

SYNTHESIS OF ACETYLCHOLINESTERASE INHIBITORS ON THE BASIS OF 9-ISOTHIOCYANATO-1,2,3,4-TETRAHYDROACRIDINE: 2-[(1,2,3,4-TETRAHYDROACRIDIN-9-YL)IMINO]-3-SUBSTITUTED 1,3-THIAZOLIDIN-4-ONES

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(Dedicated to Dr. Bernhard Withop on the occasion of his 80th birthday)

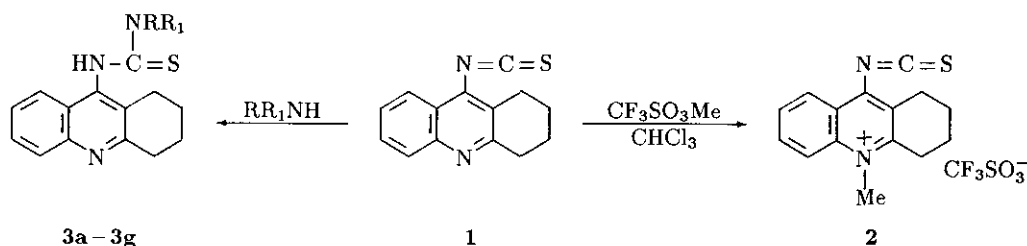
Abstract – The synthesis of 2-[(1,2,3,4-tetrahydroacridin-9-yl)imino]-3-substituted 1,3-thiazolidin-4-ones (**5a–e**) *via* cyclization of *N*-(1,2,3,4-tetrahydroacridin-9-yl)-*S*-methoxycarbonylmethyl-*N'*-substituted isothioureia hydrobromides was elaborated. As a synthon, 9-isothiocyanato-1,2,3,4-tetrahydroacridine, an analogue of tacrine, was used. The reaction represents a simple way for the preparation of new cholinergic compounds.

In the recent time an increasing attention has been paid to the investigation of Alzheimer disease which is characteristic by a progressive deterioration of memory and intellectual functions.¹ One of the most important reasons of neurochemical abnormalities ascribed to the Alzheimer disease is a decrease in the activity levels of choline acetyltransferase. Three groups of cholinesterase inhibitors as possible drugs have been tested: compounds of carbamoyl type (physostigmine),² derivatives of 9-amino-1,2,3,4-tetrahydroacridine (tacrin)³ and 1-benzyl-4-[(5,6-dimethoxy-1-oxoindan-2-yl)methyl]piperidine hydrochloride (donepezil).⁴

One of the most employed medicaments for the treatment of Alzheimer disease is tacrin hydrochloride which acts as reversible inhibitor of acetylcholinesterase.⁵ From the recent studies, Pirrung and coworkers have synthesized in one-step reaction of cyclohexanones with cyanoanilines (called the indexed combinatorial library method) 72 derivatives of tetrahydroacridine and tested them

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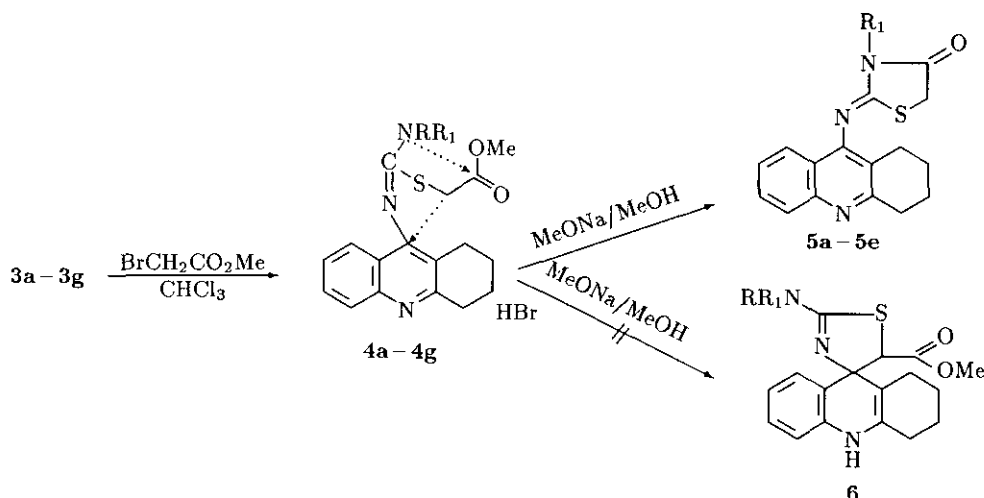
against acetylcholinesterase.⁶ In our study we used as a synthon for the synthesis of new tacrine analogues 9-isothiocyanato-1,2,3,4-tetrahydroacridine (**1**) which was obtained by the reaction of 9-chloro-1,2,3,4-tetrahydroacridine⁷ with silver thiocyanate.⁸ In the reaction with methyl trifluoromethanesulfonate isothiocyanate, **1** was transformed into a triflate salt of 9-isothiocyanato-*N*-methyl-1,2,3,4-tetrahydroacridinium (**2**) in good yield, whereas with primary and secondary amines *N*-(1,2,3,4-tetrahydroacridin-9-yl)-*N'*-substituted thioureas (**3a-g**) were formed (Scheme 1). The compound (**2**) contains all three active centers necessary for blocking of the lipophilic, anionoidic and ester region of acetylcholinesterase, as it is described for the cholinergic inhibitor model of the miotine type.⁹ The concepts mentioned concerning the substrate-enzyme interactions led us to the synthesis of 2-[(1,2,3,4-tetrahydroacridin-9-yl)imino]-3-alkyl(aryl) substituted 1,3-thiazolidin-4-ones (**5a-e**) (Scheme 2).



