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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and evaluation of anti-inflammatory and analgesic activity of some substituted thiazolyl and thaizolidinonyl tetrahydronapthalene derivatives

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Abstract A new series of 1,2,3,4-tetrahydronaphthalen-6-yl-thiazole and thiazolidinone derivatives were synthesized. Twenty four of the newly synthesized compounds were evaluated for their anti-inflammatory and analgesic activity. The study exhibited that the derivatives **7b** and **11c** produced equipotent anti-inflammatory activity to that of the reference drug indomethacin with faster onset of action. Meanwhile, the compounds **1b**, **1d**, **6**, **10c**, **12c**, **12e** exhibited interesting dual anti-inflammatory and analgesic activity. The thiazolo-coumarin derivative **6** could be identified as the most biologically active member within this study with a significant dual anti-inflammatory and analgesic activity in comparison with indomethacin. The study of ulcerogenic effects proved that all of the tested compounds revealed super GIT safety profile in the experimental rats.

Keywords 1,2,3,4-Tetrahydronaphthalene · Thiazole · Thiazolidinone · Anti-inflammatory · Analgesic activity

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Introduction

Inflammation is a defensive but exaggerated local tissue reaction in response to exogenous or endogenous insult. It is a fundamental physiological process that is not only essential for survival but also at the same time is one of the major causes of human morbidity and mortality (O'Neill, 2006, Cheeseright *et al*., 2009). Non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat a wide variety of illnesses and diseases, including inflammation (Rostom *et al*., 2009), cancers (Yao *et al*., 2004), diabetes (insulin-resistant and related metabolic syndrome) (Hiroki *et al*., 2007), and diseases of the peripheral and central nervous system, e.g., Alzheimer's and Parkinson's (Laura *et al*., 2004). This versatility is attributed to a wide variety of effects of these drugs on the cell function. The anti-inflammatory effect of NSAIDs arises from their ability to inhibit both COX-1 and COX-2 isoforms of cyclooxygenase (COX) enzyme (Joo *et al*., 2003). However, long term clinical usages of NSAIDs are associated with significant side effects such as severe gastrointestinal ulceration, bleeding, intolerance, and renal toxicity (Amin *et al*., 2010).

Different known anti-inflammatory drugs such as Naproxen (Harrington and Lodewijk, 1997) and Nabumetone (Goudie *et al*., 1978) are bearing naphthalene moiety, while Meloxicam has thiazole nucleus (Engelhardt *et al*., 1995). Additionally, literature survey exhibited that some of the synthesized derivatives comprising tetralin ring such as the compound **A** (Barker *et al*., 2006), or comprising thiazole ring such as the compounds **B** (Bekhit *et al*., 2003) and **C** (Holla *et al*., 2003) produced significant anti-inflammatory and analgesic activity with low ulcerogenic effects. Thus, in view of the above mentioned facts, we reported the synthesis, anti-inflammatory, analgesic, and

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ulcer evaluation of some novel structure hybrids incorporating both the tetrahydronaphthalene moiety with thiazole and/or thiazolidinone ring systems through hydrazine linkage having the general formulae **D** (Fig. 1). This combination was suggested in an attempt to investigate the influence of such hybridization and structure variations on the anticipated biological activities, hoping to add some synergistic biological significance to the target molecules.

Results and discussion

Chemistry

The synthetic strategies adopted to obtain the promising structures are outlined in (Schemes 1, 2). The key intermediates 1-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene) thiosemicarbazide derivatives **1a–e** were obtained via the condensation of 6-acetyl-1,2,3,4-tetrahydronaphthalene with thiosemicarbazide or with N^4-substituted thiosemicarbazides, namely, methylthiosemicarbazide, ethylthiosemicarbazide, phenylthiosemicarbazide, and/or cyclohexylthiosemicarbazide. The chemical structures of **1a–e** were confirmed by spectral data. IR spectra showed the absence of acetyl group band and instead of this the appearance of new bands at 3,204–3,253, 3,290–3,398 cm^{-1} (2NH), 1,589–1,613 cm^{-1} (C=N). ^1H NMR spectrum of compound **1b** showed singlet signal at δ 2.24 ppm due to the methyl group protons (CH_3–C=N) and singlet signals at δ 8.34, 10.14 ppm (2NH) which exchangeable with D_2O. Also, its ^{13}C NMR spectrum showed signal at δ 147.17 ppm referring to (C=N) group and at δ 177.87 ppm due to (C=S) group. Treatment the derivatives **1b–d** with chloroacetone, phenacyl bromide, and/or 6-bromoacetyl-1,2,3,4-tetrahydronaphthalene (El-Zahar *et al.*, 2009) afforded the corresponding thiazole derivatives **2a–i**, also the condensation of **1a** with phenacyl bromide and/or 4-bromophenacyl bromide afforded the corresponding thiazole derivatives **2j**, **k**.

^1H NMR spectra of the derivatives **2a** showed proton at 5-position of the thiazole moiety as singlet signal at δ 5.69 ppm, while the methyl protons at 4-position appeared as singlet signal at δ 2.13 ppm. IR spectra of the compounds **2j**, **k** showed bands at 3,121, 3,122 cm^{-1} (NH). Also ^1H NMR spectrum of compound **2j** recorded singlet signal at δ 6.76 ppm referring to the methine proton of the thiazole moiety. ^{13}C NMR spectrum of the compound **2j** exhibited signals at δ 100.43, 142.24 and 168.47 ppm (C_5, C_4 and C_2-thiazole moiety). The mass spectrum of the compound **2k** showed the molecular ion peaks at 425, 427 which represents the two isotopic peaks of bromine atom.

1-(5-(1,2,3,4-tetrahydronaphthalen-6-yl)thiazol-2-yl)hydrazine (**3**) was obtained from the treatment of 6-bromoacetyl-1,2,3,4-tetrahydronaphthalene with thiosemicarbazide according to the reported method (El-Zahar *et al.*, 2009). Upon its

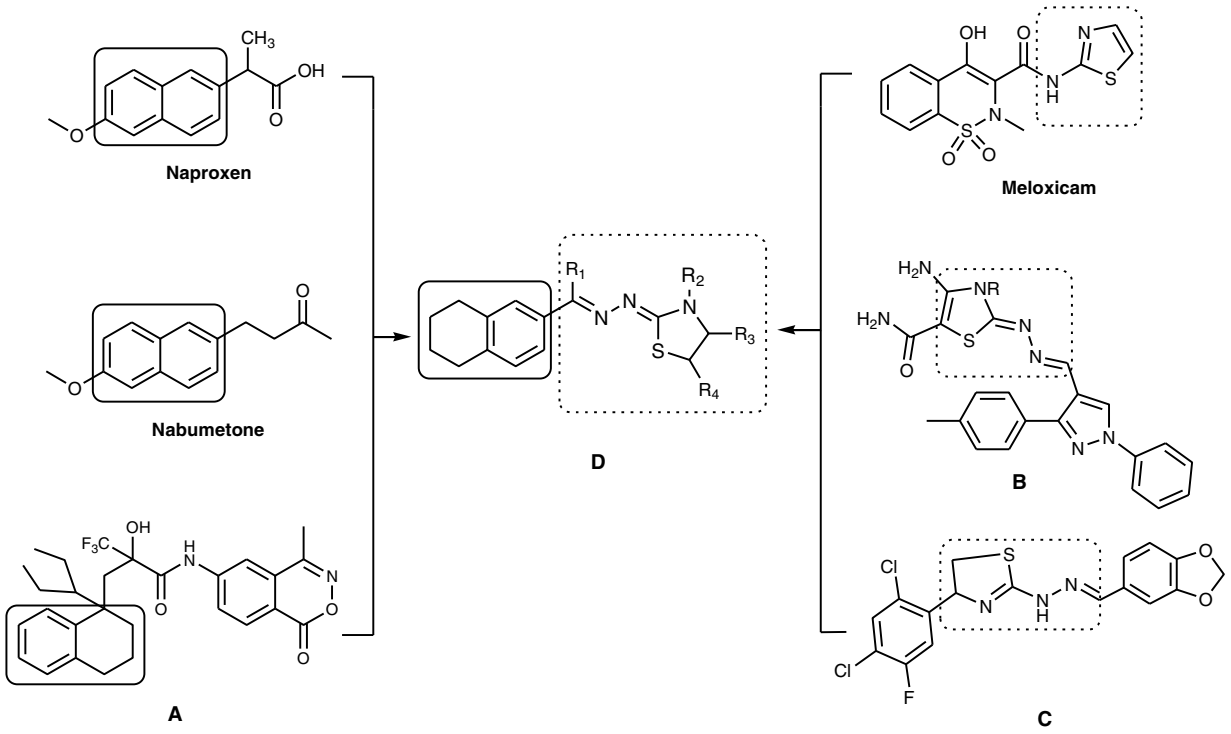
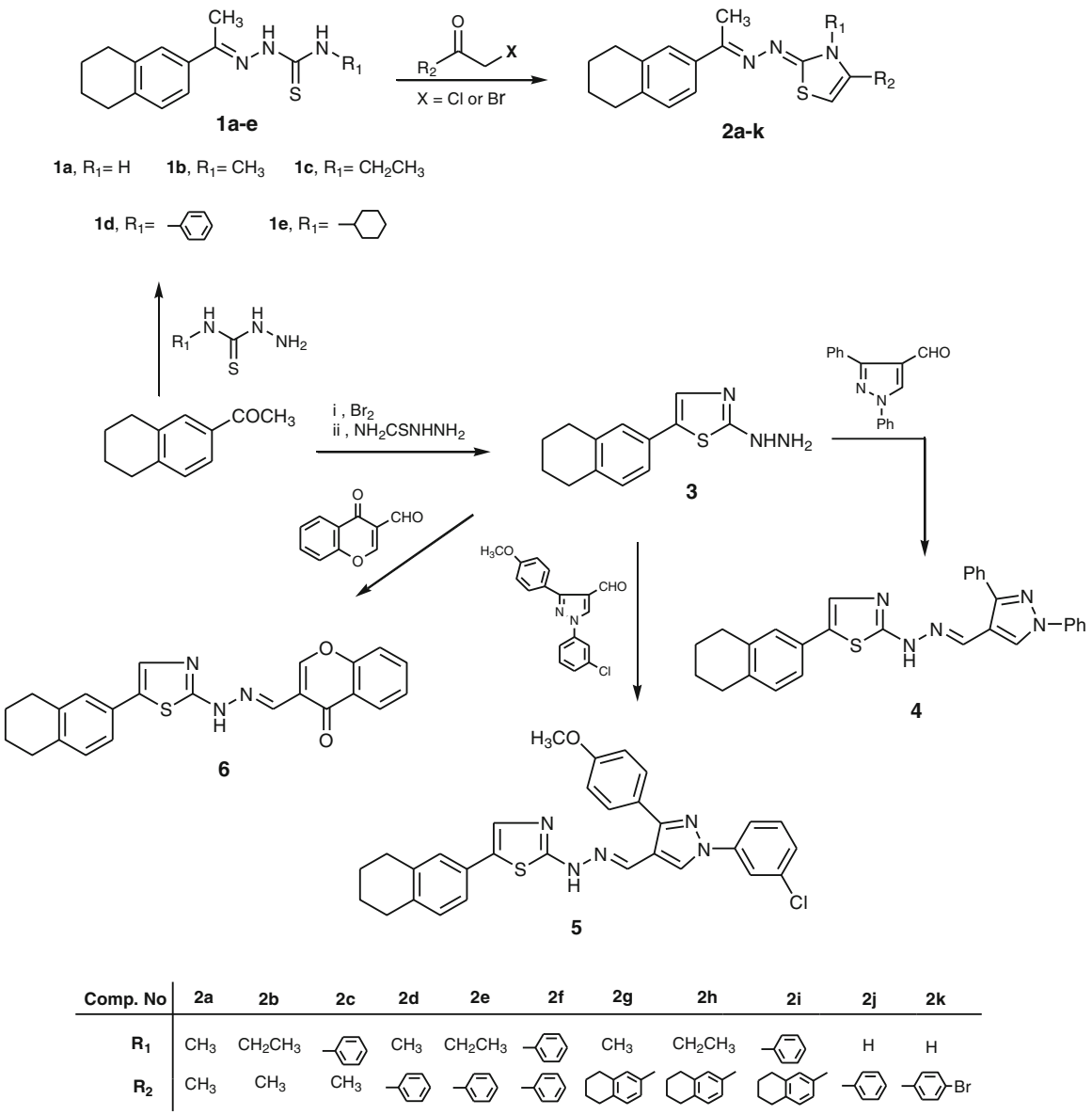


Fig. 1 Structures of anti-inflammatory naphthalene, thiazole and background for the target compound synthesis



