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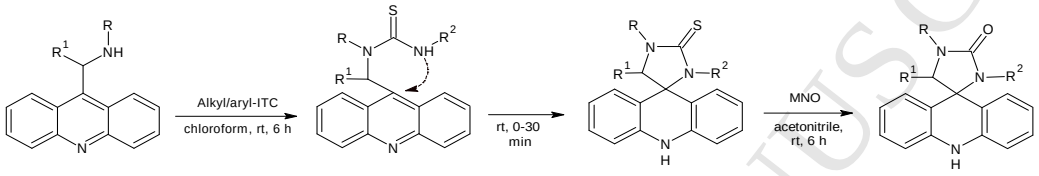
Mária Vilková, Marianna Prokaiová, and Ján Imrich*

P. J. Safarik University, Faculty of Science, Department of Organic Chemistry, Moyzesova 11, SK-041 67 Kosice, Slovak Republic



R = H, *n*-Pr, Bn R^1 = H, CH_3 R^2 = CH_3, allyl, Ph, 4-CH_3O-Ph, 4-Br-Ph, 4-F-Ph, 4-NO_2-Ph, acridin-9-yl

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P. J. Safarik University, Faculty of Science, Department of Organic Chemistry, Moyzesova 11, 041 67 Kosice, Slovak Republic

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ABSTRACT

Novel acridine spirocompounds, spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones have been prepared by the spontaneous cyclization of 1-substituted 3-(acridin-9-ylmethyl)thioureas, which were obtained from 1-(acridin-9-yl)methanamine, *N*-(acridin-9-ylmethyl)propan-1-amine, and *N*-(acridin-9-ylmethyl)benzylamine and alkyl/aryl isothiocyanates, as continuation of our previous studies on new acridine spirocycles. Imidazolidine-2-thiones thus obtained were subsequently transformed with mesitylnitrile oxide to imidazolidine-2-one analogues, some of which partly reopened to the corresponding (acridin-9-ylmethyl)ureas. An unusual spirocyclization via a CH carbanion instead of the N-1 nitrogen has been found for 3-(acridin-9-ylmethyl)-1-(acridin-9-yl)thioureas possessing two acridine rings. Structural modifications in positions 1, 3, and 4 of the spiroring together with ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy and X-ray crystallography have been employed to rationalize a general propensity of various 9-substituted acridines to undergo easy spirocyclization.

* Corresponding author. Tel.: +421-55-2342334; e-mail: jan.imrich@upjs.sk

1. Introduction

Acridine derivatives originally developed as pigments and dyestuffs are regarded currently as potent fluorescent, intercalating, and antitumor agents.[1–5] Many have been tested against bacteria,[6] prions,[7] viruses including HIV,[8] protozoa,[4] and other microorganisms.[9] Biological activity shown by acridine derivatives emphasizes the importance of the synthesis of new acridine-based structures. In our previous studies we have described numerous syntheses of novel spiro acridine compounds from acridin-9-ylthiocarbamates, dithiocarbamates, 2-(acridin-9-ylthiocarbamoyl)malonic acid diethyl esters, di- and trisubstituted thioureas, and thiosemicarbazides, in which the thiourea moiety was either directly or via a methylene bridge attached to the position 9 of the acridine skeleton. As products of these spirocyclizations, we obtained only five-membered rings attached to C-9 of the 9,10-dihydroacridin-9-ylidene moiety, namely 5-substituted-2-alkoxy- **1**[10,11] and 2-aminothiazolines **2**[12],**3**,[13,14] 2-alkylidenethiazolidines **4**,[15] 1,2-disubstituted-1,2,4-triazolidine-3-thiones **5**,[16,17] **6**,[18] and imidazolidine-2-thiones **7**[19] (Fig. 1). These papers highlighted a particular susceptibility of the acridine C-9 carbon to an intramolecular nucleophilic attack and subsequent ready formation of the five-membered spiroring attached to acridine. However, when acridine was replaced by 1,2,3,4-tetrahydroacridine, no spirocycle **2** but its thiazolidinone analogue has been formed.[12]

