Brief Report

Synthesis, characterization, and anthelmintic activity of novel 6,7,8,9-tetrahydro-5*H*-5-phenyl-2-benzylidine-3-substituted hydrazino thiazolo (2,3-*b*) quinazoline derivatives and analogues

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ABSTRACT: Several novel 6,7,8,9-tetrahydro-5*H*-5-phenyl-2-benzylidine-3-substituted hydrazino thiazolo (2,3-*b*) quinazoline derivatives were synthesized and evaluated for their anthelmintic activity in a passive avoidance test. Chemical structures of all of the newly synthesized compounds were confirmed by infrared spectroscopy, ^{1}H-nuclear magnetic resonance, mass spectroscopy, and elemental analyses. Out of 15 compounds, only 6e and 6o had good anthelmintic activity. Experimental data led to the conclusion that the synthesized compounds have anthelmintic activity.

Keywords: Thiazolo quinazoline, thiazolo quinazoline phenyl hydrazone, aromatic aldehyde substitution, benzylidine thiazolo quinazoline phenyl hydrazone, anthelmintic activity

1. Introduction

Parasitic nematodes are one of the most frequent sources of many infections in plants, animals, and humans particularly in tropical countries. Only three classes of broad-spectrum anthelmintics, benzimidazoles, imidazothiazoles, and macrocyclic lactones, are widely in use at the present. The search for novel anthelmintic drugs occupies an important role in veterinary medicine (*1*). In the course of a search for new anthelmintics, quinazoline was selected because quinazoline and substituted quinazoline rings are important building blocks of medicinal chemistry and have led to the discovery of a number of derivatives endowed with anthelmintic (*2*), antimicrobial (*3-5*), anti-inflammatory (*6,7*), diuretic (*8*), anticonvulsant (*9*), antiallergic (*10*), antihypertensive (*11,12*), and antiparkinsonian activities (*13*). These findings led to the evaluation of a novel series of 6,7,8,9-tetrahydro-5*H*-5-phenyl-2-benzylidine-3-substituted hydrazino thiazolo (2,3-*b*) quinazoline compounds (**6a-o**) for their potential use as anthelmintics.

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2. Materials and Methods

2.1. *Instruments*

Melting points were determined in an open capillary tube and are uncorrected. Infrared spectroscopy (IR) spectra were recorded with KBr pellets (ABB Bomem FT-IR spectrometer MB 104; ABB Limited India, Bangaluru, India). ^{1}H-nuclear magnetic resonance (NMR) spectra (Bruker 400 NMR spectrometer; Bruker India, Mumbai, India) were recorded with tetramethylsilane as an internal reference. Mass spectral data were recorded with a Quadrupole mass spectrometer (Shimadzu GCMS QP5000; Shimadzu India, Chennai, India), and microanalyses were performed using a vario EL V300 elemental analyzer (Elementar Analysensysteme India, Chennai, India). The purity of the compounds was checked by thin-layer chromatography on pre-coated SiO_2 gel (HF_{254}, 200 mesh) aluminium plates (E. Merck, Mumbai, India) using ethyl acetate:benzene (1:3, v/v) and visualized in an ultraviolet chamber. IR, ^{1}H-NMR, mass spectral data, and elemental analyses were consistent with the assigned structures of all compounds.

2.2. *Chemistry*

The synthesis strategy leading to key intermediate and target compounds is illustrated in Figure 1. 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxy phenyl) thiazolo (2,3-*b*) quinazolin-3(2*H*)-one **3** prepared with equimolar quantities (0.039 mol) of cyclohexanone and benzaldehyde (0.039 mol) was collected in a beaker. A sodium hydroxide solution was added to make the solution alkaline, and the resulting solution was shaken