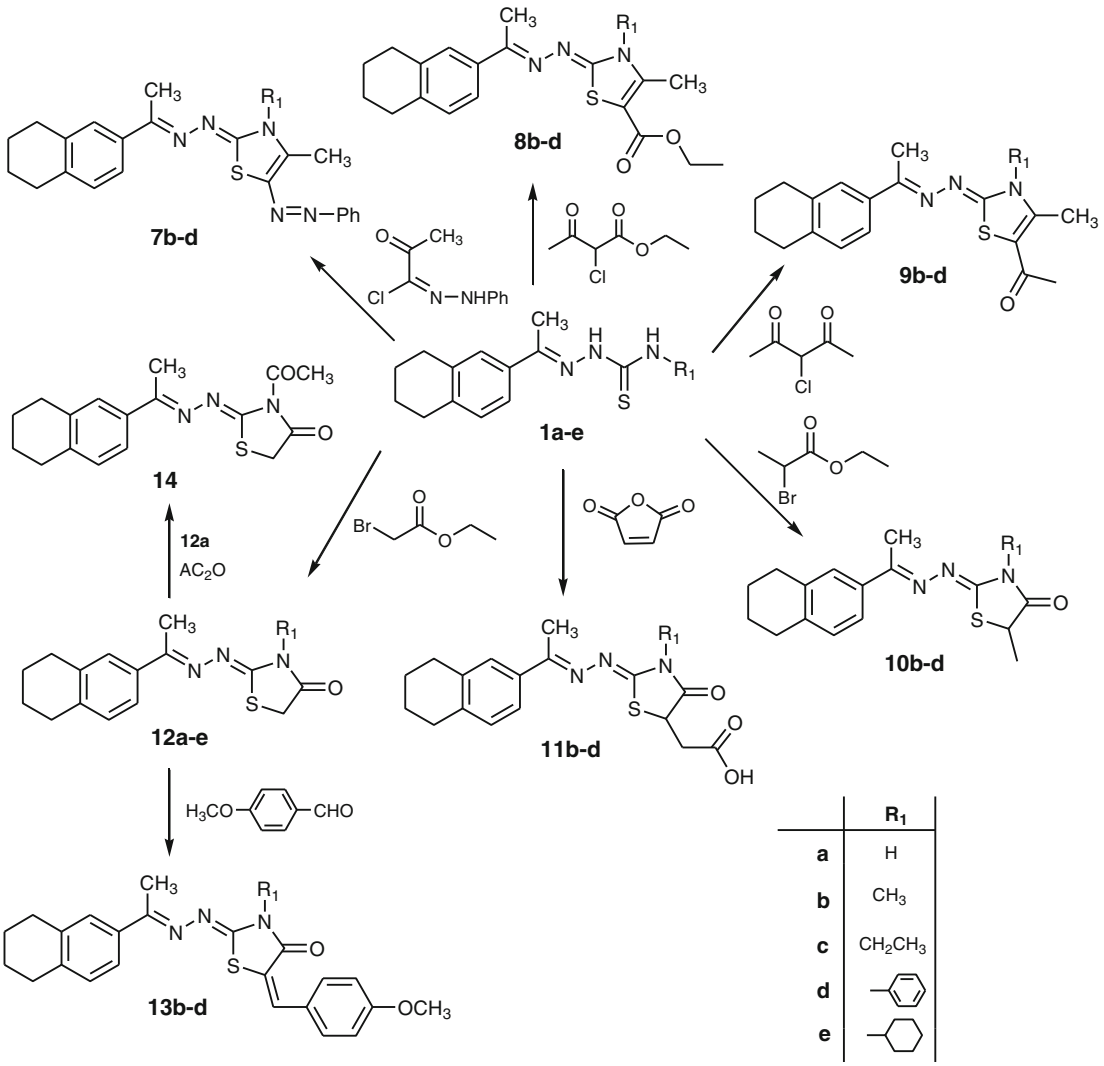
Comp. No	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k
R_1	CH_3	CH_2CH_3		CH_3	CH_2CH_3		CH_3	CH_2CH_3		H	H
R_2	CH_3	CH_3	CH_3								

Scheme 1 Synthesis of ((tetrahydronaphthalen-6-yl)ethylidene)-2-(thiazol-2-yl)hydrazine and ((tetrahydronaphthalen-6yl)thiazol-2-yl)methylene hydrazine derivatives

condensation with different aldehydes, namely, 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde (Prakash *et al*., 2006), 1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazole-4-carboxaldehyde (Fahmy *et al*., 2012), and/or 4-oxo-4*H*-chromene-3-carboxaldehyde (Nohara *et al*., 1974) in ethanol yielded the corresponding Schiff's bases **4**–**6**, respectively. IR spectra of the compounds **4**–**6** showed the absence of (NH_2) group bands and the appearance of strong absorption bands at 3,140–3,165 cm^{-1} due to (NH) group. The characteristic signals of ^1H NMR spectrum of compound **4** appeared as singlet signals at δ 6.87 ppm (C_5H-thiazole moiety), 8.06 ppm (–CH=N), 8.39 ppm (C_5H-pyrazole moiety), and NH proton at δ 10.0 ppm. Also, ^1H NMR spectrum of Schiff's base **5** indicated one singlet signal at δ 3.36 ppm, which refers to the protons of the methoxy group. (Scheme 1).

Furthermore, cyclocondensation of the thiosemicarbazone derivatives **1b**–**d** with hydrazonyl chloride yielded the corresponding 2-phenyldiazeyl thiazole derivatives **7b**–**d**. ^1H NMR spectrum of the compound **7b** represented the methyl protons of C_4–CH_3-thiazole moiety as a singlet signal at δ 2.71 ppm and ^{13}C NMR spectrum confirmed the structure by the reveling a signal at δ 12.30 ppm due to C_4–CH_3-thiazole moiety.

Ethyl 2-(2-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene) hydrazono)-2,3-dihydro-3-substituted-4-methylthiazole-5-carboxylate derivatives **8b**–**d** were obtaind by



Scheme 2 Synthesis of (((tetrahydronaphthale-6-yl)ethylidine)hydrazono)thiazole and thiazolidinone derivatives

appling Hantzsch reaction (Er *et al*., 2008) of thiosemicarbazone derivatives **1b–d** with ethyl-2-chloroacetoacetate. IR spectra of the derivatives **8b–d** indicated that the disappearance of (2NH) group bands and the appearance of bands at 1,725–1,736 cm^{-1} (C=O) ester group. ^{1}H NMR spectrum of compound **8b** exhibited the ester group signals at δ 1.37 and 4.27 ppm, respectively, and the methyl protons of the thiazole nucleus as singlet signal at δ 2.58 ppm. Also, ^{13}C NMR spectrum of the compound **8b** exhibited signals at δ 14.60, 60.74, and 166.30 ppm related to the ester group and another signal at 12.90 ppm referring to the methyl group of the thiazole nucleus.

In addition, the reaction of thiosemicarbazone derivatives **1b–d** with 3-chloro-2,4-pentanedione gave 5-acetylthiazole derivatives **9b–d**. IR spectra of the compounds **9b–d** showed bands at 1,718–1,721 cm^{-1} (C=O) acetyl group. ^{1}H NMR spectrum of compound **9b** exhibited the protons of the acetyl group as singlet signal at δ 2.60 ppm, in addition to the methyl protons of the thiazole moiety as singlet signal at δ 2.37 ppm and ^{13}C NMR spectrum showed (C=O) group at δ 189.80 ppm. Moreover, the thiosemicarbazone derivatives **1b–d** were condensed with ethyl 2-bromopropanoate to afford the corresponding 5-methylthiazolidinones **10b–d**. IR spectra of the compounds **10b–d** showed bands at 1,715–1,720 cm^{-1} (C=O) thiazolidinone moiety. ^{1}H NMR spectrum of compound **10b** showed douplet signal at δ 1.64 and quartet signal at δ 3.98 ppm attributed to the methyl protons of C_5–CH_3 and C_5–H of the thiazolidinone moiety. Also, ^{13}C NMR spectrum showed signals at δ 19.51, 41.89, and 175.69 ppm related to the corresponding 5-methylthiazolidinone moiety.

Thia-Michael reaction of thiosemicarbazone derivatives **1b–d** with maleic anhydride as Michael acceptor (Liesen *et al*., 2010) in dry toluene led to the formation

Table 1 Anti-inflammatory effects of the tested compounds on carrageenan-induced rat paw edema (mL)

Group	Paw edema volume (mL)				
	0 h	1 h	2 h	3 h	4 h
Control	0.30 ± 0.00	0.43 ± 0.02	0.47 ± 0.02	0.50 ± 0.02	0.51 ± 0.02
Indomethacin (0.03 mmol/kg)	0.30 ± 0.00	0.37 ± 0.01	0.38 ± 0.01*	0.38 ± 0.01*	0.38 ± 0.00*
1b	0.30 ± 0.00	0.38 ± 0.01	0.39 ± 0.01	0.40 ± 0.01*	0.40 ± 0.018
1c	0.29 ± 0.02	0.43 ± 0.03	0.45 ± 0.02	0.45 ± 0.02	0.44 ± 0.03
1d	0.30 ± 0.00	0.40 ± 0.01	0.41 ± 0.01	0.41 ± 0.01*	0.40 ± 0.01*
1e	0.28 ± 0.01	0.42 ± 0.02	0.43 ± 0.02	0.43 ± 0.02	0.41 ± 0.02*
2a	0.30 ± 0.00	0.38 ± 0.02	0.42 ± 0.02	0.45 ± 0.02	0.47 ± 0.01
2e	0.30 ± 0.00	0.41 ± 0.02	0.47 ± 0.02	0.52 ± 0.02	0.55 ± 0.02
2g	0.29 ± 0.00	0.35 ± 0.01	0.40 ± 0.01	0.44 ± 0.01	0.45 ± 0.01
2h	0.30 ± 0.00	0.40 ± 0.02	0.45 ± 0.01	0.47 ± 0.01	0.48 ± 0.01
2j	0.30 ± 0.00	0.40 ± 0.02	0.44 ± 0.01	0.46 ± 0.01	0.47 ± 0.01
4	0.30 ± 0.00	0.33 ± 0.01*	0.36 ± 0.01*	0.37 ± 0.01*	0.41 ± 0.02*
6	0.30 ± 0.00	0.32 ± 0.00*	0.34 ± 0.00*	0.36 ± 0.01*	0.36 ± 0.00*
7b	0.30 ± 0.00	0.33 ± 0.01*	0.35 ± 0.00*	0.39 ± 0.00*	0.39 ± 0.01*
8b	0.30 ± 0.00	0.35 ± 0.01	0.42 ± 0.01	0.45 ± 0.01	0.47 ± 0.01
8c	0.30 ± 0.00	0.35 ± 0.01	0.40 ± 0.01	0.41 ± 0.01*	0.41 ± 0.01*
9b	0.30 ± 0.00	0.35 ± 0.02	0.38 ± 0.01*	0.38 ± 0.01*	0.41 ± 0.01*
9c	0.30 ± 0.00	0.36 ± 0.01	0.41 ± 0.01	0.44 ± 0.01	0.48 ± 0.01
10b	0.30 ± 0.00	0.39 ± 0.02	0.46 ± 0.01	0.51 ± 0.01	0.54 ± 0.01
10c	0.30 ± 0.00	0.34 ± 0.01	0.37 ± 0.01*	0.39 ± 0.01*	0.41 ± 0.01*
11c	0.30 ± 0.00	0.33 ± 0.01*	0.36 ± 0.01*	0.37 ± 0.01*	0.38 ± 0.01*
12a	0.31 ± 0.01	0.39 ± 0.01	0.46 ± 0.02	0.49 ± 0.03	0.53 ± 0.03
12b	0.30 ± 0.00	0.37 ± 0.02	0.40 ± 0.02*	0.41 ± 0.01*	0.41 ± 0.01*
12c	0.29 ± 0.01	0.40 ± 0.02	0.42 ± 0.02	0.41 ± 0.02*	0.40 ± 0.02*
12e	0.29 ± 0.00	0.35 ± 0.01	0.40 ± 0.02	0.45 ± 0.02	0.46 ± 0.02
13b	0.28 ± 0.01	0.36 ± 0.02	0.41 ± 0.02	0.43 ± 0.02	0.44 ± 0.02

The data represents the mean ± standard error of the mean ($n = 6$)

Values represent the mean ± SE of six animals for each groups

$p < 0.05$: * Statistically significant from the control using one way Anova followed by Tukey test

of 4-thiazolidinone-acetic acid derivatives **11b–d**. IR spectra of the compounds **11b–d** showed broad bands centered at 3,408–3,427 cm^{-1} characteristic for (CO_2H) group and bands at 1,707–1,712 cm^{-1} (C=O) thiazolidinone moiety. ^1H NMR spectrum of the compound **11c** showed multiplet signals at 2.88–2.91, 2.98–3.01 ppm (CH_{2ab}), a multiplet signal at 4.32–4.34 (C_5–H thiazolidinone), and broad singlet signal at 12.67 ppm (CO_2H) group.