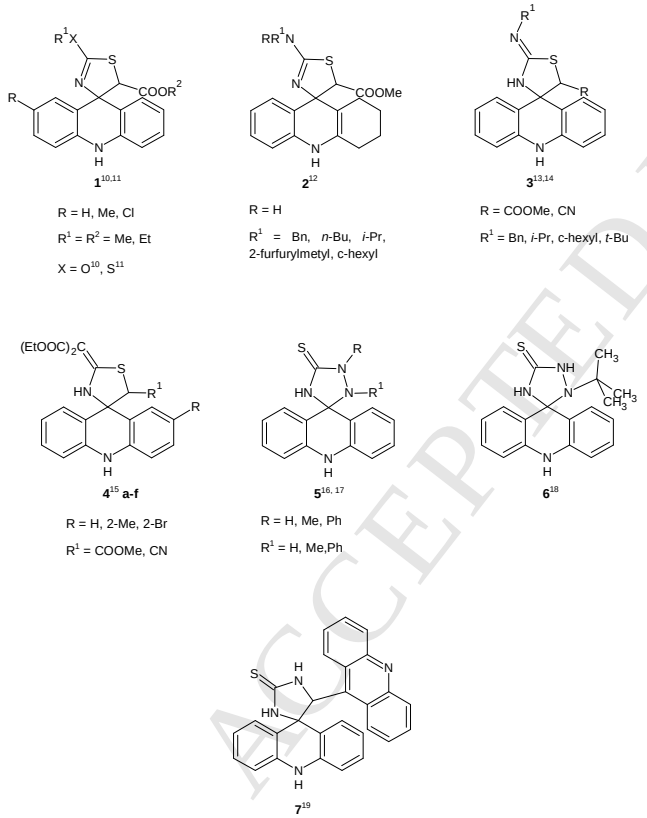
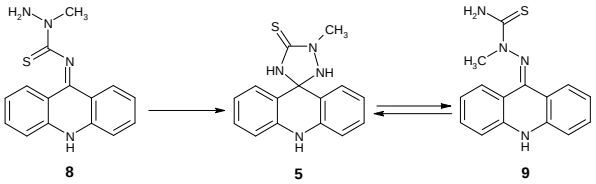


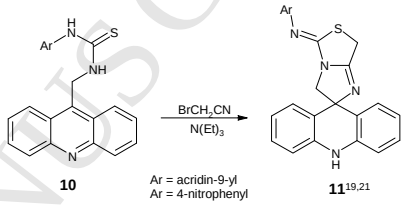
Fig. 1. Structures of 9,10-dihydroacridine spirocompounds **1**−**7** prepared in our laboratory.

In the spirocyclization of 4-(9,10-dihydroacridin-9-ylidene)-2-methylthiosemicarbazide (**8**) we have also observed an atypical rearrangement of a primarily formed 2-methyl spiro[dihydroacridine-9'(10'*H*),5-1,2,4-triazolidine]-3-thione (**5**) which underwent unexpected ring-opening of the cycle through splitting the former C-9'–N bond to give rearranged 1-(9,10-dihydroacridin-9-yliden)-2-methylthiosemicarbazide (**9**) (Scheme 1).[16,20]

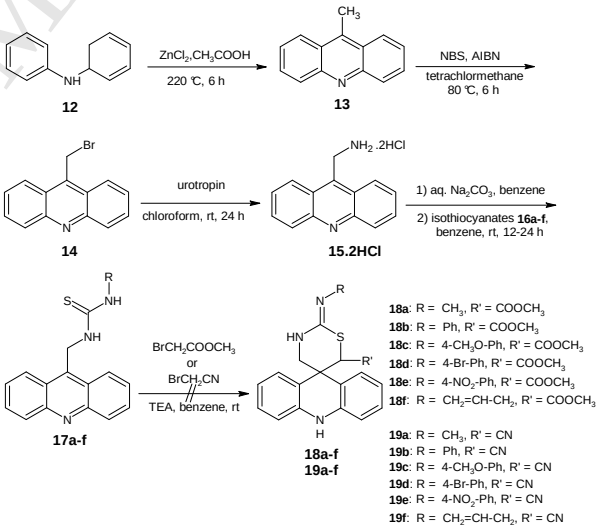


Scheme 1. Atypical ring-opening of spiro[dihydroacridine-9'(10'*H*),5-1,2,4-triazolidine]-3-thione.

When the reagent contained a reactive cyano group, we have observed three consecutive reactions in one pot leading to a new pentacyclic heterocycle, spiro[dihydroacridine-9(10*H*),2'-(2',7'-dihydro-3'*H*-imidazo[1,2-*c*]thiazol-5'-ylidene-(acridin-9-yl/*p*-nitrophenyl)amine] **11** (Scheme 2).[19,21]



Scheme 2. The formation of novel pentacyclic spiro dihydroacridines.