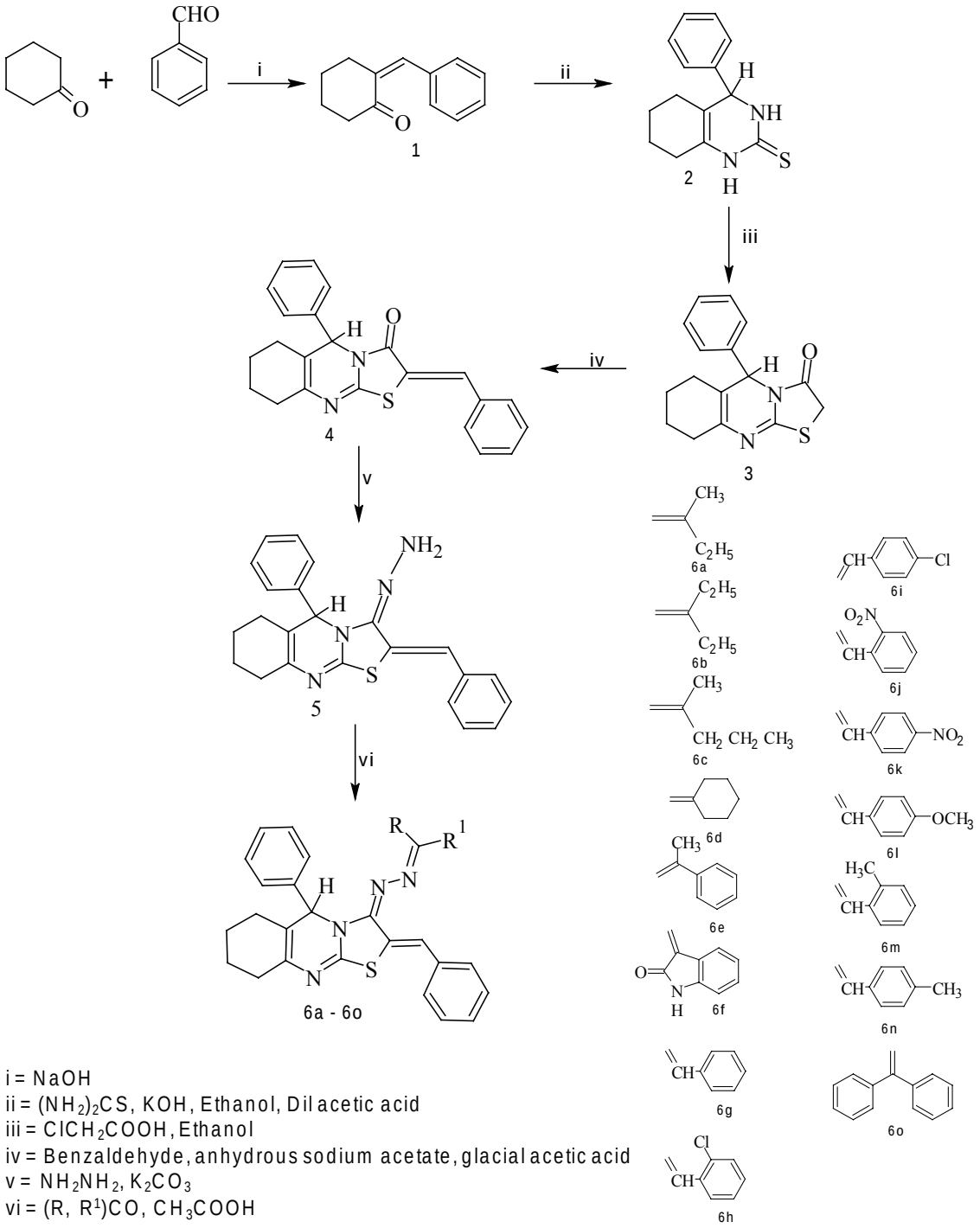

Figure 1. Synthetic scheme leading to key intermediate and target compounds.

and stored indoors. The solid thus obtained was filtered, washed with water, and recrystallized from absolute ethanol. A mixture of 2-benzylidine cyclohexanone ring **1** (0.039 mol), thiourea (0.03 mol), and potassium hydroxide (2.5 g) in ethanol (100 mL) was heated under reflux for 3 h. The reaction mixture was concentrated to half of its volume, diluted with water, and then acidified with dilute acetic acid and stored overnight. The solid thus obtained was filtered, washed with water, and recrystallized from ethanol to yield 3,4,5,6,7,8-hexahydro-4-phenyl quinazolin-2-thione **2**. Chloroacetic acid (0.096 mol) was melted in a water bath and thione (0.009 mol) was added portion-wise to maintain homogeneity. The homogeneous mixture was further heated in a water bath for 30 min and stored overnight. The solid thus obtained was washed with water until neutralized and crystallized from ethanol to yield 6,7,8,9-tetrahydro-5*H*-5-phenyl thiazolo (2,3-*b*) quinazolin-3(2*H*)-one **3** (*14*), a cream-colored solid, (yield: 83%) mp. 142-144°C. IR cm^{-1}: 3,079 (Ar-CH), 3,012 (cycloalkane C-H), 1,727 (C=O), 1,615 (C=C); ^{1}H-NMR ($CDCl_3$): δ 6.74-7.76 (m, 5H, Ar-H), 5.75 (s,

1H, H-5), 3.40 (s, 2H, CH_2, thiazole ring), 1.64-2.35 (m, 8H, 4 × CH_2); EI-MS (m/z): 284 (M^+); (Calcd for $C_{16}H_{16}N_2OS$; 284.38). Anal. Calcd for $C_{16}H_{16}N_2OS$; C, 67.58; H, 5.67; N, 9.85; Found: C, 67.60; H, 5.74; N, 9.90.

