91, 1368.42, 1220.78, 1185.93; MS (FAB): m/z = $[M + H]^+$ 389, 391 $[M + 2]^+$.

5.4. 9,9-Dimethyl-12-phenyl-8,9,10,12-tetrahydro-benzo[a] xanthene-11-thione (**2d**)

Pink solid, yield: 85%, m.p.: 128 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.86 (s, 3H, CMe), 1.06 (s, 3H, CMe), 2.75 (d, 2H, J = 6 Hz, CH_2), 2.85 (s, 2H, CH_2), 6.16 (s, 1H, Ar*CH*), 7.02 (d, 1H, J = 7.5 Hz, Ar–H), 7.13–7.18 (m, 2H, Ar–H), 7.34 (d, 2H, J = 7.8 Hz, Ar–H), 7.42–7.56 (m, 3H, Ar–H), 7.92 (d, 2H, J = 9 Hz, Ar–H), 8.17 (d, 1H, J = 8.4 Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.40, 28.28, 33.12, 37.74, 42.97, 61.09, 116.86, 118.68, 123.55, 124.14, 125.03, 126.18, 127.04, 127.92, 128.24, 128.48, 128.68, 129.27, 131.16, 131.61, 144.14, 161.34, 230.49 (C═S); IR (KBr, cm^{-1}): ν_{max} = 2956.82, 1579.51, 1369.55, 1219.63, 1186.56; MS (ES): m/z = $[M]^+$ 370.85, 372.85.

5.5. 12-(4-Methyl-phenyl)-9,9-dimethyl-8,9,10,12-tetrahydro-benzo[a]xanthene-11-thione (**2e**)

Pink solid, yield: 80%, m.p.: 162–164 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.97 (s, 3H, CMe), 1.11 (s, 3H, CMe), 1.58 (s, 3H, ArMe), 2.58–2.69 (m, 2H, CH_2), 2.80 (d, 1H, J = 16.8 Hz, CH_2CO), 2.94 (d, 1H, J = 16.8 Hz, CH_2CO), 6.25 (s, 1H, Ar*CH*), 6.94 (d, 2H, J = 8 Hz, Ar–H), 7.26–7.40 (m, 4H, Ar–H), 7.47–7.51 (m, 1H, Ar–H), 7.71–7.77 (m, 2H, Ar–H), 8.19 (d, 1H, J = 8.7 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.96, 26.43, 28.84, 33.11, 37.30, 42.93, 61.07, 116.82, 118.82, 123.53, 124.21, 124.96, 126.97, 128.44, 128.52, 128.63, 129.07, 131.11, 131.77, 135.59, 141.32, 146.72, 161.25, 231.53 (C═S); IR (KBr, cm^{-1}): ν_{max} = 2918.00, 1579.52, 1369.18, 1218.35, 1184.67; MS (ESI): m/z = $[M + H]^+$ 385.2, 387.2 $[M + 2]^+$.

5.6. 12-(4-Methoxy-phenyl)-9,9-dimethyl-8,9,10,12-tetrahydro-benzo[a]xanthene-11 thione (**2f**)

Pink solid, yield: 78%, m.p.: 148–152 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (s, 3H, CMe), 1.06 (s, 3H, CMe), 2.63 and 2.64 (AB system, 2H, J = 18.3 Hz, $CH_aCH_bCMe_2$), 2.82 (d, 1H, J = 16.8 Hz, CH_2CO), 2.94 (d, 1H, J = 16.8 Hz, CH_2CO), 3.59 (s, 3H, OMe), 6.10 (s, 1H, Ar*CH*), 6.70 (d, 2H, J = 8.8 Hz, Ar–H), 7.24 (d, 2H, J = 8.8 Hz, Ar–H), 7.43–7.50 (m, 2H, Ar–H), 7.53–7.57 (m, 1H, Ar–H), 7.88–7.92 (m, 2H, Ar–H), 8.15 (d, 1H, J = 8 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.48, 28.46, 32.84, 36.28, 41.79, 54.85, 60.44, 113.32, 116.98, 118.33, 123.05, 123.32, 125.19, 127.33, 128.70, 128.98, 129.80, 130.28, 131.23, 136.23, 146.38, 157.53, 162.68, 231.15 (C═S); IR (KBr, cm^{-1}): ν_{max} = 2961.25, 1578.88, 1508.55, 1369.27, 1250.98, 1220.23, 1186.47; MS (ESI): m/z = $[M + H]^+$ 401.2, 403.2 $[M + 2]^+$.