Scheme 3. The synthetic strategy to prepare six-membered 9-acridinyl spiro compounds **18**,**19**.

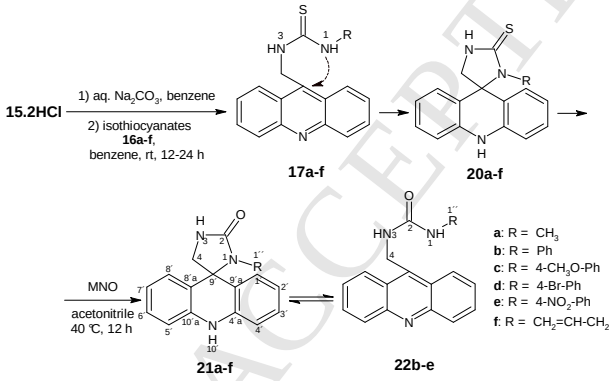
The shown examples demonstrate that spirocyclization is a general propensity of suitably substituted 9-acridinyl compounds that leads to new interesting orthogonal molecules. In the current work we originally intended to obtain novel six-membered spiro acridine compounds **18a−f, 19a−f**, for which interesting biological activity could be anticipated, by the reaction of new (acridin-9-ylmethyl)thioureas **17a−f** with bifunctional reagents based on acetic acid (Scheme 3). The intended role of the methylene group inserted between the C-9 carbon of acridine and the thiourea moiety was to decrease the spirocyclization tendency of intermediate thioureas **17a−f** to allow them to transform to the desired six-membered thiazines **18**, **19** by the reaction with

methyl bromoacetate or bromoacetonitrile. For this purpose, we have prepared three sets of starting compounds comprising disubstituted 3-(acridin-9-ylmethyl)-1-alkyl- or -1-(4-X-phenyl)thioureas, trisubstituted 3-(acridin-9-ylmethyl)-3-(*n*-propyl or benzyl)-1-alkyl- or -1-(4-X-phenyl)thioureas, and 3-(1-(acridin-9-yl)ethyl)-3-(*n*-propyl)-1-(4-X-phenyl)thioureas. We have found, however, that also these thioureas rapidly spirocyclized via the acridine C-9 carbon and therefore we decided to elucidate the kinetics and selectivity of these cyclizations to shed more light on the forces driving the formation of these novel acridine spirocycles.

2. Results and discussion

2.1. 3-(Acridin-9-ylmethyl)-1-alkyl/arylthioureas 17a–f, 1-alkyl/aryl-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones 20a–f, 1-alkyl/aryl-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-ones 21a–f, and 3-(acridin-9-ylmethyl)-1-(4-X-phenyl)ureas 22b−e

An initial substrate for the series of compounds I and II from this study, 1-(acridin-9-yl)methanamine dihydrochloride[22] (**15**.2HCl) was prepared from 9-(bromomethyl)acridine[23] (**14**), which was obtained from diphenylamine (**12**) via 9-methylacridine[23] (**13**) (Scheme 3). We have improved the yield of **13** to 73% by its extraction into *n*-heptane instead of original benzene. The heptane extract contained only the expected product unlike the benzene extracts, which were contamined by black resinous by-products. The synthon **13** reacted with *N*-bromosuccinimide and azobisisobutyronitrile in tetrachloromethane under irradiation by a halogen lamp over 6 h at 80 °C to give 80% of the bromide **14** which was further transformed by a Delepine reaction to the amine **15**.2HCl in 78% yield. The free base **15**, which was liberated from **15**.2HCl by treatment with aqueous sodium carbonate, was allowed to react with a set of isothiocyanates RNCS (R = (a) methyl, (b) phenyl, (c) 4-methoxyphenyl, (d) 4-bromophenyl, (e) 4-nitrophenyl, and (f) allyl) in benzene at room temperature to form intermediate 3-(acridin-9-ylmethyl)-1-substituted thioureas **17a–f** (Scheme 4).

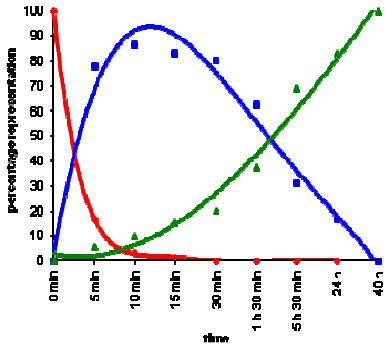


Scheme 4. Synthesis of 1-substituted spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones **20a–f** and corresponding 2-ones **21a–f**. In the case of the phenyl derivatives **b–e**, varying amounts of the open urea forms **22b–e** were also formed.