RR₁: **3f** morpholino, **3g** piperidino

(R=H) R₁: **3a** Bn, **3b** *n*-Bu, **3c** *i*-Pr, **3d** 2-furylmethyl, **3e** cyclohexyl

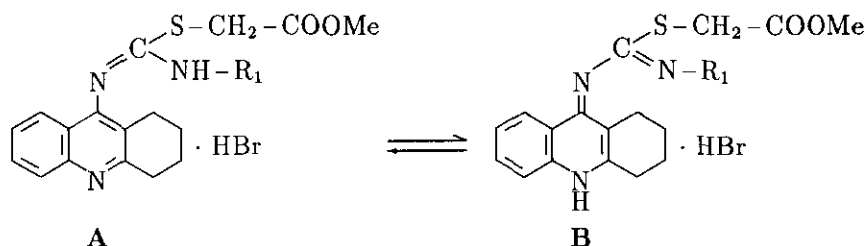
Scheme 1



Scheme 2

Derivatives (**3a-g**) afforded with methyl bromoacetate intermediate hydrobromides of *S*-methoxycarbonylmethylisothioureas (**4a-g**). Compounds (**4a-e**) which contain a primary amino substituent

(NHR₁) cyclized in the presence of sodium methoxide to final 2-[(1,2,3,4-tetrahydroacridin-9-yl)imino]-3-alkyl(aryl) substituted 1,3-thiazolidin-4-ones (**5a-e**). Isothioureas derived from secondary amines (**4f, g**) cannot undergo the same reaction because of the absent hydrogen on the nitrogen atom. According to ¹H NMR spectra isothioureas (**4a, b, d**) exist even at room temperature as two tautomers. The biggest differences observed for CH₂S, CH₂N and acridine H-5 protons indicate that besides the form **A**, the form **B** seems to be the most probable.



Isothioureas (**4c, 4e-g**) prepared from more basic amines were obtained only in the form **A**. From the MS of isothiourea (**4a**) recorded with electron and chemical ionization follows, that the compound is unobtainable and during the measurement a cyclization to **5a** takes place (the MS spectrum of **4a** is identical with the MS spectrum of **5a**).

Another possibility, the cyclization of **4f, g** to spiro[1,2,3,4,9,10-hexahydroacridine-9(10*H*),4'-thiazolines] (**6**), similar to our preparation of spiro[dihydroacridine-9(10*H*),4'-thiazolines] from corresponding *N*-(acridin-9-yl)-*N'*-substituted thioureas,¹⁰ was not successful under conditions used here and no reaction was observed. This fact may be ascribed to a diminished stabilization of the middle dihydropyridine ring by only one benzene ring in **6** in contrast to two stabilizing benzene rings at spiro[dihydroacridine-9(10*H*),4'-thiazolines].

Physicochemical and spectral characteristics of thioureas (**3a-g**), isothiourea hydrobromides (**4a-g**) and tetrahydroacridinylthiazolidinones (**5a-e**) given in the experimental prove the structure of compounds under study.

EXPERIMENTAL

Melting points were determined on a Boetius hot apparatus and are uncorrected. IR spectra in KBr tablets were recorded on a Specord M85 (Zeiss, Jena) spectrophotometer using KBr technique (0.8 mg / 300 mg KBr, $\tilde{\nu}$ in cm⁻¹). ¹H and ¹³C NMR spectra (δ , ppm) were measured on Varian VXR, Bruker ARX (both 300 MHz) and Tesla BS-587A (80 MHz) instruments at 298 K. Chemical shifts are expressed in ppm relative to TMS as the internal standard. MS spectra were taken on a Finnigan MAT 8500 (EI, 70 eV) and Finnigan MAT 90 spectrometer with chemical ionization. Microanalyses were performed with a Perkin-Elmer CHN analyzer model 2400.