Refluxing of the thiosemicarbazone derivatives **1a–e** with ethyl bromoacetate in the presence of piperidine in absolute ethanol afforded 2-(2-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-3-substituted-4-thiazolidinones **12a–e**. IR spectra of the compounds **12a–e** showed bands at 1,708–1,724 cm^{-1} (C=O) thiazolidinone moiety. Further confirmation was obtained from the ^1H NMR spectrum of compound **12b**, which exhibited singlet signal at δ 3.76 ppm contributing to the methylene protons of thiazolidinone moiety and ^{13}C NMR spectra showed signals at δ 31.55 and 171.21 ppm due to (CH_2 and C = O) groups of thiazolidinone moiety.

Condensation of **12b–d** with 4-methoxybenzaldehyde in 10 % alcoholic sodium hydroxide afforded the corresponding arylidene derivatives **13b–d**. IR spectra of the compounds **13b–d** showed bands at 1,692–1,698 cm^{-1} attributed to α,β-unsaturated ketone. ^1H NMR spectrum of compound **13b** represented the methoxy protons as singlet signal at δ 3.86 ppm and no signal derived from the methylene protons of thiazolidinone derivatives **12b–d** was observed. Furthermore, acylation of the thiazolidinone derivative **12a** with acetic anhydride led to the formation of 2-(2-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene)

hydrazono)-3-acetylthiazolidin-4-one (**14**), its IR spectrum showed a band at 1,647 cm^{-1} due to (–$NCOCH_3$) group and in ^1H NMR spectrum the acetyl protons were observed as a singlet signal at 2.41 ppm. (Scheme 2).

Biological screening

Anti-inflammatory activity

In this study, 24 newly synthesized derivatives were selected as representative examples to evaluate their anti-inflammatory activity by applying carrageenan-induced paw edema bioassay in rats (Winter *et al*., 1962) using indomethacin as a reference standard. Results were expressed as mean ± SE. The difference between control and treated groups were tested using one way ANOVA followed by Tukey test. Methods of statistical analysis were done according to Armitage (Armitage, 1971). The evaluated compounds are **1b–e**, **2a**, **2e**, **2g**, **2h**, **2j**, **4**, **6**, **7b**, **8b**, **c**, **9b**, **c**, **10b**, **c**, **11c**, **12a**, **b**, **c**, **e**, **13b**. The anti-inflammatory activity data (Tables 1, 2) revealed that the highest anti-inflammatory potency at 4 h was gained by 11 derivatives according to the following order **6 > 11c > 7b > 1d > 12 c > 1e**, **4**, **8c**, **9b**, **10c**, **12b**. It has been noticed that they exhibited early action showing percentages of edema inhibition higher than or equal to the reference drug indomethacin. The compound 6 carrying coumarin-thiazole ring system inhibited the edema volume by (25.58 %) at the 1st h post administration, and the activity was enhanced up to the 4th h giving edema volume inhibition by (29.41 %) higher than that produced by indomethacin (13.95 and 25.49 %, respectively). Also, significant edema inhibition at the first hour post compounds administration (20.93–23.25 %) was observed by the derivatives carrying pyrazolothiazole, 5-phenyldiazeyl-thiazole, 3-ethyl-5-methylthiazolidinone, and 3-ethyl-thiazolidinone-5-acetic acid nuclei (**4**, **7b**, **10c**, **11c**). A substantial reduction in the activity, but still higher than that of indomethacin, was detected by the derivatives: thiazole-5-carboxylates **8b**,**c**, 5-acetylthiazoles **9b**,**c**, 3-methyl/cyclohexylthiazolidinones **12b**,**e**, and 5-methoxybenzylidine-thiazolidinone conjugate **13b**. Regarding to the duration of actions of the tested derivatives demonstrated that the highest potency obtained at 4 h post after derivatives administration was also produced by the coumarin-thiazole compound **6**, which exhibited edema inhibition (29.41 %) higher than that of indomethacin (25.49 %). Equipotency to the reference drug indomethacin was observed by the acetic acid derivative **11c**. Slight reduction in the activity at 4 h after compounds administration (21.56–23.52 %) was noticed by the derivatives **1b**, **1d**, **7b**, and **12c**. A noteworthy decrease in the activity was obtained by the other tested derivatives.

Table 2 Percentage of edema inhibition of the tested compounds on carrageenan-induced rat paw edema

Group no.	% inhibition (potency)			
	1 h	2 h	3 h	4 h
Indomethacin (0.03 mmol/kg)	−13.95	−19.14	−24.00	−25.49
1b	−11.62	−17.02	−20.00	−21.56
1c	0.00	−4.25	−10.00	−13.72
1d	−6.97	−12.76	−18.00	−21.56
1e	−2.32	−8.51	−14.00	−19.60
2a	−11.62	−10.63	−10.00	−7.84
2e	−4.65	0.00	4.00	7.84
2g	−18.60	−14.89	−12.00	−11.76
2h	−6.97	−4.25	−6.00	−5.88
2j	−6.97	−6.38	−8.00	−7.84
4	−23.25	−23.40	−26.00	−19.60
6	−25.58	−27.65	−28.00	−29.41
7b	−23.25	−25.53	−22.00	−23.52
8b	−18.60	−10.63	−10.00	−7.84
8c	−18.60	−14.89	−18.00	−19.60
9b	−18.60	−19.14	−24.00	−19.60
9c	−16.27	−12.76	−12.00	−5.88
10b	−9.30	−2.12	2.00	5.88
10c	−20.93	−21.27	−22.00	−19.60
11c	−23.25	−23.40	−26.00	−25.49
12a	−9.30	−2.12	−2.00	3.92
12b	−13.95	−14.89	−18.00	−19.60
12c	−6.97	−10.63	−18.00	−21.56
12e	−18.60	−14.89	−10.00	−9.80
13b	−16.27	−12.76	−14.00	−13.72

Analgesic activity

The analgesic activity of the above mentioned derivatives was also evaluated in comparison with indomethacin as a standard reference drug (10 mg/kg) by applying hot plate test (Tzschentke *et al*., 2007). The results were expressed as mean ± SE. The difference between vehicle control and treatment groups was tested using one way ANOVA followed by Tukey. Methods of statistical analysis were done according to Armitage (Armitage, 1971). The analgesic activity expressed in (Table 3) showed that the longest duration of actions up to 90 min post derivatives administration was gained by the compounds bearing thiosemicarbazide, 3-methyl-4-tetralylthiazole, coumarin-thiazole, 3-ethyl-5-methylthiazolidinone, 3-methylthiazolidinone, cyclohexylthiazolidinone, 3-ethyl-4-tetralylthiazole, and 4-phenyllthiazole ring systems (**1d**, **2g**, **6**, **10c**, **12b**, **12e**, **2h**, **2j**). They exhibited equipotent analgesia to that obtained by indomethacin. A noteworthy drop in the produced analgesia was got by the other tested derivatives.

Ulcerogenic activity

The ulcerogenic potential of the tested compounds was evaluated in rats (Abouzid *et al*., 2012, El-Araby *et al*., 2012). Interestingly, all the tested derivatives showed superior GIT safety profile and exhibited no ulcerogenic effects in comparison to indomethacin which exhibited ulcer severity 22.40 ± 1.24 the same experimental conditions. These data represented the potential medicinal value of these compounds as anti-inflammatory and analgesic agents, since they have better safety margin than indomethacin on gastric mucosa.

Conclusions

This study deals with synthesis of novel derivatives of tetrahydronaphthalene nucleus incorporated with substituted thiazole moiety via hydrazine linkage. Biological evaluation of many of the derivatives as anti-inflammatory and analgesic agents showed that some of them produced higher potency than the reference drug indomethacin. Also, it is noticeable that dual anti-inflammatory and analgesic activities were obtained by thiosemicarbazide, coumarin-thiazole, 3-ethyl-5-methylthiazolidinone, and 3-methyl/cyclohexylthiazolidinone derivatives (**1d**, **6**, **10c**, **12b**, **12e**). It is noteworthy that the coumarin-thiazole compound **6** produced the highest anti-inflammatory and analgesic potency with superior GIT safety, and this result comes in agreement with the literature report (Kalkhambkar *et al*., 2007, Kashyap *et al*., 2012) that indicated the valuability of coumarin and tetralin nuclei in producing anti-inflammatory efficiency.

Experimental

Chemistry

All melting points are uncorrected and were taken in open capillary tubes using Electrothermal apparatus 9100. Elemental microanalyses were carried out at Microanalytical Unit, Central Services Laboratory, National Research Centre, Dokki, Cairo, Egypt, using Vario Elementar and were found within ± 0.4 % of the theoretical values. Infrared spectra were recorded on a Jasco FT/IR-6100, Fourier transform, Infrared spectrometer at cm^{-1} scale using KBr disk technique at Central Services Laboratory, National Research Centre, Dokki, Cairo, Egypt. ^{1}H NMR and ^{13}C NMR spectra were determined by using a JEOL AS-500 NMR spectrometer at Central Services Laboratory, National Research Centre, Dokki, Cairo, Egypt, chemical shifts are expressed in δ (ppm) downfield from TMS as an internal standard. The mass spectra were measured with a GC MS-Qp1000EX Shimadzu, Cairo University, Cairo, Egypt. Follow up of the reactions and checking the purity of the compounds were made by TLC on silica gel-precoated aluminum sheets (Type 60, F 254, Merck, Darmstadt, Germany) using chloroform/pet.ether 40–60 (5:1, v/v), and the spots were detected by exposure to UV lamp at λ_{254} nm for few seconds and by iodine vapor.

The chemical names given for the prepared compounds are according to the IUPAC system. 1-(5-(1,2,3,4-tetrahydronaphthalen-6-yl)thiazol-2-yl)hydrazine (**3**) (El-Zahar *et al*., 2009), 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde (Prakash *et al*., 2006), 1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazole-4-carboxaldehyde (Fahmy *et al*., 2012), and 4-oxo-4*H*-chromene-3-carboxaldehyde (Nohara *et al*., 1974) were prepared according to the reported method.

General procedure for the synthesis of 1-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene) thiosemicarbazide derivatives **1a–e**

A mixture of 6-acetyl-1,2,3,4-tetrahydronaphthalene (3.48 g, 0.02 mol) and thiosemicarbazide or the appropriate thiosemicarbazide derivatives, namely; methylthiosemicarbazide, ethylthiosemicarbazide, phenylthiosemicarbazide, and/or cyclohexylthiosemicarbazide (0.02 mol) in absolute ethanol (15 mL) containing a few drops of conc. hydrochloric acid was refluxed for 3 h. The formed precipitate on cooling was filtered, dried, and recrystallized from ethanol to give the title compounds **1a–e**.

*1-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene) thiosemicarbazide (**1a**)*

Yield 71 %, mp. 177–178 °C; IR (KBr, cm^{-1}): 3398, 3233, 3142 (NH, NH_2), 2929, 2853 (CH_2-tetrahydronaphthalene), 1589 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.67–1.74 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.24 (3H, s, CH_3–C=N), 2.68–2.74 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 7.00 (1H, d, CH=, J = 9.00 Hz), 7.61 (1H, d, CH=, J = 9.00 Hz), 7.87 (1H, s, CH =), 8.27, 10.16 (3H, 2 s, NH, NH_2, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 13.32, 22.10, 28.03, 28.24, 123.09, 126.43, 128.14, 134.20, 135.85, 137.42, 147.55, 178.12; MS, *m/z* (%): 246.9 [M^+] (70), 248.0 [M^+ + 1] (12), 231.9 [M^+-NH] (100). Anal. For $C_{13}H_{17}N_3S$ (247.36): Calcd. C, 63.12; H, 6.93; N, 16.99; S, 12.96; Found: C, 63.25; H, 7.03; N, 16.81; S, 12.78.