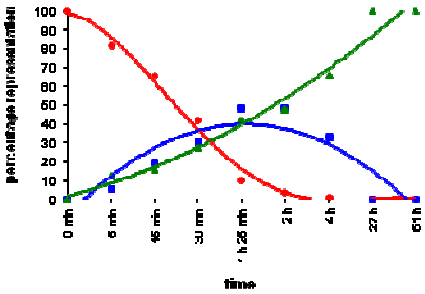
They proved to be very unstable and spontaneously cyclized in solution in tens of minutes to the corresponding isomeric 1-substituted spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones **20a–f** (Series I) in yields 57%–71% after crystallization (the yields are related to the starting amine **15**). The formation of the spiro imidazolidines **20a–f** was evident in the NMR spectra (Table 1, 2) from a new signal of quaternary, sp^3 hybridized spirocarbons, C-5,9', in the range 66.5–69.4 ppm. For the explicit presence of a thiocarbonyl group, the resonance of ^{13}C signals of the 2-C=S group between 179.4–181.7 ppm was highly indicative (Table 2). In the spirocycles **20a−f**, a new imidazolidine-2-thione ring formed by cyclization is orthogonal to a dihydroacridine skeleton arising from acridine, preserving thus a symmetry of flanking benzene rings in the latter. The assignment of chemical shifts of H-1'–H-8' acridine protons in the thiones **20a−f** was based on the NOESY correlations between a signal of the acridine proton NH-10' with H-4',5' signals and subsequent COSY and TOCSY correlations starting from these protons. Proton signals in the phenyls were assigned using the NMR increments of *para*-substituents on benzene. On the top, gHSQC and gHMBC experiments, which involved adiabatic pulses, enabled reliable assignments of all carbon signals. In the acridine ring, the signals of protons (6.74−6.90 ppm) and carbons (113.9−114.7 ppm) in the 4',5' positions were the most shielded due to +M effect of the NH-10' group. The spirocyclic structure was also evidenced by signals of the bridge dihydroacridine C-4'a,10'a carbons in a typical region 137−139 ppm,[10-18] which contrasted with those of aromatic acridines around 150 ppm. Interestingly, no thiazolidine products of potential spirocyclization on C-9 via the thiourea sulfur atom have been observed in the crude reaction mixture confirming that C-9 carbon as a hard electrophile has a greater affinity to a harder nitrogen than softer sulfur nucleophile.

The cyclization rate was significantly influenced by the character of a N-1 phenyl substituent. The cyclization of the intermediate thiourea **17e** to the spiroproduct **20e** is a charge-controlled reaction as indicated by significant charge values on the reacting centers. *E.g.*, at the B3LYP/6-311++G(2d,2p) level of theory, the charge on N-1 was calculated to be −0.1947 e and that on C-9' to be +0.6784 e. The negligible contributions of the corresponding HOMO and LUMO orbitals of $2p_z$ for N-1/C-9' (0.0335 and 0.1295 occupancy values, respectively) also allude to this notion. Repeated attempts to isolate pure thioureas **17a–f** always afforded mixtures of **17a–f** and spirocycles **20a–f** in various ratios. To elucidate the relation between the structure and reactivity of thioureas, we followed the kinetics of the reaction of 1-(acridin-9-yl)methanamine (**15**) with selected isothiocyanates, phenyl (**16b**), 4-methoxyphenyl (**16c**), and methyl (**16a**), by monitoring product distribution *vs.* time in the ^1H NMR spectra. Data shown in Fig. 2 were obtained by integration of the CH_2 proton signals of the amine **15**, thioureas **17b**, **17c**, **17a**, and spirocompounds **20b**, **20c**, **20a**, respectively, in the NMR spectra of the reaction mixtures. In the reaction of **15** with phenyl isothiocyanate, the starting amine **15** was consumed over 30 min leaving the mixture of the thiourea **17b** (80%) and the partially formed spirocompound **20b** (20%). Complete transformation to **20b** proceeded much more slowly and the thiourea **17b** was depleted after 40 h. In the reaction with 4-methoxyphenyl isothiocyanate (**16c**) with a weaker electrophilic character, the reaction speed decreased several times when the amine **15** was spent in 3 h, while the cyclization of the thiourea **17c** to the spiroproduct **20c** was somewhat faster than before (27 h). The slowest was the addition of methyl isothiocyanate (**16a**), in which the starting amine **15** was reacting for two days and full transformation to the spiroproduct **20a** took more than 50 h. It was found, in general, that spirocyclizations of **17** to **20** were completed during 30−50 hrs indicating that the spirocyclization rate was not very dependent on the isothiocyanate character, unlike the first step, where a strong influence of the isothiocyanate electrophilicity had been noted. (Fig. 2c)

a)



b)



c)