9-Isothiocyanato-*N*-methyl-1,2,3,4-tetrahydroacridinium triflate (2). Compound (**2**) was prepared by the reaction of 9-isothiocyanato-1,2,3,4-tetrahydroacridine (**1**) (0.24 g, 0.001 mol) with methyl trifluoromethanesulfonate (0.16 g, 0.001 mol) in chloroform (20 mL). Product was recrystallized from chloroform-ether. mp 130–132 °C; yield 45%. Anal. Calcd for C₁₆H₁₅N₂O₃F₃S₂: C, 47.54;

H, 3.71; N, 6.93. Found: C, 47.32; H, 3.45; N, 6.75. IR (CHCl_3) cm^{-1} : 3018; 2027; 1585; 1260; 1163; 1030; 632. ^1H NMR (CDCl_3) δ : 2.02 (m, 4H, CH_2 -2, CH_2 -3), 3.11 (m, 2H) and 3.38 (m, 2H, CH_2 -1, CH_2 -4), 4.41 (s, 3H, CH_3), 7.60–8.75 (m, 4H, CH-5 to CH-8).

Preparation of *N*-(1,2,3,4-tetrahydroacridin-9-yl)-*N'*-substituted thioureas (3a–g). General Procedure. To a solution of 9-isothiocyanato-1,2,3,4-tetrahydroacridine (0.24 g, 0.001 mol) in chloroform (20 mL) corresponding secondary or primary amine (0.001 mol) was added dropwise at stirring. The reaction mixture was stirred at room temperature until a precipitate deposited. This was collected on filter, washed with ether, dried and recrystallized from ethanol. Derivatives (3a, 3c) are white and derivatives (3b, d, e, f, g) yellow compounds.

***N*-(1,2,3,4-Tetrahydroacridin-9-yl)-*N'*-benzylthiourea (3a):** mp 200–203 °C ; yield 74%. Anal. Calcd for $\text{C}_{21}\text{H}_{21}\text{N}_3\text{S}$: C, 72.59; H, 6.09; N, 12.09. Found: C, 72.53; H, 6.01; N, 12.03. IR (KBr) cm^{-1} : 3143; 2947; 1582; 1528; 1503; 1340; 1212; 1198; 955; 759. ^1H NMR (CDCl_3 and $\text{DMSO}-d_6$) δ : 1.88 (m, 4H, CH_2 -2, CH_2 -3), 2.70–3.22 (m, 4H, CH_2 -1, CH_2 -4), 4.76 (d, $J = 5.8$ Hz, 2H, CH_2N), 7.28 (m, 5H, Ph), 7.25–8.05 (m, 4H, CH-5 to CH-8), 9.40 (br, 1H, NH).

***N*-(1,2,3,4-Tetrahydroacridin-9-yl)-*N'*-butylthiourea (3b):** mp 185–187 °C ; yield 75%. Anal. Calcd for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{S}$: C, 68.97; H, 7.40; N, 13.40. Found: C, 69.23; H, 7.72; N, 13.35. IR (KBr) cm^{-1} : 3153; 2930; 1625; 1525; 1490; 1204; 753. ^1H NMR (CDCl_3) δ : 0.84 (t, $J = 7.1$ Hz, 3H, CH_3 -Bu), 1.00–1.60 (m, 4H, CH_2CH_2 -Bu), 1.92 (m, 4H, CH_2 -2, CH_2 -3), 2.90 (m, 2H) and 3.11 (m, 2H, CH_2 -1, CH_2 -4), 3.56 (dt, $J = 6.0$ and 6.4 Hz, 2H, CH_2N), 5.57 (m, 1H, NH), 7.35–8.12 (m, 4H, CH-5 to CH-8).

***N*-(1,2,3,4-Tetrahydroacridin-9-yl)-*N'*-isopropylthiourea (3c):** mp 189–192 °C ; yield 60%. Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{N}_3\text{S}$: C, 68.19; H, 7.07; N, 14.03. Found: C, 68.40; H, 7.24; N, 13.98. IR (KBr) cm^{-1} : 3152; 2933; 1627; 1525; 1500; 1225; 753. ^1H NMR (CDCl_3) δ : 1.08 (d, $J = 6.5$ Hz, 6H, 2CH_3), 1.95 (m, 4H, CH_2 -2, CH_2 -3), 2.70–3.38 (m, 4H, CH_2 -1, CH_2 -4), 4.60 (doublet of septet, $J = 6.6$ and 6.5 Hz, 1H, CHN), 5.20 (d, $J = 6.6$ Hz, 1H, NH), 7.35–8.28 (m, 4H, CH-5 to CH-8).