5.7. 12-(2-Methoxy-phenyl)-9,9-dimethyl-8,9,10,12-tetrahydro-benzo[a]xanthene-11-thione (**2g**)

Pink solid, yield: 77%, m.p.: 220–222 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (s, 3H, CMe), 1.12 (s, 3H, CMe), 2.69 (d, 1H, J = 18.3 Hz, CH_2CO), 2.77 (d, 1H, J = 18.3 Hz, CH_2CO), 2.84 and 2.86 (AB system, 2H, J = 16.8 Hz, $CH_aCH_bCMe_2$), 3.79 (s, 3H, OMe), 6.40 (s, 1H, Ar*CH*), 6.71 (d, 1H, J = 8 Hz), 6.78–6.83 (m, 1H), 7.01–7.05 (m, 1H), 7.26–7.30 (m, 1H, Ar–H), 7.34–7.38 (m, 1H, Ar–H), 7.45–7.49 (m, 2H, Ar–H), 7.68–7.75 (m, 2H, Ar–H), 8.44 (d, 1H, J = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.04, 29.07, 32.89, 34.34, 43.05, 55.30, 61.25, 111.29, 116.61, 117.91, 120.06, 122.98, 124.14, 124.65, 126.67, 127.71, 128.23, 131.42, 132.28, 147.20, 156.92, 162.06, 230.27 (C═S); IR (KBr, cm^{-1}) ν_{max} = 2932.75, 1572.18, 1373.82, 1220.95, 1185.92; MS (ESI): m/z = $[M + H]^+$ 401.2, 403.2 $[M + 2]^+$.

5.8. 12-(4-Hydroxy-3-methoxy-phenyl)-9,9-dimethyl-8,9,10,12-tetrahydro benzo[a]xanthene-11-thione (**2h**)

Pink solid, yield: 82%, m.p.: 182–184 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (s, 3H, CMe), 1.11 (s, 3H, CMe), 2.63 (s, 2H, CH_2CMe_2), 2.81 (d, 1H, J = 16.8 Hz, CH_2CO), 2.95 (d, 1H, J = 16.8 Hz, CH_2CO), 3.82 (s, 3H, OMe), 5.39 (s, 1H, OH), 6.23 (s, 1H, Ar*CH*), 6.645 (d, 1H, J = 8 Hz, Ar–H), 6.72–6.74 (m, 1H, Ar–H), 7.06–7.07 (m, 1H, Ar–H), 7.34 (d, 1H, J = 8.8 Hz, Ar–H), 7.38–7.42 (m, 1H, Ar–H), 7.48–7.50 (m, 1H, Ar–H), 7.73–7.80 (m, 2H, Ar–H), 8.17 (d, 1H, J = 8 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.28, 28.86, 33.07, 37.11, 42.94, 55.89, 61.09, 112.38, 113.91, 116.77, 121.83, 123.51, 124.99, 126.96, 128.47, 128.56, 131.25, 131.59, 136.46, 143.70, 145.88, 146.94, 161.22, 231.40 (C═S); IR (KBr, cm^{-1}): ν_{max} = 3473.31 (−OH), 2925.31, 1583.43, 1508.61, 1369.74, 1271.39, 1216.31, 1184.15; MS (ESI): m/z = $[M + H]^+$ 417.2, 419.2 $[M + 2]^+$.