A mixture of **3** (0.002 mol)**,** benzaldehyde (0.002 mol), and anhydrous sodium acetate (0.002 mol) in glacial acetic acid (10 mL) was heated under reflux for 4 h. The reaction mixture was stored overnight and the solid thus separated was filtered, washed with water, and recrystallized from ethanol to furnish 6,7,8,9-tetrahydro-5*H*-5-phenyl-2-benzylidine thiazolo (2,3-*b*) quinazolin-3(2H)-one **4**, a pale yellow solid, (yield: 75%), mp. 146-148°C, IR cm^{-1}: 3,100 (cycloalkane C-H), 3,059 (Ar-CH), 1,742 (C=O), 1,613 (C=C); ^{1}H-NMR ($CDCl_3$): δ 6.82-7.46 (m, 10H, Ar-H), 5.86 (s, 1H, H-5), 6.57 (s, 1H, =CH), 1.82-2.24 (m, 8H, 4 × CH_2); EI-MS (m/z): 372 (M^+); (Calcd for $C_{23}H_{20}N_2OS$; 372.48). Anal. Calcd for $C_{23}H_{20}N_2OS$; C, 74.16; H, 5.41; N, 7.52; Found: C, 74.26; H, 5.31; N, 7.44.

Equimolar quantities of compound **4** (0.004 mol) and hydrazine hydrate (99%) (0.004 mol) were dissolved in 10 mL of warm ethanol and refluxed for 30 min. After standing for approximately 24 h at room temperature, the two compounds were separated by filtration, vacuum-dried, and recrystallized from warm ethanol to yield 6,7,8,9-tetrahydro-5*H*-5-phenyl-2-benzylidine-3-hydrazino thiazolo (2,3-*b*) quinazoline **5**, a dark brown solid, (yield: 69%), mp. 169-171°C, IR cm^{-1}: 3,144 (Ar-CH), 3,076 (cycloalkane C-H), 1,618 (C=C), 3,378 (N-H), 1,341 (N-H), 1,654 (C=N); ^{1}H-NMR ($CDCl_3$): δ 6.74-7.86 (m, 10H, Ar-H), 7.26 (s, 2H, NH_2), 5.56 (s, 1H, H-5), 6.38 (s, 1H, =CH), 1.90-2.42 (m, 8H, 4 × CH_2); EI-MS (m/z): 386 (M^+); (Calcd for $C_{23}H_{22}N_4S$; 386.51). Anal. Calcd for $C_{23}H_{22}N_4S$: C, 71.47; H, 5.74; N, 14.50; Found: C, 71.42; H, 5.68; N, 14.66. A mixture of **5** (0.004 mol) and appropriate ketones/aldehydes (0.004 mol) in glacial acetic acid was refluxed for 38 h. The reaction mixture was poured into ice water. The solid obtained was recrystallized from ethanol to yield 6,7,8,9-tetrahydro-5*H*-5-phenyl-2-benzylidine-3-substituted hydrazino thiazolo (2,3-*b*) quinazoline compounds **6a-o**. Chemical data for derivatives **6a-o** are presented in the Appendix.

2.3. *Animals*

Indian adult earthworms (*Pheretima posthuma*) were used to study anthelmintic activity. The earthworms were collected from moist soil and washed to remove all fecal material. Earthworms 3-5 cm in length and 0.1-0.2 cm in width were used for all experimental protocols. Earthworms resemble intestinal roundworm parasites of human beings both anatomically and physiologically and hence can be used to study anthelmintic activity (*15*).

2.4. *Anthelmintic activity*

The newly synthesized compounds were tested for anthelmintic activity (*16*). *P. posthuma* (earthworms obtained from Lalbagh Botanical Garden, Bangalore, India) of nearly equal size (6 ± 1 cm) were selected randomly for the present study (*17-19*). The worms were acclimatized to laboratory conditions before experimentation. The earthworms were divided into four groups of six earthworms each. Albendazole, diluted with normal saline solution to obtain 0.1, 0.2, 0.5, and 1% (w/v), served as a reference and was poured into Petri dishes. The synthesized compounds were dissolved in a minimal quantity of dimethyl sulfoxide and diluted to prepare four concentrations, *i.e*. 0.1, 0.2, 0.5, and 1% (w/v), for each compound. Normal saline served as the control. Six earthworms of nearly equal size (6 ± 1 cm) were selected for use with each concentration and were placed in Petri dishes at room temperature (*20*). The time taken for complete paralysis and death were recorded. The mean time until paralysis and mean time until death were calculated for each sample (each reading was done in triplicate). The time taken for worms to become motionless was denoted as time until paralysis. To ascertain the time until death, each worm was frequently subjected to external stimuli to stimulate and induce movement in the earthworm if alive (*21*).