***N*-(1,2,3,4-Tetrahydroacridin-9-yl)-*N'*-(2'-furyl)methylthiourea (3d):** mp 186–188 °C ; yield 65%. Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{N}_3\text{OS}$: C, 67.63; H, 5.68; N, 12.45. Found: C, 67.43; H, 5.46; N, 12.38. IR (KBr) cm^{-1} : 3150; 2948; 1583; 1526; 1500; 1409; 1327; 1278; 1144; 953; 760; 729. ^1H NMR (CDCl_3 and $\text{DMSO}-d_6$) δ : 1.91 (m, 4H, CH_2 -2, CH_2 -3), 2.75–3.30 (m, 4H, CH_2 -1, CH_2 -4), 4.79 (d, $J = 6.3$ Hz, 2H, CH_2N), 6.10–6.40 (m, 2H, CH-3', CH-4'), 7.25–8.10 (m, 5H, CH-5 to CH-8 and CH-5'), 9.12 (br, 1H, NH).

***N*-(1,2,3,4-Tetrahydroacridin-9-yl)-*N'*-cyclohexylthiourea (3e):** mp 190–193 °C ; yield 57%. Anal. Calcd for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{S}$: C, 70.76; H, 7.42; N, 12.38. Found: C, 70.63; H, 7.52; N, 12.25. IR (KBr) cm^{-1} : 3402; 3380; 2943; 2860; 1584; 1513; 1485; 1465; 1342; 1238; 1166; 1032; 640. ^1H NMR (CDCl_3 and $\text{DMSO}-d_6$) δ : 0.75–2.00 (m, 10H, $(\text{CH}_2)_5$), 1.93 (m, 4H, CH_2 -2, CH_2 -3), 2.65–3.50 (m, 4H, CH_2 -1, CH_2 -4), 4.18 (m, 1H, CHN), 6.25 (d, $J = 7.8$ Hz, 1H, NH), 6.75 (br, 1H, NH), 7.20–8.35 (m, 4H,

CH-5 to CH-8).

***N*-(1,2,3,4-Tetrahydroacridin-9-yl)-*N'*-morpholinylthiourea (3f):** mp 179–182 °C ; yield 65%. Anal. Calcd for C₁₈H₂₁N₃OS: C, 66.03; H, 6.46; N, 12.83. Found: C, 66.01; H, 6.71; N, 12.95. IR (KBr) cm⁻¹: 2925; 2865; 1628; 1560; 1512; 1417; 1359; 1303; 1195; 1118; 1025. ¹H NMR (CDCl₃) δ: 1.00–3.35 (m, 8H, CH₂-1 to CH₂-4), 3.85 (m, 4H, (CH₂)₂N), 4.08 (m, 4H, (CH₂)₂O), 7.15–8.17 (m, 4H, CH-5 to CH-8) 12.04 (br, 1H, NH).

***N*-(1,2,3,4-Tetrahydroacridin-9-yl)-*N'*-piperidinythiourea (3g):** mp 173–175 °C ; yield 75%. Anal. Calcd for C₁₉H₂₃N₃S: C, 70.12; H, 7.12; N, 12.91. Found: C, 70.01; H, 7.23; N, 12.86. IR (KBr) cm⁻¹: 2947; 2865; 1632; 1550; 1510; 1473; 1407; 1367; 1248; 1204; 1138; 997; 763. ¹H NMR (CDCl₃) δ: 1.00–2.20 (m, 10H, CH₂-2, CH₂-3, (CH₂)₃), 2.20–3.20 (m, 4H, CH₂-1, CH₂-4), 3.65–4.15 (m, 4H, (CH₂)₂N), 7.15–8.10 (m, 4H, CH-5 to CH-8).

Preparation of *N*-(1,2,3,4-tetrahydroacridin-9-yl)-*S*-methoxycarbonylmethyl-*N'*-substituted isothiurea hydrobromides (4a–g). General Procedure. To a solution of thiourea (3a–g) (0.001 mol) in chloroform (20 mL) methyl bromoacetate (0.15 g, 0.001 mol) was added with stirring at room temperature. The formation of isothiurea hydrobromide (4a–g) was followed by TLC on silica plates, eluent benzene–acetone (5:1), UV detection at 365 nm. Isothiurea obtained after the evaporation of chloroform was washed with ether, dried, dissolved in dry methanol (15 mL), sodium methoxide (0.22 g, 0.004 mol) was added and mixture was stirred at room temperature for 1 h. The reaction mixture was then poured into water and a precipitate formed was filtered and extracted with chloroform. Final products were obtained as yellow crystals after the evaporation of solvent and recrystallization from ethanol.