*1-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)-4-methylthiosemicarbazide (**1b**)*

Yield 77 %, mp. 114–115 °C; IR (KBr, cm^{-1}): 3319, 3211 (2 NH), 2933, 2855 (CH_2-tetrahydronaphthalene), 1609 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.69–1.72 (4H, m, 2(CH_2)-

Table 3 Analgesic activity of the tested compounds by hot plate method

Group	Reaction time/min			
	0 min	30 min	60 min	90 min
Control	4.06 ± 0.68	4.98 ± 0.25	5.78 ± 0.44	5.56 ± 0.64
Indomethacin (0.03 mmol/kg)	5.56 ± 0.23	8.04 ± 0.55*	10.86 ± 0.57*	9.86 ± 1.07*
1b	3.52 ± 0.40	5.34 ± 0.26	6.12 ± 0.61	7.90 ± 0.49
1c	3.96 ± 0.39	4.40 ± 0.43	5.50 ± 0.43	6.86 ± 0.56
1d	4.12 ± 0.57	5.62 ± 0.67	7.54 ± 0.73	10.18 ± 1.14*
1e	3.92 ± 0.59	5.16 ± 0.49	6.12 ± 0.61	7.36 ± 0.81
2a	2.67 ± 0.40	4.00 ± 0.31	4.34 ± 0.18	4.60 ± 0.28
2e	2.72 ± 0.32	4.00 ± 0.22	6.30 ± 0.59	7.72 ± 1.08
2g	3.44 ± 0.55	6.00 ± 0.54	6.90 ± 0.57	10.12 ± 0.57*
2h	4.06 ± 0.18	5.80 ± 0.43	6.88 ± 0.38	9.82 ± 0.75*
2j	3.54 ± 0.54	6.06 ± 0.50	7.92 ± 0.41	9.82 ± 0.37*
4	2.82 ± 0.23	4.00 ± 0.26	4.88 ± 0.36	6.30 ± 0.49
6	3.48 ± 0.22	4.74 ± 0.35	5.38 ± 0.53	10.20 ± 0.37*
7b	2.94 ± 0.43	4.12 ± 0.26	6.04 ± 6.04	7.94 ± 0.56
8b	2.64 ± 0.25	3.76 ± 0.22	5.02 ± 0.38	5.48 ± 0.30
8c	3.08 ± 0.34	4.34 ± 0.246	6.18 ± 0.48	6.80 ± 0.51
9b	3.08 ± 0.39	4.48 ± 0.42	6.26 ± 0.50	7.56 ± 0.91
9c	3.00 ± 0.46	5.06 ± 0.61	5.96 ± 0.69	6.98 ± 0.78
10b	2.48 ± 0.43	3.86 ± 0.20	7.80 ± 0.53	6.88 ± 0.77
10c	3.38 ± 0.60	5.20 ± 0.48	6.36 ± 0.55	10.40 ± 0.81*
11c	3.18 ± 0.42	4.46 ± 0.46	5.96 ± 0.20	6.64 ± 0.45
12a	3.64 ± 0.53	4.60 ± 0.43	5.40 ± 0.36	6.16 ± 0.60
12b	3.48 ± 0.31	5.92 ± 0.75	7.58 ± 0.68	10.78 ± 1.02*
12c	4.12 ± 0.57	5.16 ± 0.62	5.76 ± 0.52	6.32 ± 0.34
12e	3.36 ± 0.63	5.14 ± 0.60	6.28 ± 0.57	10.18 ± 0.36*
13b	3.36 ± 0.62	5.70 ± 0.63	6.58 ± 0.80	7.92 ± 0.83

Values represent the mean ± SE of six animals for each group

$p < 0.05$: * Statistically significant from control using one way Anova followed by Tukey test

tetrahydronaphthalene protons), 2.24 (3H, s, CH_3–C=N), 2.69–2.73 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.06 (3H, s, N–CH_3), 7.02 (1H, d, CH=, $J = 8.10$ Hz), 7.54 (1H, s, CH =), 7.65 (1H, d, CH=, $J = 8.10$ Hz), 8.37, 10.14 (2H, 2 s, 2NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 13.24, 21.97, 27.93, 28.21, 30.37, 122.95, 126.33, 128.01, 134.17, 135.71, 137.23, 147.17, 177.87; MS, *m/z* (%): 261.0 [M^+] (36), 262.0 [M^++1] (12), 246.0 [M^+-CH_3] (60), 107.2 [C_8H_{11}] (100). Anal. For $C_{14}H_{19}N_3S$ (261.39): Calcd. C, 64.33; H, 7.33; N, 16.08; S, 12.27; Found: C, 64.64; H, 7.25; N, 16.21; S, 12.35.

*4-Ethyl-1-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene) thiosemicarbazide (**1c**)*

Yield 80 %, mp. 107–108 °C; IR (KBr, cm^{-1}): 3366, 3253 (2 NH), 2927, 2860 (CH_2-tetrahydronaphthalene), 1600 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.30 (3H, t, N–$CH_2\underline{CH_3}$, $J = 6.90$ Hz), 1.80–1.82 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.29 (3H, s, CH_3–C=N), 2.77–2.79 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.76 (2H, q, N–$\underline{CH_2}CH_3$, $J = 6.90$ Hz), 7.09 (1H, d, CH=, $J = 7.50$ Hz), 7.35 (1H, s, CH =), 7.40 (1H, d, CH=, $J = 7.50$ Hz), 7.58, 8.56 (2H, 2 s, 2NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ 13.95, 14.66, 23.13, 29.36, 29.59, 39.40, 123.51, 127.12, 129.39, 134.80, 137.32, 139.23, 147.63, 177.64; MS, *m/z* (%): 275.2 [M^+] (47), 260.2 [M^+-CH_3] (18), 187.2 [M^+-C_3H_6NS] (19), 174.2 [M^+-$C_3H_5N_2S$] (100). Anal. For $C_{15}H_{21}N_3S$ (275.41): Calcd. C, 65.41; H, 7.69; N, 15.26; S, 11.64; Found: C, 65.39; H, 7.81; N, 15.44; S, 11.78.

*1-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)-4-phenylthiosemicarbazide (**1d**)*

Yield 82 %, mp. 167–168 °C; IR (KBr, cm^{-1}): 3290, 3250 (2 NH), 2931, 2852 (CH_2-tetrahydronaphthalene), 1590

(C=N); ^{1}H NMR (DMSO-d_6): δ 1.72–1.74 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.33 (3H, s, CH_3–C=N), 2.72–2.75 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 7.05–7.75 (8H, m, CH-tetrahydronaphthalene protons and Ar–H), 9.97, 10.52 (2H, 2 s, 2NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 13.90, 22.15, 28.16, 28.38, 123.47, 124.82, 125.33, 126.83, 127.57, 128.30, 134.18, 136.00, 137.81, 138.68, 148.91, 176.34; MS, *m/z* (%): 323.0 [M^+] (25), 308.0 [M^+-CH_3] (40), 230.0 [M^+-C_6H_7N] (31), 93.0 [C_6H_7N] (100). Anal. For $C_{19}H_{21}N_3S$ (323.46): Calcd. C, 70.55; H, 6.54; N, 12.99; S, 9.91; Found: C, 70.46; H, 6.77; N, 12.79; S, 9.68.

*4-Cyclohexyl-1-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene)thiosemicarbazide (**1e**)*

Yield 52 %, mp. 160–161 °C; IR (KBr, cm^{-1}): 3330, 3204 (2 NH), 2927, 2847 (CH_2-tetrahydronaphthalene and cyclohexyl moieties), 1613 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.13–1.60 (10H, m, 5(CH_2)-cyclohexyl protons), 1.66–1.76 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.25 (3H, s, CH_3–C=N), 2.68–2.76 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 4.17–4.24 (1H, m, –NCH-cyclohexyl moiety), 7.04 (1H, d, CH=, J = 7.70 Hz), 7.44 (1H, s, CH =), 7.56 (1H, d, CH=, J = 7.70 Hz), 7.93, 10.15 (2H, 2 s, 2NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 13.90, 22.31, 24.35, 24.72, 28.30, 28.51, 31.33, 51.98, 123.18, 126.81, 128.63, 134.59, 136.22, 137.70, 147.96, 176.23; MS, *m/z* (%): 328.8 [M^+] (14), 174.0 [$C_{12}H_{16}N$] (100), 98 [$C_6H_{12}N$] (97). Anal. For $C_{19}H_{27}N_3S$ (329.50): Calcd. C, 69.26; H, 8.26; N, 12.75; S, 9.73; Found: C, 69.44; H, 8.11; N, 12.42; S, 9.88.

General procedure for the synthesis of 1-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene)-2-(3,4-disubstituted thiazol-2(3H)-ylidene)hydrazine **2a–f**

A mixture of the thiosemicarbazone derivatives **1b–d** (0.002 mol), chloroacetone and/or phenacyl bromide (0.002 mol), and anhydrous sodium acetate (0.17 g, 0.002 mol) in absolute ethanol (15 mL) was heated under reflux for 6 h. The formed precipitate on cooling was filtered, washed several times with water, dried, and recrystallized from ethanol to give the title compounds **2a–f**.

*1-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)-2-(3,4-dimethylthiazol-2(3H)-ylidene)hydrazine (**2a**)*

Yield 75 %, mp. 153–154 °C; IR (KBr, cm^{-1}): 2926, 2842 (CH_2-tetrahydronaphthalene), 1597, 1566 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.79–1.83 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.13 (3H, s, C_4–CH_3-thiazole protons), 2.44 (3H, s, CH_3–C=N), 2.76–2.80 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.44 (3H, s, N–CH_3), 5.69 (1H, s, C_5H-thiazole proton), 7.04 (1H, d, CH=, J = 8.00 Hz), 7.53 (1H, s, CH =), 7.59 (1H, d, CH=, J=8.00 Hz); ^{13}C NMR ($CDCl_3$): δ 14.44, 23.43, 29.44, 29.75, 31.37, 96.48, 123.52, 126.93, 129.03, 135.33, 136.80, 137.83, 155.34, 169.49; MS, *m/z* (%): 299.0 [M^+] (100), 300.0 [M^++1] (23), 298.0 [M^+-1] (86); Anal. For $C_{17}H_{21}N_3S$ (299.43): Calcd. C, 68.19; H, 7.07; N, 14.03; S, 10.71; Found: C, 68.33; H, 7.27; N, 14.26; S, 10.65.

*2-(3-Ethyl-4-methylthiazol-2(3H)-ylidene)-1-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene)hydrazine (**2b**)*

Yield 77 %, mp. 114–115 °C; IR (KBr, cm^{-1}): 2934, 2856 (CH_2-tetrahydronaphthalene), 1595, 1563 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.32 (3H, t, N–$CH_2\underline{CH_3}$, J = 6.90 Hz) 1.79–1.83 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.14 (3H, s, C_4–CH_3–thiazole protons), 2.37 (3H, s, CH_3–C=N), 2.76–2.80 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.94 (2H, q, N–$\underline{CH_2}CH_3$, J = 6.90 Hz), 5.65 (1H, s, C_5H-thiazole proton), 7.03 (1H, d, CH=, J = 8.00 Hz), 7.53 (1H, s, CH =), 7.59 (1H, d, CH=, J = 8.00 Hz); MS, *m/z* (%): 312.9 [M^+] (33), 314 [M^++1] (22), 299.6 [M^+-CH] (31), 158.2 [$C_{12}H_{15}$] (40), 59.6 [$C_3H_{10}N$] (100); Anal. For $C_{18}H_{23}N_3S$ (313.46): Calcd. C, 68.97; H, 7.40; N, 13.41; S, 10.23; Found: C, 69.12; H, 7.72; N, 13.68; S, 10.44.

*1-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)-2-(4-methyl-3-phenylthiazol-2(3H)-ylidene)hydrazine (**2c**)*

Yield 85 %, mp. 130-131 °C; IR (KBr, cm^{-1}): 2942, 2835 (CH_2-tetrahydronaphthalene), 1594, 1563 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.79–1.82 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 1.89 (3H, s, C_4–CH_3-thiazole protons), 2.20 (3H, s, CH_3–C=N), 2.77–2.79 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 5.81 (1H, s, C_5H-thiazole proton), 7.10–7.60 (8H, m, CH-tetrahydronaphthalene protons and Ar–H); MS, *m/z* (%): 361.0 [M^+] (100), 362.0 [M^++1] (33), 130.0 [$C_{10}H_{10}$] (48), 77.0 [C_6H_5] (75); Anal. For $C_{22}H_{23}N_3S$ (361.50): Calcd. C, 73.09; H, 6.41; N, 11.62; S, 8.87; Found: C, 73.28; H, 6.11; N, 11.81; S, 8.64.

*1-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)-2-(3-methyl-4-phenylthiazol-2(3H)-ylidene)hydrazine (**2d**)*

Yield 73 %, mp. 141–142 °C; IR (KBr, cm^{-1}): 2921, 2842 (CH_2-tetrahydronaphthalene), 1590, 1564 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.80–1.82 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.46 (3H, s, CH_3–C=N), 2.78–2.82 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.38 (3H, s, N–CH_3), 5.95 (1H, s, C_5H-thiazole proton), 7.36–7.65 (8H, m, CH-tetrahydronaphthalene protons and Ar–H); ^{13}C NMR

($CDCl_3$): δ 13.33, 22.06, 28.15, 28.44, 32.49, 98.62, 122.31, 124.24, 125.75, 127.55, 127.76, 127.85, 128.04, 128.13, 130.07, 135.56, 136.74, 139.67, 154.78, 168.24; MS, *m/z* (%): 361.0 [M^+] (100), 362 [M^++1] (29), 175.8 [$C_{12}H_{18}N$] (43); Anal. For $C_{22}H_{23}N_3S$ (361.50): Calcd. C, 73.09; H, 6.41; N, 11.62; S, 8.87; Found: C, 73.34; H, 6.56; N, 11.43; S, 8.91.