3. Results and Discussion

3.1. *Chemistry*

The series of heterocycles **6a-o** were synthesized by the reaction of **3** with appropriate hydrazine hydrate and ketones/aldehydes in the presence of anhydrous sodium acetate and glacial acetic acid, as indicated in Figure 1. Results of IR, ^{1}H-NMR, mass spectroscopy, and elemental analyses of the new compounds were in accordance with the assigned structures. The IR spectra of compounds **3** and **4** had stretching bands of the keto group at 1,715-1,740 cm^{-1}. In **5**, stretching and bending NH bands of thiazolo quinazoline moiety appeared at 3,300-3,400 cm^{-1} and 1,300-1,350 cm^{-1}, respectively. The absence of keto group absorption at 1,715-1,740 cm^{-1} and appearance of a strong intensity band in the IR spectra of compound **5** in the range of 1,610-1,655 cm^{-1}, attributable to C=N, provides strong evidence for condensation and also confirms the formation of azomethine **5**. The proton NMR spectra of thiazolo quinazoline and their corresponding derivatives have been recorded in $CDCl_3$. For **5**, the NH signal of 6,7,8,9-tetrahydro-5*H*-5-phenyl-2-benzylidine-3-hydrazino thiazolo (2,3-*b*) quinazoline moiety appeared at 7.26 (s) ppm. The position and presence of an NH signal in the ^{1}H-NMR spectra of final compounds confirmed the secondary NH proton in the thiazolo

quinazoline moiety. This clearly indicates that the thiazole-3-one moiety is involved in 6,7,8,9-tetrahydro-5*H*-5-phenyl-2-benzylidine-3-hydrazino thiazolo (2,3-*b*) quinazoline formation. All of these findings clearly demonstrate that the 3rd position of the keto group in the thiazole ring is converted into a secondary amino group, as indicated in Figure 1, and confirms the proposed structure of **5**.

3.2. *Anthelmintic activity*

Anthelmintic screening of 6,7,8,9-tetrahydro-5*H*-5-phenyl-2-benzylidine-3-substituted hydrazino thiazolo (2,3-*b*) quinazoline compounds **6a-o** indicated that they had better activity than albendazole, a standard anthelminthic. Of the compounds, 6,7,8,9-tetrahydro-5*H*-5-phenyl-2-benzylidine-3-(*N'*-3-pentylidene-hydrazino) thiazolo (2,3-*b*) quinazoline **6b** had maximum anthelmintic activity that was close to that of albendazole, a standard anthelminthic. Compound **6a** with the *N'*-sec-butylidene substituent had good activity; increased lipophilicity (1-ethylpropylidene group, compound **6b;** Figure 2) resulted in increased activity. Replacement of the 1-ethyl-propylidene group with its isomer 1-methyl-butylidene group (compound **6c**) retained this activity. Replacement of the alkyl chain with a cycloalkyl group and aryl alkyl groups (compounds **6d-6i**, respectively) resulted in decreased anthelmintic activity and replacement with an aryl group (compounds **6j-6o**) resulted in poor activity. The anthelmintic activity of test compounds decreased in the order of **6b** > **6c** > **6a** > **6d** > **6e** > **6f** > **6g** > **6h** > **6i**, as summarized in Table 1.

In conclusion, this paper describes the synthesis of novel substituted 6,7,8,9-tetrahydro-5*H*-5-phenyl-2-benzylidine-3-substituted hydrazino thiazolo (2,3-*b*) quinazolines **6a-o** with strong anthelmintic activity compared to albendazole, a standard anthelminthic. The results demonstrate that substituents of the pentylidine and butylidine side chains had exceptional anthelmintic activity. Groups such as cycloalkyl, aryl alkyl, and aryl side chains in the 3-hydarzino position of the thiazolo quinazoline ring resulted in decreased or poor anthelmintic activity. Therefore, a similar range of lipophilicity could prove important to anthelmintic activity.

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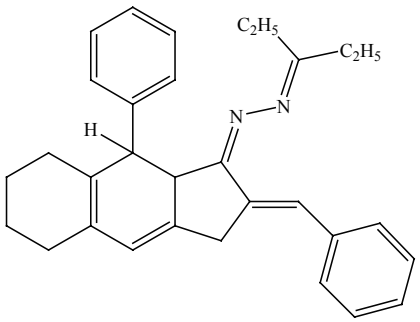

Figure 2. Structure of 6,7,8,9-tetrahydro-5*H*-5-phenyl-2-benzylidine-3-(*N'*-3-pentylidene-hydrazino) thiazolo (2,3-*b*) quinazoline.