***N*-(1,2,3,4-Tetrahydroacridin-9-yl)-*S*-methoxycarbonylmethyl-*N'*-benzylisothiurea hydrobromide (4a):** mp 123–125 °C ; yield 75%. Anal. Calcd for C₂₄H₂₆N₃O₂BrS: C, 57.60; H, 5.24; N, 8.40. Found: C, 57.88; H, 5.35; N, 8.48. MS spectrum is identical with 5a. IR (CHCl₃) cm⁻¹: 3303; 2950; 2700; 1718; 1625; 1570; 1370; 1295; 1158. Major tautomer A: ¹H NMR (CDCl₃) δ: 1.90 (m, 4H, CH₂-2, CH₂-3), 2.57 (m, 2H) and 3.45 (m, 2H, CH₂-1, CH₂-4), 3.73 (s, 3H, CH₃O), 3.80 (s, 2H, CH₂S), 4.65 (d, J = 5.5 Hz, 2H, CH₂N), 7.10–8.10 (m, 9H) and 8.52 (d, J = 8.0 Hz, 1H, CH-5 to CH-8, Ph, NH). ¹³C NMR (CDCl₃) δ: 20.8, 21.5, 23.8, 28.6 (CH₂-1 to CH₂-4), 33.1 (CH₂S), 47.3 (CH₂N), 53.2 (CH₃O). Minor tautomer B: ¹H NMR (CDCl₃) δ: 1.90 (m, 4H, CH₂-2, CH₂-3), 2.57 (m, 2H) and 3.50 (m, 2H, CH₂-1, CH₂-4), 3.73 (s, 3H, CH₃O), 4.06 (s, 2H, CH₂S), 5.09 and 5.17 (AB quartet, J = 14.1 Hz, 2H, CH₂N), 7.10–8.10 (m, 9H) and 8.83 (d, J = 8.5 Hz, 1H, CH-5 to CH-8, Ph, NH). ¹³C NMR (CDCl₃) δ: 20.6, 21.2, 23.6, 28.6 (CH₂-1 to CH₂-4), 33.7 (CH₂S), 46.8 (CH₂N), 53.2 (CH₃O).

***N*-(1,2,3,4-Tetrahydroacridin-9-yl)-*S*-methoxycarbonylmethyl-*N'*-butylisothiurea hydrobromide (4b):** mp 152–154 °C ; yield 80%. Anal. Calcd for C₂₁H₂₈N₃O₂BrS: C, 54.08; H, 6.05; N, 9.01. Found: C, 54.30; H, 6.21; N, 8.94. IR (CHCl₃) cm⁻¹: 3305; 2945; 2720; 1720; 1623; 1567;

1373; 1295; 1152. ^1H NMR (CDCl_3) δ : Major tautomer A: 0.96 (t, $J = 6.6$ Hz, 3H, CH_3), 1.14–1.85 (m, 4H, CH_2CH_2), 1.93 (m, 4H, CH_2 -2, CH_2 -3), 2.70 (m, 2H) and 3.38 (m, 2H, CH_2 -1, CH_2 -4), 3.46 (m, 2H, CH_2N), 3.75 (s, 3H, CH_3O), 3.79 (s, 2H, CH_2S), 6.94 (t, $J = 5.2$ Hz, 1H, NH), 7.35–8.03 (m, 3H) and 8.42 (d, $J = 8.0$ Hz, 1H, CH-5 to CH-8). Minor tautomer B: 0.96 (t, $J = 6.6$ Hz, 3H, CH_3), 1.14–1.85 (m, 4H, CH_2CH_2), 1.93 (m, 4H, CH_2 -2, CH_2 -3), 2.70 (m, 2H) and 3.38 (m, 2H, CH_2 -1, CH_2 -4), 3.90–4.10 (overlapped signal, 2H, CH_2N), 3.75 (s, 3H, CH_3O), 4.00 (s, 2H, CH_2S), 7.35–8.03 (m, 3H) and 8.85 (d, $J = 7.8$ Hz, 1H, CH-5 to CH-8).

***N*-(1,2,3,4-Tetrahydroacridin-9-yl)-*S*-methoxycarbonylmethyl-*N'*-isopropylisothiourea hydrobromide (4c):** mp 193–196 °C; yield 80%. Anal. Calcd for $\text{C}_{20}\text{H}_{26}\text{N}_3\text{O}_2\text{BrS}$: C, 53.10; H, 5.79; N, 9.29. Found: C, 52.84; H, 5.63; N, 9.18. IR (CHCl_3) cm^{-1} : 3302; 2957; 2725; 1713; 1615; 1563; 1376; 1292; 1150. ^1H NMR (CDCl_3) δ : 1.36 (d, $J = 6.5$ Hz, 3H, CH_3), 1.39 (d, $J = 6.5$ Hz, 3H, CH_3), 1.93 (m, 4H, CH_2 -2, CH_2 -3), 2.69 (m, 2H) and 3.47 (m, 2H, CH_2 -1, CH_2 -4), 3.68 (s, 2H, CH_2S), 3.77 (s, 3H, CH_3O), 4.14 (doublet of septet, $J = 7.3$ and 6.8 Hz, 1H, CHN), 6.72 (d, $J = 7.3$ Hz, 1H, NH), 7.40–7.95 (m, 3H) and 8.63 (d, $J = 8.9$ Hz, 1H, CH-5 to CH-8).