*2-(3-Ethyl-4-phenylthiazol-2(3H)-ylidene)-1-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene)hydrazine (**2e**)*

Yield 68 %, mp. 83–84 °C; IR (KBr, cm^{-1}): 2924, 2840 (CH_2-tetrahydronaphthalene), 1597, 1565 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.24 (3H, t, N–$CH_2\underline{CH_3}$, J = 6.90 Hz), 1.79–1.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.46 (3H, s, CH_3–C=N), 2.78–2.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.89 (2H, q, N–$\underline{CH_2}CH_3$, J = 6.90 Hz), 5.91 (1H, s, C_5H-thiazole proton), 7.38–7.63 (8H, m, CH-tetrahydronaphthalene protons and Ar–H); MS, *m/z* (%): 361.0 [M^+-CH_2] (23), 362 [M^+-CH] (23), 56.9 [C_4H_9] (100); Anal. For $C_{23}H_{25}N_3S$ (375.53): Calcd. C, 73.56; H, 6.71; N, 11.19; S, 8.54; Found: C, 73.74; H, 6.86; N, 11.28; S, 8.32.

*1-(1-(1,2,3,4–tetrahydronaphthalen–6–yl)ethylidene)-2-(3,4-diphenylthiazol-2(3H)-ylidene)hydrazine (**2f**)*

Yield 59 %, mp. 140-141 °C; IR (KBr, cm^{-1}): 2927, 2839 (CH_2-tetrahydronaphthalene), 1591, 1569 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.78–1.80 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.35 (3H, s, CH_3–C=N), 2.77–2.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 6.16 (1H, s, C_5H-thiazole proton), 7.12–7.70 (13H, m, CH-tetrahydronaphthalene protons and Ar–H); MS, *m/z* (%): 423.0 [M^+] (100), 424.0 [M^++1] (35), 422.4 [M^+-1] (48); Anal. For $C_{27}H_{25}N_3S$ (423.57): Calcd. C, 76.56; H, 5.95; N, 9.92; S, 7.57; Found: C, 76.38; H, 6.21; N, 9.74; S, 7.36.

General procedure for the synthesis of 2-(4-(1,2,3,4-tetrahydronaphthalen-6-yl)-3-substituted thiazol-2(3H)-ylidene)-1-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene)hydrazine **2g–i**

A mixture of the thiosemicarbazone derivatives **1b–d** (0.002 mol) and 6-bromoacetyl-1,2,3,4-tetrahydronaphthalene (0.51 g, 0.002 mol) in absolute ethanol (15 mL) containing few drops of piperidine was heated under reflux for 4 h. After cooling, the mixture was poured onto ice/cold water, the formed precipitate was filtered, washed several times with water, dried, and recrystallized from ethylacetate/pet.ether to give the title compounds **2g–i**.

*2-(4-(1,2,3,4-Tetrahydronaphthalen-6-yl)-3-methylthiazol-2(3H)-ylidene)-1-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene) hydrazine (**2g**)*

Yield 80 %, mp. 139–140 °C; IR (KBr, cm^{-1}): 2927, 2847 (CH_2-tetrahydronaphthalene), 1593, 1566 (C = N); ^{1}H NMR ($CDCl_3$): δ 1.81–1.83 (8H, m, 4(CH_2)-tetrahydronaphthalene protons), 2.51 (3H, s, CH_3–C = N), 2.78–2.82 (8H, m, 4(CH_2)-tetrahydronaphthalene protons), 3.48 (3H, s, N–CH_3), 5.99 (1H, s, C_5H-thiazole proton), 7.06–7.65 (6H, m, CH-tetrahydronaphthalene protons); ^{13}C NMR ($CDCl_3$): δ 15.09, 23.12, 23.39, 29.48, 29.74, 34.45, 100.12, 123.66, 125.91, 127.12, 128.03, 129.09, 129.59, 136.39, 136.89, 137.90, 138.32, 138.73, 141.65, 156.43, 169.81; MS, *m/z* (%): 415.0 [M^+] (100), 416.0 [M^++1] (32), 414.0 [M^+-1] (35); Anal. For $C_{26}H_{29}N_3S$ (415.59): Calcd. C, 75.14; H, 7.03; N, 10.11; S, 7.72; Found: C, 75.23; H, 6.85; N, 10.24; S, 7.91.

*2-(3-Ethyl-4-(1,2,3,4-tetrahydronaphthalen-6-yl)thiazol-2(3H)-ylidene)-1-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene)hydrazine (**2h**)*

Yield 78 %, mp. 119–120 °C; IR (KBr, cm^{-1}): 2927, 2855 (CH_2-tetrahydronaphthalene), 1595, 1560 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.28 (3H, t, N–$CH_2\underline{CH_3}$, J = 6.90 Hz), 1.81–1.83 (8H, m, 4(CH_2)-tetrahydronaphthalene protons), 2.48 (3H, s, CH_3–C=N), 2.78–2.82 (8H, m, 4(CH_2)-tetrahydronaphthalene protons), 3.39 (2H, q, N–$\underline{CH_2}CH_3$, J = 6.90 Hz), 5.90 (1H, s, C_5H-thiazole proton), 7.05–7.67 (6H, m, CH-tetrahydronaphthalene protons); MS, *m/z* (%): 429.0 [M^+] (50), 430.0 [M^++1] (16), 428 [M^+-1] (9), 257 [M^+-$C_{12}H_{14}N$] (32), 115 [C_9H_7] (100); Anal. For $C_{27}H_{31}N_3S$ (429.62): Calcd. C, 75.48; H, 7.27; N, 9.78; S, 7.46; Found: C, 75.66; H, 7.31; N, 9.67; S, 7.51.

*2-(4-(1,2,3,4-Tetrahydronaphthalen-6-yl)-3-phenylthiazol-2(3H)-ylidene)-1-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene) hydrazine (**2i**)*

Yield 61 %, mp. 114–115 °C; IR (KBr, cm^{-1}): 2924, 2856 (CH_2-tetrahydronaphthalene), 1598, 1562 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.72–1.81 (8H, m, 4(CH_2)-tetrahydronaphthalene protons), 2.30 (3H, s, CH_3–C=N), 2.67–2.80 (8H, m, 4(CH_2)-tetrahydronaphthalene protons), 6.11 (1H, s, C_5H-thiazole proton), 7.17–7.65 (11H, m, CH-tetrahydronaphthalene protons and Ar–H); MS, *m/z* (%): 476.9 [M^+] (62), 478.0 [M^++1] (30), 476.4 [M^+-1] (34); 60.0 [C_2H_4S] (100); Anal. For $C_{31}H_{31}N_3S$ (477.66): Calcd. C, 77.95; H, 6.54; N, 8.80; S, 6.71; Found: C, 77.74; H, 6.41; N, 8.62; S, 6.84.

General procedure for the synthesis of 1-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene)-2-(4-phenyl/(4 bromophenyl)thiazol-2-yl)hydrazine **2j**, **k**

A mixture of the thiosemicarbazone derivative **1a** (0.5 g, 0.002 mol) and α-haloketone namely; phenacyl bromide and/or 4-bromophenacyl bromide (0.002 mol) in absolute ethanol (15 mL) was heated under reflux for 6 h. The formed precipitate on cooling was filtered, washed with sodium carbonate solution (5 %) and then with water, dried, and recrystallized from ethanol to give the title compounds **2j**, **k**.

*1-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)-2-(4-phenylthiazol-2-yl)hydrazine (**2j**)*

Yield 71 %, mp. 215–216 °C; IR (KBr, cm^{-1}): 3122 (NH), 2922, 2855 (CH_2-tetrahydronaphthalene), 1613 (C=N); ^1H NMR ($CDCl_3$): δ 1.80–1.82 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.44 (3H, s, CH_3–C=N), 2.79–2.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 6.76 (1H, s, C_5H-thiazole proton), 7.07–7.74 (8H, m, CH-tetrahydronaphthalene protons and Ar–H), 8.48 (1H, s, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ 14.16, 21.84, 28.14, 28.33, 100.43, 122.40, 124.46, 126.06, 127.94,128.16, 128.55, 132.45, 136.21, 138.80, 142.24, 153.07, 168.47; MS, *m/z* (%): 347.0 [M^+] (73), 348.0 [M^++1] (18), 172.0 [$C_{12}H_{14}N$] (72), 91 [C_7H_7] (100), 77 [C_7H_5] (52); Anal. For $C_{21}H_{21}N_3S$ (347.48): Calcd. C, 72.59; H, 6.09; N, 12.09; S, 9.23; Found: C, 72.74; H, 6.41; N, 12.13; S, 9.38.

2-(4-(4-Bromophenyl)thiazol-2-yl)-1-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene)hydrazine (2 k)

Yield 80 %, mp. 246–247 °C; IR (KBr, cm^{-1}): 3121 (NH), 2917, 2850 (CH_2-tetrahydronaphthalene), 1613 (C=N); ^1H NMR ($CDCl_3$): δ 1.80–1.82 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.52 (3H, s, CH_3–C=N), 2.79–2.80 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 6.77 (1H, s, C_5H-thiazole proton), 7.09–7.60 (7H, m, CH-tetrahydronaphthalene protons and Ar–H); MS, *m/z* (%): 425.0, 427.0 [M^+] (38, 42), 426.0, 428.0 [M^++1] (18, 13), 254.0, 256 [M^+-$C_{12}H_{14}N$] (20, 25), 172 [$C_{12}H_{14}N$] (100); Anal. For $C_{21}H_{20}BrN_3S$ (426.37): Calcd. C, 59.16; H, 4.73; N, 9.86; S, 7.52; Found: C, 59.32; H, 4.42; N, 9.74; S, 7.71.

General procedure for the synthesis of 1-(5-(1,2,3,4-tetrahydronaphthalen-6-yl)thiazol-2-yl)-2((substituted)methylene) hydrazine **4**–**6**

A mixture of 1-(5-(1,2,3,4-tetrahydronaphthalen-6-yl)thiazol-2-yl)hydrazine (**3**) (0.49 g, 0.002 mol) and different aromatic aldehydes, namely, 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde, 1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazole-4-carboxaldehyde, and/or 4-oxo-4*H*-chromene-3-carboxaldehyde (0.002 mol) in absolute ethanol (15 mL) was heated under reflux for 10 h. The formed precipitate on cooling was filtered, dried, and recrystallized from ethanol to give the title compounds **4**–**6**.

*1-(5-(1,2,3,4-Tetrahydronaphthalen-6-yl)thiazol-2-yl)-2-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)hydrazine (**4**)*

Yield 56 %, mp. 185–186 °C; IR (KBr, cm^{-1}): 3165 (NH), 2923, 2851 (CH_2-tetrahydronaphthalene), 1595 (C=N); ^1H NMR ($CDCl_3$): δ 1.80–1.82 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.78–2.80 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 6.87 (1H, s, C_5H-thiazole proton), 7.25–7.81 (13H, m, CH-tetrahydronaphthalene protons, and Ar–H), 8.06 (1H, s, –CH=N–), 8.39 (1H, s, CH-pyrazole proton), 10.0 (1H, s, NH, D_2O exchangeable); MS, *m/z* (%): 475.1 [M^+] (12), 245.9 [$C_{13}H_{16}N_3S$] (90), 230.2 [$C_{13}H_{14}N_2S$] (90), 77 [C_6H_5] (100); Anal. For $C_{29}H_{25}N_5S$ (475.61): Calcd. C, 73.23; H, 5.30; N, 14.73; S, 6.74; Found: C, 73.42; H, 5.51; N, 14.63; S, 6.81.

*2-((1-(3-Chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-4-yl)methylene)-1-(5-(1,2,3,4-tetrahydronaphthalen-6-yl)thiazol-2-yl)hydrazin (**5**)*

Yield 59 %, mp. 133–134 °C; IR (KBr, cm^{-1}): 3150 (NH), 2927, 2851 (CH_2-tetrahydronaphthalene), 1593 (C=N); ^1H NMR ($CDCl_3$): δ 1.79–1.83 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.77–2.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.36 (3H, s, OCH_3), 6.65 (1H, s, C_5H-thiazole proton), 7.19–7.83 (11H, m, CH-tetrahydronaphthalene protons, and Ar–H), 8.01 (1H, s, –CH=N–), 8.41 (1H, s, CH-pyrazole proton), 9.80 (1H, s, NH, D_2O exchangeable); MS, *m/z* (%): 539.0, 540.0 [M^+] (61, 20), 230.2 [$C_{13}H_{14}N_2S$] (28), 64 [C_5H_4] (100); Anal. For $C_{30}H_{26}ClN_5OS$ (540.08): Calcd. C, 66.72; H, 4.85; N, 12.97; S, 5.94; Found: C, 66.41; H, 5.02; N, 12.71; S, 5.77.

*1-(5-(1,2,3,4-Tetrahydronaphthalen-6-yl)thiazol-2-yl)-2-((4H-chromen-4-one-3-yl)methylene)hydrazine (**6**)*

Yield 62 %, mp. 187–188 °C; IR (KBr, cm^{-1}): 3140 (NH), 2923, 2854 (CH_2-tetrahydronaphthalene), 1665 (C=O), 1607 (C=N); ^1H NMR ($CDCl_3$): δ 1.75–1.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.71–2.79 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 6.95 (1H, s, C_5H-thiazole proton), 7.01–7.80 (8H, m, CH-tetrahydronaphthalene protons, CH-chromone and Ar–H), 8.21 (1H, s, –CH=N–), 10.39 (1H, s, NH, D_2O exchangeable); MS, *m/z* (%): 401.2 [M^+] (14), 245.9 [$C_{13}H_{16}N_3S$] (90), 230.2 [$C_{13}H_{14}N_2S$] (90), 94 [C_6H_6O] (100); Anal. For

$C_{23}H_{19}N_3O_2S$ (401.48): Calcd. C, 68.81; H, 4.77; N, 10.47; S, 7.99; Found: C, 68.93; H, 4.85; N, 10.62; S, 7.75.