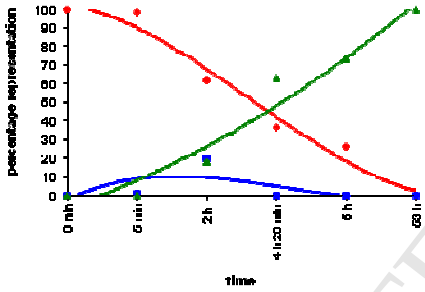


Fig. 2. The course of the reaction of 1-(acridin-9-yl)methanamine (**15**) with a) phenyl isothiocyanate, b) 4-methoxyphenyl isothiocyanate, and c) methyl isothiocyanate in $CDCl_3$ monitored by ^1H NMR. Percentages of the amine **15** (♦), thioureas **17b**, **17c**, **17a** (■), and spirocompounds **20b**, **20c**, **20a** (▲) are plotted *vs.* time.

Pure isolated spiro-2-thiones **20a**–**f** were quantitatively converted into the corresponding spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-ones **21a**–**f** by treatment with mesitylnitrile oxide (MNO), a reagent specific for the transformation of a thiocarbonyl group into a carbonyl (Scheme 4). Interestingly, the equilibrium open-chain – spiro did not totally favor the spiroform once replacement of sulfur by oxygen had occurred in the phenyl derivatives, but the spiroproducts **21b**–**e** reopened partly to the ureas **22b**–**e** in varying amounts. In a shorter reaction time, sufficient amounts of the urea to enable characterization were present only in the case of the phenyl (1.12:1.0) and 4-bromophenyl derivative (4.9:1.0). Again, the identification of the spiroderivatives **21** was readily evident by the resonance of a quaternary sp^3 hybridized carbon, C-5,9', in the range 61.7–63.0 ppm and the carbonyl resonance between 157.9–160.8 ppm (Table 2). Transformation of the 2-C=S to 2-C=O group caused a drop in chemical shifts of atoms close to the carbonyl: for spirocarbons C-5,9', a decrease of 5–6 ppm in the ones **21a**–**f** was found compared to the thiones **20a**–**f**, while chemical shifts of imidazolidine NH-3 protons decreased by 1.5–1.8 ppm. The 4-methylene group of imidazolidine-2-thiones **20** had ^1H (^{13}C) signals at 3.62−3.87 ppm (62.3−62.5 ppm) for alkyl derivatives **a**,**f** and 4.08−4.25 ppm (62.5−63.1 ppm) for phenyl derivatives **b**–**e** (Table 1, 2). Upon replacement to their 2-oxo analogues **21**, methylene ^1H chemical shifts decreased by about 0.3−0.7 ppm to 3.37−3.56 ppm (**a**,**f**) and 3.54−3.64 ppm (**b**–**e**), and methylene ^{13}C chemical shifts also decreased by about 3 ppm to 58.9−59.8 ppm (**a**–**f**). As can be seen, ^1H chemical shifts of 4-CH_2 were different with 1-alkyl vs. 1-aryl substituents, but ^{13}C ones not. Surprisingly, the 4-CH_2 ring protons became more shielded in 4-nitrophenyl derivatives **20e** (4.08 ppm), **21e** (3.54 ppm) than in 4-methoxy derivatives **20c** (4.25 ppm), **21c** (3.64 ppm), which is evidence of a cross-conjugation within the imidazolidine-2-(thi)ones. These observations show a weaker electronacceptor effect of the 2-oxo group compared to the 2-thione group. The effect of S→O replacement was transferred also to a N-1-phenyl ring, where *ortho* H-2",6" protons in the ones **21b**–**21e** were more deshielded (6.76–7.46 ppm) than in the thiones **20b**–**20e** (6.43−7.04 ppm), due to a 2-carbonyl magnetic anisotropy, while attached carbons C-2",6" became more shielded (120.2–125.6 ppm) in the ones than in the thiones (128.9–130.8 ppm), due to a weaker withdrawing effect of the carbonyl group. Small changes in chemical shifts have been observed for the other close protons and carbons in positions 1',8' and 8'a,9'a of dihydroacridine because of different anisotropic effects of the C=S *versus* C=O group.