***N*-(1,2,3,4-Tetrahydroacridin-9-yl)-*S*-methoxycarbonylmethyl-*N'*-(2'-furylmethyl)isothiourea hydrobromide (4d):** mp 207–210 °C; yield 90%. Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_3\text{O}_3\text{BrS}$: C, 53.88; H, 4.93; N, 8.57. Found: C, 53.92; H, 4.75; N, 8.33. IR (CHCl_3) cm^{-1} : 3302; 2957; 2725; 1717; 1624; 1567; 1373; 1297; 1142. ^1H NMR (CDCl_3) δ Major tautomer A: 1.92 (m, 4H, CH_2 -2, CH_2 -3), 2.64 (m, 2H) and 3.53 (m, 2H, CH_2 -1, CH_2 -4), 3.69 (s, 2H, CH_2S), 3.77 (s, 3H, CH_3O), 4.66 (d, $J = 5.7$ Hz, 2H, CH_2N), 6.36 (m, 2H, furyl H-3', H-4'), 7.12–8.05 (m, 5H) and 8.55 (d, $J = 8.4$ Hz, 1H, CH-5 to CH-8, furyl H-5', NH). Minor tautomer B: 1.92 (m, 4H, CH_2 -2, CH_2 -3), 2.64 (m, 2H) and 3.53 (m, 2H, CH_2 -1, CH_2 -4), 3.77 (s, 3H, CH_3O), 4.02 (s, 2H, CH_2S), 5.15 (s, 2H, CH_2N), 6.45–6.49 (m, 2H, furyl CH-3', CH-4'), 7.12–8.05 (m, 5H) and 8.92 (d, $J = 8.2$ Hz, 1H, CH-5 to CH-8, furyl CH-5', NH).

***N*-(1,2,3,4-Tetrahydroacridin-9-yl)-*S*-methoxycarbonylmethyl-*N'*-cyclohexylisothiourea hydrobromide (4e):** mp 191–193 °C; yield 80%. Anal. Calcd for $\text{C}_{23}\text{H}_{30}\text{N}_3\text{O}_2\text{BrS}$: C, 56.09; H, 6.14; N, 8.53. Found: C, 56.31; H, 5.73; N, 8.27. IR (CHCl_3) cm^{-1} : 3305; 2942; 2730; 1715; 1615; 1563; 1377; 1290; 1147. ^1H NMR (CDCl_3) δ : 1.00–2.40 (m, 10H, $(\text{CH}_2)_5$), 1.94 (m, 4H, CH_2 -2, CH_2 -3), 2.68 (m, 2H) and 3.48 (m, 2H, CH_2 -1, CH_2 -4), 3.68 (s, 2H, CH_2S), 3.77 (s, 3H, CH_3O), 3.80 (m, 1H, CHN), 6.67 (d, $J = 6.6$ Hz, 1H, NH), 7.40–8.05 (m, 3H) and 8.63 (d, $J = 8.0$ Hz, 1H, CH-5 to CH-8).

***N*-(1,2,3,4-Tetrahydroacridin-9-yl)-*S*-methoxycarbonylmethyl-*N'*-morpholinylisothiourea hydrobromide (4f):** mp 115–117 °C; yield 80%. Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_3\text{BrS}$: C, 52.50; H, 5.45; N, 8.75. Found: C, 52.79; H, 5.53; N, 8.50. IR (CHCl_3) cm^{-1} : 2957; 2720; 1728; 1613; 1595; 1557; 1373; 1160; 1108. ^1H NMR (CDCl_3) δ : 1.93 (m, 4H, CH_2 -2, CH_2 -3), 2.63 (m, 2H) and 3.50 (m, 2H, CH_2 -1, CH_2 -4), 3.46 (s, 2H, CH_2S), 3.58 (s, 3H, CH_3O), 3.50–3.90 (m, 8H, $\text{N}(\text{CH}_2)_4\text{O}$), 7.42–8.05 (m, 3H) and 8.75 (d, $J = 8.7$ Hz, 1H, CH-5 to CH-8).