Table1. Anthelmintic activity of 6,7,8,9-tetrahydro-5*H*-5-phenyl-2-benzylidine-3-substituted hydrazino thiazolo (2,3-*b*) quinazoline

Compound	Time until paralysis (min)				Time until death (min)			
	Concentration (%)				Concentration (%)			
	0.1	0.2	0.5	1	0.1	0.2	0.5	1
6a	2.12 ± 0.11	2.53 ± 0.13	2.13 ± 0.02	1.22 ± 0.12	4.42 ± 0.01	3.12 ± 0.24	3.12 ± 0.01	1.43 ± 0. 21
6b	2.12 ± 0.11	2.02 ± 0.12	1.51 ± 0.02	0.63 ± 0.11	3.11 ± 0.04	2.53 ± 0.01	1.41 ± 0.13	1.12 ± 0.01
6c	2.12 ± 0.12	2.13 ± 0.15	1.51 ± 0.05	1.01 ± 0.10	3.22 ± 0.05	2.61 ± 0.19	1.81 ± 0.24	1.13 ± 0.15
6d	4.22 ± 0.12	4.15 ± 0.17	3.80 ± 0.17	2.31 ± 0.10	5.15 ± 0.12	4.10 ± 0.32	4.16 ± 0.31	2.11 ± 0.13
6e	5.31 ± 0.02	4.21 ± 0.13	3.22 ± 0.04	3.52 ± 0.02	6.51 ± 0.13	6.11 ± 0.02	4.71 ± 0.13	3.22 ± 0.12
6f	5.12 ± 0.01	4.13 ± 0.12	3.11 ± 0.15	2.32 ± 0.14	5.25 ± 0.13	4.13 ± 0.32	4.12 ± 0.31	2.13 ± 0.13
6g	5.33 ± 0.01	4.22 ± 0.13	3.22 ± 0.07	2.11 ± 0.03	6.11 ± 0.43	6.42 ± 0.05	4.43 ± 0.14	3.22 ± 0.14
6h	5.15 ± 0.52	4.55 ± 0.17	3.51 ± 0.16	2.52 ± 0.50	5.55 ± 0.52	4.15 ± 0.36	4.53 ± 0.35	2.15 ± 0.16
6i	5.62 ± 0.07	4.23 ± 0.14	3.61 ± 0.14	2.16 ± 0.16	6.61 ± 0.13	6.16 ± 0.62	4.63 ± 0.13	3.27 ± 0.16
6j	6.37 ± 0.02	5.23 ± 0.12	4.21 ± 0.03	4.51 ± 0.40	7.94 ± 0.18	8.13 ± 0.01	6.13 ± 0.14	5.29 ± 0.13
6k	6.12 ± 0.12	5.15 ± 0.17	4.81 ± 0.18	4.32 ± 0.10	7.15 ± 0.12	7.14 ± 0.33	6.13 ± 0.32	5.12 ± 0.14
6l	6.32 ± 0.02	5.22 ± 0.14	4.21 ± 0.04	4.51 ± 0.01	7.91 ± 0.13	7.12 ± 0.01	6.73 ± 0.12	5.29 ± 0.12
6m	6.22 ± 0.10	5.12 ± 0.11	4.42 ± 0.15	4.22 ± 0.24	7.75 ± 0.23	7.44 ± 0.13	6.18 ± 0.13	5.22 ± 0.14
6n	6.20 ± 0.02	5.21 ± 0.11	4.22 ± 0.25	4.72 ± 0.42	7.14 ± 0.27	8.22 ± 0.22	6.23 ± 0.13	5.14 ± 0.13
6o	6.11 ± 0.15	5.17 ± 0.13	4.12 ± 0.15	4.22 ± 0.14	7.26 ± 0.18	7.27 ± 0.22	6.11 ± 0.31	5.23 ± 0.15
Albendazole	2.13 ± 0.17	2.03 ± 0.19	1.52 ± 0.03	0.83 ± 0.14	3.11 ± 0.05	2.52 ± 0.09	1.81 ± 0.14	1.13 ± 0.05

Values are expressed as mean ± S.E.M.

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Appendix

6a. 6,7,8,9-Tetrahydro-5H-5-phenyl-2-benzylidine-3-(N'-2-butylidene-hydrazino) thiazolo (2,3-b) quinazoline

Yellow solid; yield: 78%; mp. 176-178°C; IR cm^{-1}: 3,078 (Ar-CH), 2,912 (cycloalkane C-H), 1,534 (C=C), 2,868 (C-H in CH_3), 1,656 (C=N); ^{1}H-NMR ($CDCl_3$): δ 6.82-7.46 (m, 10H, Ar-H), 6.18 (s, 1H, =CH), 5.18 (s, 1H, H-5), 2.64 (s, 3H, CH_3), 1.80-2.32 (m, 8H, 4 × CH_2), 1.4 (q, 2H, CH_2CH_3),1.82 (t, J = 7.0 Hz, 3H, CH_2CH_3); EI-MS (m/z): 440 (M^+); (Calcd for $C_{27}H_{28}N_4S$; 440.60). Ana. Calcd for $C_{27}H_{28}N_4S$: C, 73.60; H, 6.41; N, 12.72; Found: C, 73.56; H, 6.49; N, 12.78.