5.9. 9,9-Dimethyl-12-naphthalen-2-yl-8,9,10,12-tetrahydro-benzo[a]xanthene-11-thione (**2i**)

Pink solid, yield: 88%, m.p.: 162 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.78 (s, 3H, CMe), 0.99 (s, 3H, CMe), 2.71–2.72 (m, 2H, CH_2CO), 2.78 (s, 2H, CH_2), 6.27 (s, 1H, Ar*CH*), 7.30–7.38 (m, 4H, Ar–H), 7.45–7.48 (m, 2H, Ar–H), 7.60–7.65 (m, 2H, Ar–H), 7.74 (d, 1H, J = 12 Hz, Ar–H), 7.82–7.86 (m, 3H, Ar–H), 8.20 (d, 1H, J = 8.4 Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.38, 28.84, 33.09, 37.91, 42.98, 61.09, 116.85, 118.42, 123.54, 123.85, 125.02, 125.43, 125.71, 127.05, 127.24, 127.35, 127.68, 127.94, 128.29, 128.46, 128.79, 131.18, 131.62, 131.96, 132.99, 141.43, 146.85, 161.31, 230.48; IR (KBr, cm^{-1}) ν_{max} = 2926.16, 1577.02, 1369.47, 1220.31, 1185.54; MS (FAB): m/z = $[M + H]^+$ 421, 423 $[M + 2]^+$.

5.10. 9,9-Dimethyl-12-thiophen-2yl-8,9,10,12-tetrahydro-benzo[a] xanthenes-11-thione (**2j**)

Pink solid, yield: 87%, m.p.: 145–147 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.59 and 2.61 (AB system, 2H, J = 18.3 Hz, CH_aCH_bCO), 2.83 (d, 1H, J = 16.8 Hz, CH_2CO), 3.03 (d, 1H, J = 16.8 Hz, CH_2CO), 6.66 (s, 1H, Ar*CH*), 6.69–6.71 (m, 2H, Ar–H), 6.96–6.97 (m, 1H, Ar–H), 7.33 (d, 1H, J = 8 Hz, Ar–H),

7.40–7.44 (m, 1H, Ar–H), 7.50–7.54 (m, 1H, Ar–H), 7.76–7.82 (m, 2H, Ar–H), 8.14 (d, 1H, $J = 8.8$ Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.40, 28.92, 32.47, 33.01, 42.84, 60.79, 117.92, 123.39, 123.68, 123.88, 125.16, 125.62, 127.19, 128.45, 128.89, 131.03, 131.49, 147.18, 147.48, 161.91, 231.58 (C=S); IR (KBr, cm^{-1}): ν_{max} = 2918.83, 1581.32, 1370.69, 1215.93, 1186.64; MS (ESI): $m/z = [M + H]^+$ 377.15, 379.15 $[M + 2]^+$.

5.11. 12-Phenyl-8,9,10,12-tetrahydro-benzo[a]xanthene-11-thione (**2k**)

Pink solid, yield: 80%, m.p.: 110 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.23–1.29 (m, 2H, CH_2), 1.89–2.18 (m, 2H, CH_2), 2.74–3.14 (m, 2H, CH_2), 6.24 (s, 1H, Ar*CH*), 7.03–7.30 (m, 3H, Ar–H), 7.35–7.58 (m, 5H, Ar–H), 7.93–7.03 (m, 2H, Ar–H), 8.16–8.19 (d, 1H, $J = 8$ Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.81, 29.51, 37.64, 47.46, 116.78, 118.75, 123.56, 125.05, 125.52, 126.22, 127.06, 128.00, 128.47, 128.69, 129.25, 131.17, 131.62, 144.45, 146.87, 162.60, 231.17 (C=S); IR (KBr, cm^{-1}): ν_{max} = 2925.13, 157.63, 1372.32, 1232.16, 1176.34; MS (FAB): $m/z = [M + H]^+$ 343, 345 $[M + H]^+$.