***N*-(1,2,3,4-Tetrahydroacridin-9-yl)-*S*-methoxycarbonylmethyl-*N'*-piperidinylisothiourea hydrobromide (4g):** mp 158–160 °C; yield 75%. Anal. Calcd for $C_{22}H_{28}N_3O_2BrS$: C, 55.23; H, 5.90; N, 8.78. Found: C, 55.48; H, 5.82; N, 8.73. IR ($CHCl_3$) cm^{-1} : 2951; 2760; 1736; 1622; 1598; 1557; 1379; 1356; 1158. 1H NMR ($CDCl_3$) δ : 1.30–2.20 (m, 10H, CH_2 -2, CH_2 -3, $(CH_2)_3$), 2.60 (m, 2H) and 3.50 (m, 2H, CH_2 -1, CH_2 -4), 3.50 (s, 2H, CH_2S), 3.56 (s, 3H, CH_3O), 3.25–3.80 (m, 4H, $N(CH_2)_2$), 7.37–8.12 (m, 3H) and 8.71 (d, $J = 8.6$ Hz, 1H, CH-5 to CH-8).

Preparation of 2-[(1,2,3,4-tetrahydroacridin-9-yl)imino]-3-substituted 1,3-thiazolidin-4-ones (5a–e). General Procedure. Isothiourea hydrobromide (0.001 mol) (4a–e) was dissolved in dry methanol (15 mL), sodium methoxide (0.22 g, 0.004 mol) was added and the mixture was stirred at room temperature another 1 h. Reaction mixture was poured into water and a precipitate formed after filtration was extracted with chloroform. Yellow crystalline products (5a, 5c–e) obtained after the evaporation of solvent were recrystallized from chloroform–heptane.

2-[(1,2,3,4-Tetrahydroacridin-9-yl)imino]-3-benzyl-1,3-thiazolidin-4-one (5a): mp 62–65 °C; yield 30%. Anal. Calcd for $C_{23}H_{21}N_3OS$: C, 71.29; H, 5.46; N, 10.84. Found: C, 71.73; H, 5.42; N, 10.84. MS m/z (rel intensity): 387 (100, M^+), 340 (6), 312 (9), 296 (22), 270 (62), 222 (17), 195 (12), 180 (8), 91 (63). IR ($CHCl_3$) cm^{-1} : 2880; 1725; 1638; 1558; 1487; 1375. 1H NMR ($CDCl_3$) δ : 1.85 (m, 4H, CH_2 -2, CH_2 -3), 2.54 (m, 2H) and 3.10 (m, 2H, CH_2 -1, CH_2 -4), 3.86 (br, 2H, CH_2S), 5.12 (d, $J = 13.0$ Hz, 1H,) and 5.17 (d, $J = 13.0$ Hz, 1H, CH_2N), 7.20–7.42 (m, 5H) and 7.50–7.62 (m, 3H) and 7.96 (d, $J = 8.6$ Hz, 1H, ArH and CH-5 to CH-8). ^{13}C NMR ($CDCl_3$) δ : 22.6, 22.8, 24.6, 33.2 (CH_2 -1 to CH_2 -4), 33.9 (CH_2S), 46.4 (CH_2N), 119.2, 120.0 (C-8a, C-9a), 122.5, 125.1, 128.2, 128.3, 128.9 (CH-5 to CH-8 and CH-para), 128.6, 129.1 (2CH-ortho, 2CH-meta), 135.5 (C-ipso), 146.7, 149.5, 154.6, (C-9, C-10a, C=N), 159.7 (C-4a), 171.3 (C=O).

2-[(1,2,3,4-Tetrahydroacridin-9-yl)imino]-3-butyl-1,3-thiazolidin-4-one (5b): yellow oil; yield 55%. Anal. Calcd for $C_{20}H_{23}N_3OS$: C, 67.96; H, 6.56; N, 11.89. Found: C, 67.73; H, 6.69; N, 11.95. IR ($CHCl_3$) cm^{-1} : 2942; 1723; 1634; 1558; 907. 1H NMR ($CDCl_3$) δ : 1.02 (t, $J = 7.3$ Hz, 3H, CH_3 -Bu), 1.20–1.80 (m, 4H, CH_2CH_2 -Bu), 1.91 (m, 4H, CH_2 -2, CH_2 -3), 2.67 (m, 2H) and 3.13 (m, 2H, CH_2 -1, CH_2 -4), 3.80 (s, 2H, CH_2S), 4.00 (t, $J = 7.2$ Hz, 2H, CH_2N), 7.30–7.75 (m, 3H, CH-6 to CH-8), 7.98 (d, $J = 7.8$ Hz, 1H, CH-5).