6b. 6,7,8,9-Tetrahydro-5H-5-phenyl-2-benzylidine-3-(N'-3-pentylidene-hydrazino) thiazolo (2,3-b) quinazoline

Pale yellow crystals; yield: 72%; mp. 164-166°C; IR cm^{-1}: 3,065 (Ar-CH), 2,987 (cycloalkane, C-H), 1,541 (C=C), 2,833 (C-H in CH_3), 1,649 (C=N); ^{1}H-NMR ($CDCl_3$): δ 6.44-7.88 (m, 10H, Ar-H), 6.20 (s, 1H, =CH), 5.08 (s, 1H, H-5), 1.76-2.46 (m, 8H, 4 × CH_2), 1.92 (t, J = 7.0 Hz, 6H, CH_2CH_3), 1.52 (q, 4H, CH_2CH_3); EI-MS (m/z): 454 (M^+); (Calcd for $C_{28}H_{30}N_4S$; 454.63). Ana. Calcd for $C_{28}H_{30}N_4S$: C, 73.97; H, 6.65; N, 12.32; Found: C, 73.85; H, 6.68; N, 12.34.

6c. 6,7,8,9-Tetrahydro-5H-5-phenyl-2-benzylidine-3-(N'-2-pentylidene-hydrazino) thiazolo (2,3-b) quinazoline

Cream-colored crystals; yield: 68%; mp. 178-180°C; IR cm^{-1}: 3,068 (Ar-CH), 2,952 (cycloalkane C-H), 2,870 (C-H in CH_3), 1,544 (C=C), 1,660 (C=N); ^{1}H-NMR ($CDCl_3$): δ 6.72-7.36 (m, 10H, Ar-H), 6.24 (s, 1H, =CH), 5.22 (s, 1H, H-5), 2.84 (t, 3H, CH_2 CH_2CH_3), 2.68 (s,

3H, CH_3), 1.82-2.36 (m, 8H, 4 × CH_2), 1.33 (sext, 2H, CH_2 CH_2CH_3), 0.91 (t, 2H, CH_2 CH_2CH_3); EI-MS (m/z): 454 (M^+); (Calcd for $C_{28}H_{30}N_4S$; 454.63). Ana. Calcd for $C_{28}H_{30}N_4S$: C, 73.97; H, 6.65; N, 12.32; Found: C, 73.99; H, 6.63; N, 12.28.

6d. 6,7,8,9-Tetrahydro-5H-5-phenyl-2-benzylidine-3-(N'-cyclohexylidene-hydrazino) thiazolo (2,3-b) quinazoline

Yellow crystals; yield: 82%; mp. 182-184°C; IR cm^{-1}: 3,028 (Ar-CH), 2,924 (cycloalkane C-H), 1,666 (C=N), 1,544 (C=C); ^{1}H-NMR ($CDCl_3$): δ 6.92-7.86 (m, 10H, Ar-H), 6.24 (s, 1H, =CH), 5.26 (s, 1H, H-5), 1.60-2.04 (m, 18H, 9 × CH_2); EI-MS (m/z): 466 (M^+); (Calcd for $C_{29}H_{30}N_4S$; 466.64). Ana. Calcd for $C_{29}H_{30}N_4S$: C, 74.64; H, 6.48; N, 12.01; Found: C, 74.68; H, 6.52; N, 12.11.

6e. 6,7,8,9-Tetrahydro-5H-5- phenyl-2-benzylidine -3-(N'-1-phenylethylidene-hydrazino) thiazolo (2,3-b) quinazoline

Yellow solid; yield: 84%; mp. 146-148°C; IR cm^{-1}: 3,098 (Ar-CH), 2,928 (cycloalkane C-H), 2,918 (C-H in CH_3), 1,606 (C=N), 1,542 (C=C); ^{1}H-NMR ($CDCl_3$): δ 6.62-7.16 (m, 15H, Ar-H), 6.06 (s, 1H, =CH), 2.74 (s, 3H, CH_3), 5.06 (s, 1H, H-5), 1.74-2.38 (m, 8H, 4 × CH_2); EI-MS (m/z): 488 (M^+); (Calcd for $C_{31}H_{28}N_4S$; 488.65). Ana. Calcd for $C_{31}H_{28}N_4S$: C, 76.20; H, 5.78; N, 11.47; Found: C, 76.30; H, 5.82; N, 11.49.

6f. 6,7,8,9-Tetrahydro-5H-5-phenyl-2-benzylidine-3-(N'-1-oxo-indolin-2-one-3-ylidene-hydrazino) thiazolo (2,3-b) quinazoline

Pale yellow solid; yield: 70%; mp. 156-158°C; IR cm^{-1}: 3,086 (Ar-CH), 2,934 (cycloalkane C-H), 1,726 (C=O), 1,616 (C=N), 1,538 (C=C), 1,338 (C-N); ^{1}H-NMR ($CDCl_3$): δ 8.06 (s, 1H, NH), 6.60-7.18 (m, 14H, Ar-H), 6.12 (s, 1H, =CH), 5.16 (s, 1H, H-5), 1.78-2.32 (m, 8H, 4 × CH_2); EI-MS (m/z): 515 (M^+); (Calcd for $C_{31}H_{25}N_5OS$; 515.63). Ana. Calcd for $C_{31}H_{25}N_5OS$: C, 72.21; H, 4.89; N, 13.58; Found: C, 72.18; H, 4.92; N, 13.48.