General procedure for the synthesis of (2-(2-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene)hydrazono))-3-substituted-4-methyl-5-(2-phenyldiazenyl)thiazole **7b–d**

A mixture of the thiosemicarbazone derivatives **1b–d** (0.002 mol), hydrazonyl chloride (0.40 g, 0.002 mol), and anhydrous sodium acetate (0.17 g, 0.002 mol) in absolute ethanol (20 mL) was heated under reflux for 3 h and then left to cool. The formed precipitate was filtered, washed several times with water, dried, and recrystallized from ethanol to give the title compounds **7b–d**.

*(2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono))-3,4-dimethyl-5-(2-phenyldiazenyl)thiazole (**7b**)*

Yield 81 %, mp. 163–164 °C; IR (KBr, cm^{-1}): 2927, 2851 (CH_2-tetrahydronaphthalene), 1593, 1561 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.79–1.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.47 (3H, s, CH_3–C=N), 2.71 (3H, s, C_4–CH_3-thiazole protons), 2.79–2.83 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.72 (3H, s, N–CH_3) 7.09–7.78 (8H, m, CH-tetrahydronaphthalene protons and Ar–H); ^{13}C NMR ($CDCl_3$): δ 12.30, 14.70, 23.39, 29.51, 29.75, 31.48, 122.11, 123.90, 127.33, 128.84, 129.03, 134.21, 135.99, 136.98, 138.84, 145.43, 152.98, 159.17, 164.50; MS, *m/z* (%): 403.0 [M^+] (38), 404.0 [M^++1] (11), 402.0 [M^+-1] (15), 56.0 [C_3H_6N] (100); Anal. For $C_{23}H_{25}N_5S$ (403.54): Calcd. C, 68.46; H, 6.24; N, 17.35; S, 7.95; Found: C, 68.62; H, 6.41; N, 17.50; S, 8.11.

*(2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono))-3-ethyl-4-methyl-5-(2-phenyldiazenyl)thiazole (**7c**)*

Yield 79 %, mp. 137–138 °C; IR (KBr, cm^{-1}): 2928, 2854 (CH_2-tetrahydronaphthalene), 1594, 1567 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.24 (3H, t, N–$CH_2\underline{CH_3}$, J = 6.90 Hz), 1.79–1.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.48 (3H, s, CH_3–C=N), 2.67 (3H, s, C_4–CH_3-thiazole protons), 2.80–2.83 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.70 (2H, q, N–$\underline{CH_2}CH_3$, J = 6.90 Hz), 7.25–7.66 (8H, m, CH-tetrahydronaphthalene protons and Ar–H); MS, *m/z* (%): 417.2 [M^+] (32), 418.2[M^++1] (23), 386.6 [M^+-C_2H_3] (26), 68.9 [C_4H_7N] (100); Anal. For $C_{24}H_{27}N_5S$ (417.57): Calcd. C, 69.03; H, 6.52; N, 16.77; S, 7.68; Found: C, 69.11; H, 6.71; N, 16.58; S, 7.53.

*(2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono))-4-methyl-3-phenyl-5-(2-phenyldiazenyl)thiazole (**7d**)*

Yield 77 %, mp. 204–205 °C; IR (KBr, cm^{-1}): 2925, 2849 (CH_2-tetrahydronaphthalene), 1597, 1562 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.78–1.82 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.44 (3H, s, CH_3–C=N), 2.56 (3H, s, C_4–CH_3-thiazole protons), 2.77–2.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 7.24–7.82 (13H, m, CH-tetrahydronaphthalene protons and Ar–H); MS, *m/z* (%): 465.0 [M^+] (59), 466.0 [M^++1] (19), 464.0 [M^+-1] (25), 118.0 [C_8H_8N] (100); Anal. For $C_{28}H_{27}N_5S$ (465.61): Calcd. C, 72.23; H, 5.84; N, 15.04; S, 6.89; Found: C, 72.44; H, 5.91; N, 15.13; S, 6.62.

General procedure for the synthesis of ethyl 2-(2-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene) hydrazono)-2,3-dihydro-3-substituted-4-methylthiazole-5-carboxylate **8b–d**

A mixture of the thiosemicarbazone derivatives **1b–d** (0.002 mol), ethyl-2-chloroacetoacetate (0.42 mL, 0.003 mol), and anhydrous sodium acetate (0.25 g, 0.003 mol) in absolute ethanol (15 mL) was heated under reflux for 12 h. The formed precipitate on cooling was filtered, washed several times with water, dried, and recrystallized from ethanol to give the title compounds **8b–d**.

*Ethyl 2-(2-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene) hydrazono)-2,3-dihydro-3,4-dimethylthiazole-5-carboxylate (**8b**)*

Yield 79 %, mp. 148–149 °C; IR (KBr, cm^{-1}): 2925, 2856 (CH_2-tetrahydronaphthalene), 1735 (C=O, ester), 1595, 1564 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.37 (3H, t, $CO_2CH_2\underline{CH_3}$, J = 7.00 Hz), 1.79–1.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.46 (3H, s, CH_3–C=N), 2.58 (3H, s, C_4–CH_3-thiazole protons), 2.77–2.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.55 (3H, s, N–CH_3), 4.27 (2H, q, $CO_2\underline{CH_2}CH_3$, J = 7.00 Hz), 7.07(1H, d, CH=, J = 8.00 Hz), 7.54 (1H, s, CH =), 7.63 (1H, d, CH=, J = 8.00 Hz); ^{13}C NMR ($CDCl_3$): δ 12.90, 14.60, 23.37, 29.47, 29.72, 31.56, 60.74, 103.30, 123.70, 127.16, 129.09, 136.21, 136.90, 138.46, 146.98, 157.93, 162.56, 166.30; MS, *m/z* (%): 345.0 [M^+-C_2H_2] (12), 344.0 [M^+-C_2H_3] (20), 299.0 [M^+-$C_3H_4O_2$] (14), 244.0 [M^+-$C_7H_{11}O_2$] (100); Anal. For $C_{20}H_{25}N_3O_2S$ (371.50): Calcd. C, 64.66; H, 6.78; N, 11.31; S, 8.63; Found: C, 64.85; H, 6.81; N, 11.21; S, 8.34.

*Ethyl 2-(2-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene) hydrazono)-2,3-dihydro-3-ethyl-4-methylthiazole-5-carboxylate (**8c**)*

Yield 85 %, mp. 136–137 °C; IR (KBr, cm^{-1}): 2934, 2865 (CH_2-tetrahydronaphthalene), 1732 (C=O, ester), 1592, 1561 (C=N); ^1H NMR ($CDCl_3$): δ 1.33–1.36 (6H, m, $–CO_2CH_2\underline{CH_3}$, $N–CH_2\underline{CH_3}$), 1.80–1.84 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.41(3H, s, $CH_3–C=N$), 2.62 (3H, s, $C_4–CH_3$-thiazole protons), 2.77–2.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 4.03 (2H, q, $N–\underline{CH_2}CH_3$, $J = 6.90$ Hz), 4.27 (2H, q, $CO_2\underline{CH_2}CH_3$, $J = 7.00$ Hz), 7.06 (1H, d, CH=, $J = 8.40$ Hz), 7.54 (1H, s, CH =), 7.63 (1H, d, CH=, $J = 8.40$ Hz); MS, *m/z* (%): 384.9 [M^+] (100), 385.8 [M^++1] (24); Anal. For $C_{21}H_{27}N_3O_2S$ (385.52): Calcd. C, 65.42; H, 7.06; N, 10.90; S, 8.32; Found: C, 65.23; H, 7.21; N, 10.87; S, 8.41.

*Ethyl 2-(2-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-2,3-dihydro-4-methyl-3-phenylthiazole-5-carboxylate (**8d**)*

Yield 70 %, mp. 122–123 °C; IR (KBr, cm^{-1}): 2927, 2857 (CH_2-tetrahydronaphthalene), 1730 (C=O, ester), 1600, 1554 (C=N); ^1H NMR ($CDCl_3$): δ 1.35 (3H, t, $CO_2CH_2\underline{CH_3}$, $J = 7.00$ Hz), 1.78–1.80 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.15 (3H, s, $CH_3–C=N$), 2.28 (3H, s, $C_4–CH_3$-thiazole protons), 2.79–2.79 (4H, m, 2(CH_2) tetrahydronaphthalene protons), 4.29 (2H, q, $CO_2\underline{CH_2}CH_3$, $J = 7.00$ Hz), 7.07–7.59 (8H, m, CH-tetrahydronaphthalene protons and Ar–H); MS, *m/z* (%): 433.0 [M^+] (100), 434.0 [M^++1] (31), 363.0 [M^+-$C_3H_2O_2$] (96); Anal. For $C_{25}H_{27}N_3O_2S$ (433.57): Calcd. C, 69.26; H, 6.28; N, 9.69; S, 7.40; Found: C, 69.38; H, 6.44; N, 9.81; S, 7.61.

General procedure for the synthesis of 2-(2-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-5-acetyl-2,3-dihydro-3-substituted-4-methylthiazole **9b–d**

A mixture of the thiosemicarbazone derivatives **1b–d** (0.002 mol), 3-chloro-2,4-pentanedione (0.36 mL, 0.003 mol), and anhydrous sodium acetate (0.25 g, 0.003 mol) in absolute ethanol (20 mL) was heated under reflux for 10 h. The formed precipitate on cooling was filtered, washed several times with water, dried, and recrystallized from ethanol to give the title compounds **9b–d**.

*2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene) hydrazono)-5-acetyl-2,3-dihydro-3,4-dimethylthiazole (**9b**)*

Yield 75 %, mp. 139–140 °C; IR (KBr, cm^{-1}): 2932, 2874 (CH_2-tetrahydronaphthalene), 1721 (C=O), 1595, 1548 (C=N); ^1H NMR ($CDCl_3$): δ 1.79–1.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.37 (3H, s, $C_4–CH_3$-thiazole protons), 2.45 (3H, s, $CH_3–C=N$), 2.60 (3H, s, $–COCH_3$), 2.78–2.82 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.53 (3H, s, $N–CH_3$), 7.07 (1H, d, CH=, $J = 8.00$ Hz), 7.54 (1H, s, CH =), 7.63 (1H, d, CH=, $J = 8.00$ Hz); ^{13}C NMR ($CDCl_3$): δ 13.55, 14.74, 23.33, 29.45, 29.72, 30.26, 31.56, 113.00, 123.71, 127.19, 129.15, 136.06, 137.00, 138.67, 146.43, 158.65, 165.28, 189.80; MS, *m/z* (%): 341.3 [M^+] (38), 342.0 [M^{+1}] (38), 54.6 [C_3H_5N] (100); Anal. For $C_{19}H_{23}N_3OS$ (341.47): Calcd. C, 66.83; H, 6.79; N, 12.31; S, 9.39; Found: C, 66.59; H, 6.60; N, 12.41; S, 9.45.

*2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-5-acetyl-2,3-dihydro-3-ethyl-4-methylthiazole (**9c**)*

Yield 82 %, mp. 148–149 °C; IR (KBr, cm^{-1}): 2920, 2854 (CH_2-tetrahydronaphthalene), 1720 (C=O), 1590, 1542 (C=N); ^1H NMR ($CDCl_3$): δ 1.35 (3H, t, $N–CH_2\underline{CH_3}$, $J = 6.90$ Hz), 1.80–1.85 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.35 (3H, s, $C_4–CH_3$-thiazole protons), 2.42 (3H, s, $CH_3–C=N$), 2.60 (3H, s, $–COCH_3$), 2.77–2.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 4.06 (2H, q, $N–\underline{CH_2}CH_3$, $J = 6.90$ Hz), 7.06 (1H, d, CH=, $J = 8.50$ Hz), 7.54 (1H, s, CH =), 7.61 (1H, d, CH=, $J = 8.50$ Hz); MS, *m/z* (%): 355.0 [M^+] (100), 356.0 [M^++1] (24), 353.9 [M^+-1] (14); Anal. For $C_{20}H_{25}N_3OS$ (355.50): Calcd. C, 67.57; H, 7.09; N, 11.82; S, 9.02; Found: C, 67.38; H, 7.22; N, 11.67; S 9.31.