2-[(1,2,3,4-Tetrahydroacridin-9-yl)imino]-3-isopropyl-1,3-thiazolidin-4-one (5c): mp 176–178 °C; yield 66%. Anal. Calcd for $C_{19}H_{21}N_3OS$: C, 67.23; H, 6.24; N, 12.38. Found: C, 67.15; H, 6.42; N, 12.15. MS m/z (rel intensity): 339 (100, M^+), 297 (18), 223 (31), 222 (54), 196 (10), 195 (19), 180 (13). IR ($CHCl_3$) cm^{-1} : 2945; 1720; 1635. 1H NMR ($CDCl_3$) δ : 1.65 (d, $J = 6.9$ Hz, 3H, CH_3), 1.66 (d, $J = 6.9$ Hz, 3H, CH_3), 1.85–2.04 (m, 4H, CH_2 -2, CH_2 -3), 2.66 (dt, $J = 16.8, 6.9$ Hz, 1H, CH_2 -1) and 2.73 (dt, $J = 16.8, 5.6$ Hz, 1H, CH_2 -1), 3.13 (m, 2H, CH_2 -4), 3.76 (s, 2H, CH_2 -5), 4.98 (septet, $J = 6.9$ Hz, 1H, CH), 7.39 (dd, $J = 7.6$ and 7.7 Hz, 1H) and 7.60 (dd, $J = 7.7$ and 8.2 Hz, 1H, CH-6, CH-7), 7.59 (d, $J = 7.6$ Hz, 1H, CH-8), 7.98 (d, $J = 8.2$ Hz, 1H, CH-5). ^{13}C NMR ($CDCl_3$) δ : 18.9 (CH_3), 18.9 (CH_3), 22.7, 22.9, 24.7, 32.9 (CH_2 -1 to CH_2 -4), 34.0 (CH_2S), 48.1 (CH), 119.2,

120.0 (C-8a, C-9a), 122.4, 125.2, 128.5, 128.8 (CH-5 to CH-8), 146.9, 149.8, 154.8 (C-9, C-10a, C=N), 159.7 (C-4a), 171.4 (C=O).

2-[(1,2,3,4-Tetrahydroacridin-9-yl)imino]-3-(2'-furylmethyl)-1,3-thiazolidin-4-one (5d):

mp 167–169 °C ; yield 45%. Anal. Calcd for $C_{21}H_{19}N_3O_2S$: C, 66.82; H, 5.07; N, 11.13 Found: C, 66.78; H, 5.12; N, 10.95. IR ($CHCl_3$) cm^{-1} : 2947; 2870; 1725; 1640; 1556; 1487; 1372; 1310; 1164; 1075; 1009. 1H NMR ($CDCl_3$) δ : 1.92 (m, 4H, CH_2 -2, CH_2 -3), 2.65 (m, 2H) and 3.16 (m, 2H, CH_2 -1, CH_2 -4), 3.86 (s, 2H, CH_2S), 5.17 (s, 2H CH_2N), 6.30–6.60 (m, 2H, furyl CH-3', CH-4'), 7.20–7.80 (m, 4H) and 8.02 (d, J = 8.3 Hz, 1H, CH-5 to CH-8, furyl CH-5'). ^{13}C NMR ($CDCl_3$) δ : 22.6, 22.8, 24.6, 33.2 (CH_2 -1 to CH_2 -4), 33.9 (CH_2S), 46.4 (CH_2N), 119.2, 120.0 (C-8a, C-9a), 122.5, 125.1, 128.2, 128.3, 128.9 (CH-5 to CH-8 and CH-para), 128.6, 129.1 (2CH-orto, 2CH-meta), 135.5 (C-ipso), 146.7, 149.5, 154.6, (C-9, C-10a, C=N), 159.7 (C-4a), 171.3 (C=O).

2-[(1,2,3,4-Tetrahydroacridin-9-yl)imino]-3-cyclohexyl-1,3-thiazolidin-4-one (5e):

mp 160–163°C ; yield 50%. Anal. Calcd for $C_{22}H_{25}N_3OS$: C, 69.62; H, 6.64; N, 11.07 Found: C, 69.36; H, 6.56; N, 11.05. MS m/z (rel intensity): 387 (100, M^+), 340 (6), 312 (9), 296 (22), 270 (62), 222 (17), 195 (12), 180 (8), 91 (63). IR ($CHCl_3$) cm^{-1} : 2944; 2864; 1722; 1633; 1555; 1487; 1338; 1074. 1H NMR ($CDCl_3$) δ : 0.90–2.20 (m, 14H, CH_2 -2, CH_2 -3, $(CH_2)_5$), 2.25–2.90 (m, 3H) and 3.15 (m, 2H, CH_2 -1, CH_2 -4, CHN), 3.75 (s, 2H, CH_2S), 7.22–7.80 (m, 3H) and 8.01 (d, J = 8.2 Hz, 1H, CH-5 to CH-8).

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