6g. 6,7,8,9-Tetrahydro-5H-5-phenyl-2-benzylidine-3-(N'-benzylidene-hydrazino) thiazolo (2,3-b) quinazoline

Cream-colored crystals; yield: 72%; mp. 159-160°C; IR cm^{-1}: 3,048 (Ar-CH), 2,934 (cycloalkane C-H), 1,608 (C=N), 1,568 (C=C); ^{1}H-NMR ($CDCl_3$): δ 8.1 (s, 1H, CH), 6.90-7.68 (m, 15H, Ar-H), 6.34 (s, 1H, =CH), 5.22 (s, 1H, H-5), 1.61-2.10 (m, 8H, 4 × CH_2); EI-MS (m/z): 474 (M^+); (Calcd for $C_{30}H_{26}N_4S$; 474.62). Ana. Calcd for $C_{30}H_{26}N_4S$: C, 75.92; H, 5.52; N, 11.80; Found: C, 75.96; H, 5.58; N, 11.90.

6h. 6,7,8,9-Tetrahydro-5H-5-phenyl-2-benzylidine-3-(N'-(2-chloro-benzylidene-hydrazino) thiazolo (2,3-b) quinazoline

Brown crystals; yield: 77%; mp. 162-164°C; IR cm^{-1}: 3,056 (Ar-CH), 2,926 (cycloalkane C-H), 1,598 (C=N), 1,562 (C=C), 816 (C-Cl); ^{1}H-NMR ($CDCl_3$): δ 8.12 (s, 1H, CH), 6.80-7.58 (m, 14H, Ar-H), 6.38 (s, 1H, =CH), 5.32 (s, 1H, H-5), 1.66-2.20 (m, 8H, 4 × CH_2); EI-MS (m/z): 511 (M^{+2}); (Calcd for $C_{30}H_{25}ClN_4S$; 509.60). Ana. Calcd for $C_{30}H_{25}ClN_4S$: C, 70.78; H, 4.95; N, 11.01; Found: C, 70.80; H, 4.99; N, 11.11.

6i. 6,7,8,9-Tetrahydro-5H-5-phenyl-2-benzylidine-3-(N'-(4-chloro-benzylidene-hydrazino) thiazolo (2,3-b) quinazoline

Yellow solid; yield: 79%; mp. 144-146°C; IR cm^{-1}: 3,058 (Ar-CH), 2,928 (cycloalkane C-H), 1,590 (C=N), 1,566 (C=C), 826 (C-Cl); ^{1}H-NMR ($CDCl_3$): δ 8.22 (s, 1H, CH), 6.76-7.52 (m, 14H, Ar-H), 6.36 (s, 1H, =CH), 5.34 (s, 1H, H-5), 1.68-2.28 (m, 8H, 4 × CH_2); EI-MS (m/z): 511 (M^{+2}); (Calcd for $C_{30}H_{25}ClN_4S$; 509.60). Ana. Calcd for $C_{30}H_{25}ClN_4S$: C, 70.78; H, 4.95; N, 11.01; Found: C, 70.82; H, 4.98; N, 11.08.

6j. 6,7,8,9-Tetrahydro-5H-5-phenyl-2-benzylidine-3-(N'-(2-nitro-benzylidene-hydrazino) thiazolo (2,3-b) quinazoline

Cream-colored crystals; yield: 77%; mp. 166-168°C; IR cm^{-1}: 3,048 (Ar-CH), 2,930 (cycloalkane C-H), 1,584 (C=N), 1542 (C=C); ^{1}H-NMR ($CDCl_3$): δ 8.44 (s, 1H, CH), 6.72-7.58 (m, 14H, Ar-H), 6.22 (s, 1H, =CH), 5.24 (s, 1H, H-5), 1.52-2.18 (m, 8H, 4 × CH_2); EI-MS (m/z): 519 (M^+); (Calcd for $C_{30}H_{25}N_5O_2S$; 519.62). Ana. Calcd for $C_{30}H_{25}N_5O_2S$: C, 69.34; H, 4.85; N, 13.48; Found: C, 69.38; H, 4.89; N, 13.54.