*2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-5-acetyl-2,3-dihydro-4-methyl-3-phenylthiazole (**9d**)*

Yield 76 %, mp. 65–66. IR (KBr, cm^{-1}): 2926, 2850 (CH_2-tetrahydronaphthalene), 1718 (C=O), 1594, 1546 (C=N); ^1H NMR ($CDCl_3$): δ 1.78–1.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.18 (3H, s, $C_4–CH_3$-thiazole protons), 2.35 (3H, s, $CH_3–C=N$), 2.43 (3H, s, $–COCH_3$), 2.75–2.79 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 7.01–7.68 (8H, CH-tetrahydronaphthalene protons and Ar–H); MS, *m/z* (%): 403.0 [M^+] (67), 404.0 [M^++1] (20), 402.0 [M^+-1] (35), 360.0 [M^+-$COCH_3$] (40), 361.0 [M^+-$COCH_2$] (93), 77.0 [C_6H_5] (100); Anal. For $C_{24}H_{25}N_3OS$ (403.54): Calcd. C, 71.43; H, 6.24; N, 10.41; S, 7.95; Found: C, 71.25; H, 6.51; N, 10.22; S 8.04.

General procedure for the synthesis of 2-(2-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-3-substituted-5-methylthiazolidin-4-one **10b–d**

A mixture of the thiosemicarbazone derivatives **1b–d** (0.002 mol), ethyl 2-bromopropanoate (0.27 mL, 0.002 mol),

and anhydrous sodium acetate (0.17 g, 0.002 mol) in absolute ethanol (15 mL) was heated under reflux for 6 h. The formed precipitate on cooling was filtered, washed several times with water, dried, and recrystallized from ethanol to give the title compounds **10b–d**.

*2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-3,5-dimethylthiazolidin-4-one (**10b**)*

Yield 66 %, mp. 69–70 °C; IR (KBr, cm^{-1}): 2926, 2858 (CH_2 tetrahydronaphthalene), 1715 (C=O), 1605, 1559 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.63 (3H, d, C_5–CH_3-thiazolidinone protons, $J = 7.00$ Hz), 1.80–1.82 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.43 (3H, s, CH_3–C=N), 2.78–2.80 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.33 (3H, s, N-CH_3), 3.98 (1H, q, C_5H-thiazolidinone proton, $J = 7.00$ Hz), 7.07 (1H, d, CH=, $J = 8.00$ Hz), 7.55 (1H, s, CH =), 7.59 (1H, d, CH=, $J = 8.00$ Hz); ^{13}CNMR ($CDCl_3$): δ 14.97, 19.51, 23.28, 29.48, 29.67, 29.98, 41.89, 123.95, 127.54, 129.20, 135.43, 137.09, 139.55, 160.90, 163.07, 175.69; MS, *m/z* (%): 315.0 [M^+] (100), 316.0 [M^++1] (22), 314.0 [M^+-1] (23), 300.0 [M^+-CH_3] (71); Anal. For $C_{17}H_{21}N_3OS$ (315.43): Calcd. C, 64.73; H, 6.71; N, 13.32; S, 10.17; Found: C, 64.38; H, 6.44; N, 13.50; S, 10.31.

*2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-3-ethyl-5-methylthiazolidin-4-one (**10c**)*

Yield 77 %, mp. 75–76 °C; IR (KBr, cm^{-1}): 2927, 2850 (CH_2-tetrahydronaphthalene), 1717 (C=O), 1605, 1565 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.31 (3H, t, –$NCH_2\underline{CH_3}$, $J = 6.90$ Hz) 1.64 (3H, d, C_5–CH_3-thiazolidinone protons, $J = 7.00$ Hz), 1.79–1.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.42 (3H, s, CH_3–C=N), 2.78–2.80 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.90 (2H, q, –$N\underline{CH_2}CH_3$, $J = 6.90$ Hz), 3.98 (1H, q, C_5H-thiazolidinone proton, $J = 7.00$ Hz), 7.09 (1H, d, CH=, $J = 9.10$ Hz), 7.56 (1H, s, CH =), 7.61 (1H, d, CH=, $J = 9.10$ Hz); MS, *m/z* (%): 329.0 [M^+] (84), 330 [M^++1] (30), 328.0 [M^+-1] (51), 158.0 [$C_{12}H_{14}$] (100); Anal. For $C_{18}H_{23}N_3OS$ (329.46): Calcd. C, 65.62; H, 7.04; N, 12.75; S, 9.73; Found: C, 65.72; H, 6.95; N, 12.46; S, 9.82.

*2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-5-methyl-3-phenylthiazolidin-4-one (**10d**)*

Yield 62 %, mp. 128–129 °C; IR (KBr, cm^{-1}): 2927, 2850 (CH_2-tetrahydronaphthalene), 1720 (C=O), 1611, 1568 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.75 (3H, d, C_5–CH_3-thiazolidinone protons, $J = 7.00$ Hz), 1.80–1.83 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.20 (3H, s, CH_3–C=N), 2.79–2.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 4.15 (1H, q, C_5H-thiazolidinone proton, $J = 7.00$ Hz), 7.07–7.70 (8H, m, CH-tetrahydronaphthalene protons and Ar–H); MS, *m/z* (%): 377.0 [M^+] (100), 377.9 [M^++1] (36), 376.1 [M^+-1] (28), 130.0 [$C_{10}H_{10}$] (75); Anal. For $C_{22}H_{23}N_3OS$ (377.50): Calcd. C, 70.00; H, 6.14; N, 11.13; S, 8.49; Found: C, 70.23; H, 6.28; N, 11.22; S, 8.56.

General procedure for the synthesis of 2-(2-(2-(1-(1,2,3,4-tetrahydronaphthalen-6-yl) ethylidene) hydrazono)-4-oxo-3-substituted thiazolidin-5-yl)acetic acid **11b–d**

A mixture of the thiosemicarbazone derivatives **1b–d** (0.002 mol) and maleic anhydride (0.40 g, 0.004 mol) in dry toluene (15 mL) was heated under reflux for 8 h. The solvent was evaporated under reduced pressure and the crude product was treated with pet.ether. The formed precipitate was filtered, dried, and recrystallized from acetic acid to give the title compounds **11b–d**.

*2-(2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-4-oxo-3-methylthiazolidin-5-yl)acetic acid (**11b**)*

Yield 85 %, mp. 119–120 °C; IR (KBr, cm^{-1}): Broad band centered at 3421 (CO_2H), 2921, 2855 (CH_2-tetrahydronaphthalene), 1712 (C=O), 1607, 1582 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.70–1.71 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.36 (3H, s, CH_3–C=N), 2.69–2.72 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.85–2.89 (1H, m, CH_{2a}), 2.99–3.04 (1H, m, CH_{2b}), 3.16 (3H, s, N–CH_3), 4.32–4.34 (1H, m, C_5H-thiazolidinone proton), 7.07 (1H, d, CH=, $J = 8.40$ Hz), 7.48 (1H, s, CH =), 7.54 (1H, d, CH=, $J = 8.40$ Hz), 12.92 (1H, br s, CO_2H, D_2O exchangeable); MS, *m/z* (%): 359.0 [M^+] (100), 360.0 [M^++1] (23), 358.0 [M^+-1] (19), 344 [M^+-CH_3] (56); Anal. For $C_{18}H_{21}N_3O_3S$ (359.44): Calcd. C, 60.15; H, 5.89; N, 11.69; S, 8.92; Found: C, 60.32; H, 5.71; N, 11.48; S, 8.75.

*2-(2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-4-oxo-3-ethylthiazolidin-5-yl)acetic acid (**11c**)*

Yield 78 %, mp. 151-152 °C; IR (KBr, cm^{-1}): Broad band centered at 3408 (CO_2H), 2932, 2858 (CH_2-tetrahydronaphthalene), 1707 (C=O), 1602, 1580 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.17 (3H, t, N–$CH_2\underline{CH_3}$, $J = 6.90$ Hz), 1.70–1.74 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.33 (3H, s, CH_3–C=N), 2.70–2.72 (4H, m, 2(CH_2)-

tetrahydronaphthalene protons), 2.88–2.91 (1H, m, CH_{2a}), 2.98–3.01 (1H, m, CH_{2b}), 3.74 (2H, q, N–$\underline{CH_2}CH_3$, $J = 6.90$ Hz), 4.32–4.34 (1H, m, C_5H-thiazolidinone proton), 7.06 (1H, d, CH=, $J = 8.40$ Hz), 7.48 (1H, s, CH =), 7.54 (1H, d, CH=, $J = 8.40$ Hz), 12.67 (1H, br s, CO_2H, D_2O exchangeable); MS, *m/z* (%): 373.0 [M^+] (65), 374.0 [M^{+1}] (15), 358.0 [M^+-CH_3] (54), 327.0 [M^+-HCO_2H] (22); 158.0 [$C_{11}H_{12}N$] (100); Anal. For $C_{19}H_{23}N_3O_3S$ (373.47): Calcd. C, 61.10; H, 6.21; N, 11.25; S, 8.59; Found: C, 61.34; H, 6.38; N, *11.34; S, 8.64.*

*2-(2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-4-oxo-3-phenylthiazolidin-5-yl)acetic acid (**11d**)*

Yield 87 %, mp. 206–207 °C; IR (KBr, cm^{-1}): Broad band centered at 3427 (CO_2H), 2924, 2851 (CH_2-tetrahydronaphthalene), 1712 (C=O), 1613, 1587 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.70–1.74 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.13 (3H, s, CH_3–C=N), 2.67–2.70 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.74–2.78 (1H, m, CH_{2a}), 3.06–3.11 (1H, m, CH_{2b}), 4.48–4.50 (1H, m, C_5H-thiazolidinone proton), 7.05–7.60 (8H, m, CH-tetrahydronaphthalene protons and Ar–H), 12.79 (1H, br s, CO_2H, D_2O exchangeable); MS, *m/z* (%): 374.9 [M^+-HCO_2H] (36); 158.0 [$C_{11}H_{12}N$] (26); 59.7 [C_4H_{12}] (100); Anal. For $C_{23}H_{23}N_3O_3S$ (421.51): Calcd. C, 65.54; H, 5.50; N, 9.97; S, 7.61; Found: C, 65.67; H, 5.41; N, 9.82; S, 7.33.

General procedure for the synthesis of 2-(2-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-3-substituted thiazolidin-4-one **12a–e**

A mixture of the thiosemicarbazone derivatives **1a–e** (0.002 mol) and ethyl bromoacetate (0.23 mL, 0.002 mol) in absolute ethanol (10 mL) containing few drops of piperidine was heated under reflux for 3 h. The formed precipitate on cooling was filtered, washed several times with cyclohexane, dried, and recrystallized from ethanol to give the title compounds **12a–e**.

*2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono)thiazolidin-4-one (**12a**)*

Yield 69 %, mp. 208-209 °C; IR (KBr, cm^{-1}): 3110 (NH), 2926, 2850 (CH_2-tetrahydronaphthalene), 1708 (C=O), 1618, 1561 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.69–1.71 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.31 (3H, s, CH_3–C=N), 2.69–2.71 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.82 (2H, s, CH_2-thiazolidinone protons) 7.06 (1H, d, CH=, $J = 8.40$ Hz), 7.46 (1H, s, CH =), 7.53 (1H, d, CH=, $J = 8.40$ Hz), 11.76 (1H, s, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 15.10, 23.23, 29.24, 29.47, 33.60, 124.01, 127.55, 129.43, 135.60, 136.9, 139.22, 160.85, 163.97, 174.41; MS, *m/z* (%): 287.0 [M^+] (99), 288.0[M^++1] (22), 286 [M^+-1] (55), 158.0 [$C_{12}H_{14}$] (100); Anal. For $C_{15}H_{17}N_3OS$ (287.38): Calcd. C, 62.69; H, 5.96; N, 14.62; S, 11.16; Found: C, 62.73; H, 5.81; N, 14.47; S, 11.22.

*2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-3-methylthiazolidin-4-one (**12b**)*

Yield 81 %, mp. 161–162 °C; IR (KBr, cm^{-1}): 2928, 2854 (CH_2-tetrahydronaphthalene), 1722 (C=O), 1602, 1576 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.79–1.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.42 (3H, s, CH_3–C=N), 2.78–2.80 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.31 (3H, s, N–CH_3), 3.76 (2H, s, CH_2-thiazolidinone protons) 7.07 (1H, d, CH=, $J = 8.07$ Hz), 7.56 (1H, s, CH =), 7.62 (1H, d, CH=, $J = 8.07$ Hz); ^{13}C NMR ($CDCl_3$): δ 13.98, 22.15, 28.43, 28.59, 28.86, 31.55, 122.96, 126.56, 128.17, 134.18, 136.09, 138.69, 161.01, 162.35, 171.21; MS, *m/z* (%): 301.0 [M^+] (81), 301.9[M^++1] (16), 285.9 [M^+-CH_3] (66), 129.1 [$C_{10}H_9$] (100); Anal. For $C_{16}H_{19}N_3OS$ (301.41): Calcd. C, 63.76; H, 6.35; N, 13.94; S, 10.64; Found: C, 63.58; H, 6.46; N, 14.08; S, 10.71.