5.12. 12-(2-Bromo-phenyl)-8,9,10,12-tetrahydro-benzo[a] xanthene-11-thione (**2l**)

Pink solid, yield: 78%, m.p.: 190 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.86–2.04 (m, 2H, CH_2), 2.88–2.89 (m, 2H, CH_2), 3.04–3.10 (m, 2H, CH_2), 6.30 (s, 1H, Ar*CH*), 6.96–7.01 (m, 1H, Ar–H), 7.22–7.27 (m, 1H, Ar–H), 7.37–7.61 (m, 5H, Ar–H), 7.92 (d, 2H, $J = 9$ Hz, Ar–H), 8.42 (d, 1H, $J = 8.4$ Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.68, 29.63, 39.29, 47.94, 116.79, 117.04, 123.14, 124.00, 124.92, 126.79, 126.87, 128.03, 128.47, 129.17, 131.56, 134.19, 134.49, 142.29, 147.19, 163.05, 231.01 (C=S); IR (KBr, cm^{-1}) ν_{max} = 2922.65, 1571.95, 1371.33, 1236.85, 1178.21. MS (FAB): $m/z = [M + H]^+$ 421, 423 $[M + 2]^+$.

5.13. 12-(3-Chloro-phenyl)-8,9,10,12-tetrahydro-benzo[a] xanthene-11-thione (**2m**)

Pink solid, yield: 80%, m.p.: 174 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.89–2.01 (m, 2H, CH_2), 2.84–2.91 (m, 2H, CH_2), 3.0–3.1 (m, 2H, CH_2), 6.22 (s, 1H, Ar*CH*), 7.09 (d, 1H, $J = 9$ Hz, Ar–H), 7.16–7.22 (t, 1H, $J = 7.8$ Hz, Ar–H), 7.28–7.31 (d, 1H, $J = 9$ Hz, Ar–H), 7.36 (s, 1H, Ar–H), 7.44–7.60 (m, 3H, Ar–H), 7.93 (d, 2H, $J = 9$ Hz, Ar–H), 8.14 (d, 1H, $J = 9$ Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.75, 29.69, 37.39, 47.39, 116.81, 117.89, 123.30, 124.88, 125.17, 126.52, 127.21, 127.66, 128.56, 129.01, 129.15, 130.99, 131.63, 133.90, 146.32, 146.91, 162.77, 231.02 (C=S); IR (KBr, cm^{-1}) ν_{max} = 2927.30, 1573.21, 1368.62, 1224.58, 1172.00; MS (FAB): $m/z = [M + H]^+$ 377, 379 $[M + 2]^+$.

5.14. 12-(4-Nitro-phenyl)-8,9,10,12-tetrahydro-benzo[a]xanthene-11-thione (**2n**)

Pink solid, yield: 85%, m.p.: 198 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.77–0.81 (m, 1H, CH_2), 1.17 (d, 1H, $J = 15.9$ Hz, CH_2), 1.82–1.95 (m, 2H, CH_2), 2.79–2.84 (m, 2H, CH_2), 6.27 (s, 1H, Ar*CH*), 7.37–7.42 (m, 1H, Ar–H), 7.45–7.52 (m, 2H, Ar–H), 7.56 (d, 2H, $J = 8.4$ Hz, Ar–H), 7.85–7.89 (m, 2H, Ar–H), 7.94 (d, 2H, $J = 8.4$ Hz, Ar–H), 8.06 (d, 1H, $J = 8.1$ Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.76, 29.51, 37.74, 47.35, 116.83, 117.11, 122.97, 123.34, 124.25, 125.39, 127.45, 128.75, 129.48, 130.14, 130.82, 131.68, 146.21, 146.89, 151.59, 163.13, 231.02 (C=S); IR (KBr, cm^{-1}) ν_{max} = 2927.36, 1579.13, 1513.13, 1345.71, 1230.67, 1107.66; MS (FAB): $m/z = [M + H]^+$ 388, 390 $[M + 2]^+$.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2012.10.025.

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