6k. 6,7,8,9-Tetrahydro-5H-5-phenyl-2-benzylidine-3-(N'-(4-nitro-benzylidene-hydrazino) thiazolo (2,3-b) quinazoline

Pale yellow crystals; yield: 71%; mp. 142-144°C; IR cm^{-1}: 3,066 (Ar-CH), 2,922 (cycloalkane C-H), 1,562 (C=N), 1,538 (C=C); ^{1}H-NMR ($CDCl_3$): δ 8.32 (s, 1H, CH), 6.68-7.52 (m, 14H, Ar-H), 6.12 (s, 1H, =CH), 5.32 (s, 1H, H-5), 1.40-2.20 (m, 8H, 4 × CH_2); EI-MS (m/z): 519 (M^+); (Calcd for $C_{30}H_{25}N_5O_2S$; 519.62). Ana. Calcd for $C_{30}H_{25}N_5O_2S$: C, 69.34; H, 4.85; N, 13.48; Found: C, 69.40; H, 4.82; N, 13.46.

6l. 6,7,8,9-Tetrahydro-5H-5-phenyl-2-benzylidine-3-(N'-(4-methoxy-benzylidene-hydrazino) thiazolo (2,3-b) quinazoline

Brown solid; yield: 75%; mp. 150-152°C; IR cm^{-1}: 3,050 (Ar-CH), 2,968 (cycloalkane C-H), 1,560 (C=N), 1,550

(C=C); ^{1}H-NMR ($CDCl_3$): δ 8.44 (s, 1H, CH), 6.75-7.56 (m, 14H, Ar-H), 6.35 (s, 1H, =CH), 5.22 (s, 1H, H-5), 3.73 (s, 3H, OCH_3), 1.80-2.60 (m, 8H, 4 × CH_2); EI-MS (m/z): 504 (M^+); (Calcd for $C_{31}H_{28}N_4OS$; 504.65). Ana. Calcd for $C_{31}H_{28}N_4OS$: C, 73.78; H, 5.59; N, 11.10; Found: C, 73.82; H, 5.63; N, 11.14.

6m. 6,7,8,9-Tetrahydro-5H-5-phenyl-2-benzylidine-3-(N'-(2-methyl-benzylidene-hydrazino) thiazolo (2,3-b) quinazoline

Cream-colored crystals; yield: 80%; mp. 136-138°C; IR cm^{-1}: 3,054 (Ar-CH), 2,972 (cycloalkane C-H), 1,568 (C=N), 1,548 (C=C); ^{1}H-NMR ($CDCl_3$): δ 8.64 (s, 1H, CH), 6.70-7.52 (m, 14H, Ar-H), 6.36 (s, 1H, =CH), 5.33 (s, 1H, H-5), 3.73 (s, 3H, CH_3), 1.88-2.66 (m, 8H, 4 × CH_2); EI-MS (m/z): 488 (M^+); (Calcd for $C_{31}H_{28}N_4S$; 488.65). Ana. Calcd for $C_{31}H_{28}N_4S$: C, 76.20; H, 5.78; N, 11.47; Found: C, 76.24; H, 5.82; N, 11.49.

6n. 6,7,8,9-Tetrahydro-5H-5-phenyl-2-benzylidine-3-(N'-(4-methyl-benzylidene-hydrazino) thiazolo (2,3-b) quinazoline

Cream-colored crystals; yield: 82%; mp. 148-150°C; IR cm^{-1}: 3,060 (Ar-CH), 2,976 (cycloalkane C-H), 1,574 (C=N), 1,554 (C=C); ^{1}H-NMR ($CDCl_3$): δ 8.60 (s, 1H, CH), 6.77-7.57 (m, 14H, Ar-H), 6.40 (s, 1H, =CH), 5.38 (s, 1H, H-5), 3.75 (s, 3H, CH_3), 1.90-2.70 (m, 8H, 4 × CH_2); EI-MS (m/z): 488 (M^+); (Calcd for $C_{31}H_{28}N_4S$; 488.65). Ana. Calcd for $C_{31}H_{28}N_4S$: C, 76.20; H, 5.78; N, 11.47; Found: C, 76.26; H, 5.88; N, 11.52.

6o. 6,7,8,9-Tetrahydro-5H-5-phenyl-2-benzylidine-3-(N'-(2-phenyl-benzylidene-hydrazino) thiazolo (2,3-b) quinazoline

Pale brown solid; yield: 78%; mp. 152-154°C; IR cm^{-1}: 3,088 (Ar-CH), 2,988 (cycloalkane C-H), 1,584 (C=N), 1,572 (C=C); ^{1}H-NMR ($CDCl_3$): δ 6.90-7.70 (m, 20H, Ar-H), 6.32 (s, 1H, =CH), 5.36 (s, 1H, H-5), 1.84-2.52 (m, 8H, 4 × CH_2); EI-MS (m/z): 550 (M^+); (Calcd for $C_{36}H_{30}N_4S$; 550.72). Ana. Calcd for $C_{36}H_{30}N_4S$: C, 78.51; H, 5.49; N, 10.17; Found: C, 78.55; H, 5.54; N, 10.22.