*2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-3-ethylthiazolidin-4-one (**12c**)*

Yield 84 %, mp. 132–133 °C; IR (KBr, cm^{-1}): 2935, 2848 (CH_2-tetrahydronaphthalene), 1718 (C=O), 1598, 1572 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.30 (3H, t, –$NCH_2\underline{CH_3}$, $J = 6.96$ Hz), 1.79–1.82 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.43 (3H, s, CH_3–C=N), 2.78–2.80 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.74 (2H, s, CH_2-thiazolidinone protons), 3.90 (2H, q, –$N\underline{CH_2}CH_3$, $J = 6.96$ Hz), 7.07 (1H, d, CH=, $J = 8.07$ Hz), 7.55 (1H, s, CH =), 7.59 (1H, d, CH=, $J = 8.07$ Hz); ^{13}C NMR ($CDCl_3$): δ 11.57, 14.06, 22.24, 28.50, 28.68, 31.71, 37.78, 122.98, 126.57, 128.24, 134.44, 136.14, 138.59,160.13, 162.10, 171.04; MS, *m/z* (%): 314.9 [M^+] (100), 316.0 [M^++1] (22), 157.8 [$C_{12}H_{14}$] (86); Anal. For $C_{17}H_{21}N_3OS$ (315.43): Calcd. C, 64.73; H, 6.71; N, 13.32; S, 10.17; Found: C, 64.81; H, 6.53; N, 13.23; S, 10.31.

*2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl) ethylidene)hydrazono)-3-phenylthiazolidin-4-one (**12d**)*

Yield 85 %, mp. 171–172 °C; IR (KBr, cm^{-1}): 2930, 2853 (CH_2-tetrahydronaphthalene), 1724 (C=O), 1601, 1573 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.79–1.81 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.22 (3H, s, CH_3–C=N), 2.78–2.79 (4H, m, 2(CH_2)-tetrahydronaphthalene protons),

3.94 (2H, s, CH_2-thiazolidinone protons), 7.06–7.60 (8H, m, CH-tetrahydronaphthalene protons and Ar–H); ^{13}C NMR ($CDCl_3$): δ 14.30, 22.23, 28.61, 31.76, 123.08, 126.76, 127.90, 128.27, 134.04, 136.19, 138.89, 160.82, 162.97, 170.82; MS, *m/z* (%): 362.9 [M^+] (49), 363.9 [M^++1] (12), 77.0 [C_6H_5] (100); Anal. For $C_{21}H_{21}N_3OS$ (363.48): Calcd. C, 69.39; H, 5.82; N, 11.56; S, 8.82; Found: C, 69.45; H, 5.93; N, 11.44; S, 8.74.

*2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-3-cyclohexylthiazolidin-4-one (**12e**)*

Yield 88 %, mp. 171–172 °C; IR (KBr, cm^{-1}): 2928, 2852 (CH_2-tetrahydronaphthalene), 1714 (C=O), 1599, 1565 (C=N); ^1H NMR ($CDCl_3$): δ 1.20–1.26, 1.33–1.40, 1.67–1.70 (10H, m, cyclohexyl protons), 1.81–1.85 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.45 (3H, s, CH_3–C=N), 2.78–2.80 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.71 (2H, s, CH_2-thiazolidinone protons), 4.40–4.45 (1H, m, N-CH cyclohexyl proton), 7.09 (1H, d, CH=, $J = 8.50$ Hz), 7.55(1H, s, CH =), 7.61(1H, d, CH=, $J = 8.50$ Hz); ^{13}C NMR ($CDCl_3$): δ 15.41, 23.27, 25.44, 26.58, 28.86, 29.49, 29.65, 32.61, 56.58, 123.98, 129.23, 131.07, 135.39, 137.12, 139.55, 161.76, 162.74, 172.34; MS, *m/z* (%): 369.0 [M^+] (23), 370.0 [M^++1] (8), 354.0 [M^+-CH_3] (58), 288.0 [M^+-C_6H_9] (78), 172.0 [$C_{12}H_{14}N$] (100); Anal. For $C_{21}H_{27}N_3OS$ (369.52): Calcd. C, 68.26; H, 7.36; N, 11.37; S, 8.68; Found: C, 68.34; H, 7.25; N, 11.42; S, 8.50.

General procedure for the synthesis of 2-(2-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-5-(4-methoxybenzylidene)-3-substituted thiazolidin-4-one (**13b–d**)

A mixture of the thiazolidinone derivatives **12b–d** (0.002 mol) and 4-methoxybenzaldehyde (0.25 mL, 0.002 mol) in 10 % alcoholic sodium hydroxide (15 mL) was stirred at room temperature overnight. The reaction mixture was filtered, washed several times with water, dried, and recrystallized from absolute ethanol to give the title compounds **13b–d**.

*2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-5-(4-methoxybenzylidene)-3-methylthiazolidin-4-one (**13b**)*

Yield 87 %, mp. 189–190 °C; IR (KBr, cm^{-1}): 2924, 2859 (CH_2-tetrahydronaphthalene), 1698 (α,β unsaturated ketone), 1613, 1561 (C=N); ^1H NMR ($CDCl_3$): δ 1.80–1.83 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.48 (3H, s, CH_3–C=N), 2.80–2.84 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.46 (3H, s, N–CH_3), 3.86 (3H, s, OCH_3), 6.97–7.68 (8H, m, CH-tetrahydronaphthalene protons, Ar–H and CH-olifinic); MS, *m/z* (%): 418.8 [M^+] (100), 419.8 [M^++1] (28), 404.0 [M^+-CH_3] (41); Anal. For $C_{24}H_{25}N_3O_2S$ (419.54): Calcd. C, 68.71; H, 6.01; N, 10.02; S, 7.64; Found: C, 68.66; H, 6.21; N, 10.18; S, 7.78.

*2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-5-(4-methoxybenzylidene)-3-ethylthiazolidin-4-one (**13c**)*

Yield 82 %, mp. 144–145 °C; IR (KBr, cm^{-1}): 2929, 2844 (CH_2-tetrahydronaphthalene), 1692 (α,β unsaturateded ketone), 1599, 1557 (C=N); ^1H NMR ($CDCl_3$): δ 1.36 (3H, t, –$NCH_2\underline{CH_3}$, $J = 6.90$ Hz), 1.80–1.82 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.48 (3H, s, CH_3–C=N), 2.80–2.84 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.85 (3H, s, OCH_3), 4.08 (2H, q, –$N\underline{CH_2}CH_3$, $J = 6.90$ Hz), 6.97–7.70 (8H, m, CH-tetrahydronaphthalene protons, Ar–H and CH-olifinic); MS, *m/z* (%): 432.7 [M^+] (98), 433.8 [M^++1] (33), 418.0 [M^+-CH_3] (43), 164.1 [$C_{10}H_{12}O_2$] (100); Anal. For $C_{25}H_{27}N_3O_2S$ (433.57): Calcd. C, 69.26; H, 6.28; N, 9.69; S, 7.40; Found: C, 69.31; H, 6.38; N, 9.57; S, 7.23.

*2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-5-(4-methoxybenzylidene)-3-phenylthiazolidin-4-one (**13d**)*

Yield 79 %, mp. 177–178 °C; IR (KBr, cm^{-1}): 2928, 2856 (CH_2-tetrahydronaphthalene), 1694 (α,β unsaturateded ketone), 1610, 1565 (C=N); ^1H NMR ($CDCl_3$): δ 1.79–1.82 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.43 (3H, s, CH_3–C=N), 2.81–2.83 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 3.82 (3H, s, –OCH_3), 6.95– 7.72 (13H, m, CH-tetrahydronaphthalene protons, Ar–H and CH-olifinic); MS, *m/z* (%): 481.0 [M^+] (21), 481.9 [M^++1] (19), 466.0 [M^+-CH_3] (41), 77 [C_6H_5] (100); Anal. For $C_{29}H_{27}N_3O_2S$ (481.61): Calcd. C, 72.32; H, 5.65; N, 8.72; S, 6.66; Found: C, 72.54; H, 5.47; N, 8.52; S, 6.42.

*2-(2-(1-(1,2,3,4-Tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-3-acetylthiazolidin-4-one (**14**)*

A mixture of thiazolidinone derivative **12a** (0.57 g, 0.002 mol) and acetic anhydride (10 mL) was refluxed for 1 h and then poured onto ice/cold water. The formed precipitate was filtered, washed several times with water, dried, and recrystallized from ethanol to give the title compounds **14**.

Yield 64 %, mp. 159–160 °C; IR (KBr, cm^{-1}): 2927, 2862 (CH_2-tetrahydronaphthalene), 1723 (C=O), 1647 (–$NCOCH_3$), 1611, 1569 (C=N); ^1H NMR ($CDCl_3$): δ 1.72–1.75 (4H, m, 2(CH_2)-tetrahydronaphthalene protons),

2.21 (3H, s, CH_3–C=N), 2.72–2.80 (4H, m, 2(CH_2)-tetrahydronaphthalene protons), 2.41 (3H, s, –$NCOCH_3$), 3.48 (2H, s, CH_2-thiazolidinone protons) 7.04 (1H, d, CH=, $J = 8.40$ Hz), 7.15 (1H, s, CH =), 7.25 (1H, d, CH=, $J = 8.40$ Hz); MS, *m/z* (%): 329.0 [M^+] (17), 330.0 [M^++1] (14), 286.2 [M^+-$COCH_3$] (20), 59.7 [C_2H_6NO] (100); Anal. For $C_{17}H_{19}N_3O_2S$ (329.42): Calcd. C, 61.98; H, 5.81; N, 12.76; S, 9.73; Found: C, 61.83; H, 5.94; N, 12.59; S, 9.90.

Biological screening

Anti-inflammatory assay

Male Wistar rats weighing (120–150 g) were used throughout the assay. Animals were housed under standardized conditions for light and temperature and received standard rat chow and tap water ad libitum. Animals were randomly assigned to different experimental groups, each of six rats and kept in separate cages. One group of six rats was kept as a control and another group received the standard drug indomethacin. All animal procedures were performed after approval from the Ethics Committee of the National Research Centre and in accordance with the recommendations for the proper care and use of laboratory animals (NIH publication No. 85-23, revised 1985).

Carrageenan lambda from Sigma Aldrich Chemical Co. (USA), indomethacin from Khahira Pharmaceutical, and Chemical Co. (Cairo, Egypt).

Paw edema was induced by subplantar injection of 100 µL of 1 % sterile carrageenan in saline into the right hind paw (1 % suspension of carrageenan in sterile saline was prepared, the suspension was placed in a refrigerator (4 °C) overnight to allow complete hydration of the carrageenan (Winter *et al.*, 1962).

Twenty six groups of rats, each of six animals, were used. One group received saline and served as control. Indomethacin (0.03 mmol/kg) was administered to a group of rats that served as a positive control. Tested groups received the compounds in a dose of (0.3 mmol/kg). All the tested compounds and indomethacin were orally administered 1 h before induction of inflammation.

The hind paw volume was measured immediately before carrageenan injection and at selected times (1, 2, 3, and 4 h) thereafter by water displacement method using 7410, Ugo Basile, plythesmometer, Comerio, Italy (Chattopadhyay *et al.*, 2002). The apparatus depends on measurement of the volume of an electrolyte solution displaced by the animal paw. The increased water level in the cell compartment increases the immersed portion of two parallel platinum electrodes, thus increasing conductivity between the two electrodes. The increased conductivity is converted to volume by a transducer (7153 Conductance Transducer).

The percent edema inhibition was calculated from the mean effect in the control and treated animals according to the following equation:

$$\% \text{ edema inhibition} = (vt - vc) / vc \times 100.$$

Where v*t* represents the mean increase in paw volume in rats treated with tested compounds and v*c* represents the mean increase in paw volume in the control group of rats (Armitage, 1971).

Analgesic assay

The apparatus consists of a hot plate on which the rat was placed for testing (7280 Ugo Basile Biological Research Apparatus Company, Comerio, Italy). It consists of a 20 cm diameter metal hot plate surface set at 50 °C, a plexiglass cage that fits the hot metal surface and a timer operated by a foot-switch (Laviola and Alleva, 1990).

For three consecutive days preceding the experiment, rats were adapted on the hot plate by placing them on a plate maintained at room temperature for 15 min each day. All groups were given vehicle and/or the different compounds and the last group received indomethacin (10 mg/Kg) 60 min prior to testing. Each animal was then placed gently onto a 50 °C hot plate to perform the test. Latency to exhibit nociceptive responses, such as licking paws or jumping off the hot plate was determined 30, 60, and 90 min after administration of test substances or the saline (Tzschentke *et al.*, 2007).

Ulcerogenic assay

Groups of male Wistar rats with a weight between 120 and 150 g were used. They were starved 18 h prior to drug administration. The test compounds were administered orally in 100 mg/kg as aqueous suspension. The animals were sacrificed after 5 h. Stomachs were removed and examined. A longitudinal incision along the greater curvature was made with fine scissor. The presence of a single or multiple lesions (erosion, ulcer or perforation) was evaluated (Manivannan and Chaturvedi, 2011). The number of ulcers and the occurrence of hyperemia were noted.

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