The fraction of the urea form **22b**−**22e** in the reaction mixture increased in repeated experiments with extended reaction time, raised temperature, and stronger electronacceptor character of the *para* substituents on the 1-phenyl ring. Thus, the *p*-nitrophenyl urea derivative **22e** was found as the exclusive product after extended reaction time. It may be assumed that aromatic ureas **22b,d,e** are preferred thermodynamic products of this reaction besides **22c** (*p*-methoxyphenyl), in which the spiroform always prevailed. On the other hand, with alkyl spiroderivatives, methyl (**21a**) and allyl (**21f**), the conversion to ureas did not occur under mild conditions, perhaps due to +I effect of the 1-substituents. The most distinct NMR differences between the spiro and urea structures were as follows (Tables 1, 2):

a) in ureas **22b**,**d**,**e**, the acridine C-9' carbon signals at 142.1–143.9 ppm were restored, instead of the sp^3 spirocarbons of **21** at 63.0 ppm,

b) ^1H chemical shifts of all acridine protons in ureas **22b**–**e** were strongly deshielded by 0.7–1.3 ppm compared to the respective dihydroacridine protons of the spirocompounds **21b**–**e**, due to the withdrawing character of the aromatic acridine structure, unlike 9,10-dihydroacridine, whose NH-10' group is a donor of electrons into the flanking acridine rings,

c) the protons of the 4-CH_2 group of the spiro ones **21b**–**e**, which are fixed above the flanking benzene rings of the dihydroacridine due to its orthogonal orientation toward imidazolidinone, were strongly shielded by ring currents of these benzenes to 3.54–3.64 ppm in contrast with deshielded, freely rotating 4-methylene protons in ureas **22b**–**e** (5.32–5.37 ppm),

d) on the other hand, carbons of the 4-CH_2 group in the spiro-structures were strongly deshielded (59.5–59.8 ppm) due to *in-plane* deshielding by flanking rings compared to ureas (34.4–35.1 ppm).

Table 1

[1]H chemical shifts of 1-alkyl/aryl-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-(thi)ones **20–21** and 3-(acridin-9-ylmethyl)-1-aryl-ureas **22** (Series I)

		Dihydroacridine						Spiro ring		1-Me, 1-Ph, or 1-allyl (R)				
	R	1'8'	2'7'	3'6'	4'5'	NH-10'	NH-1	NH-3	CH_2-4	1''	2'' 6''	3'' 5''	4''	MeO
Imidazolidine-2-thiones (Acr-CH_2-NH-CS-NR-)														
20a[a]	CH_3	7.12	6.79	7.08	6.77	7.98		6.86	3.68	2.71			-	
20a	CH_3	7.09	6.91	7.36	6.90	9.40		8.39	3.62	2.61				
20b	Ph	7.54	6.96	7.19	6.75	9.22		8.86	4.14	-	6.54	7.00	7.00	-
20c	4-CH_3O-Ph	7.60	6.95	7.16	6.74	8.99		8.56	4.25	-	6.43	6.48	-	3.61
20d	4-Br-Ph	7.51	7.00	7.21	6.77	9.29		9.00	4.15		6.48	7.23	-	
20e	4-NO_2-Ph	7.44	6.93	7.22	6.84	9.42		9.36	4.08	-	7.04	7.94	-	-
20f	allyl	7.24	6.91	7.22	6.88	9.45		8.49	3.87	3.74	5.31[b]	4.59, 4.62[c]		
Imidazolidine-2-ones (Acr-CH_2-NH-CO-NR-)														
21a	CH_3	7.19	6.91	7.21	6.90	9.30		6.58	3.37	2.36				
21b	Ph	7.29	6.83	7.16	6.87	9.34		7.20	3.57		7.02	7.02	6.89	
21c	4-CH_3O-Ph	7.38	6.86	7.16	6.82	9.27		7.05	3.64		6.76	6.59		3.57
21d	4-Br-Ph	7.23	6.83	7.18	6.89	9.39		7.35	3.54		7.02	7.22		
21e	4-NO_2-Ph	7.16	6.83	7.20	6.95	9.53		7.76	3.54		7.46	7.95		
21f	allyl	7.32	6.88	7.19	6.85	9.31		6.67	3.56	3.39	5.35[b]	4.66, 4.71[c]		
Ureas (Acr-CH_2-NH-CO-NHR)														
22b	Ph	8.59	7.71	7.88	8.19		8.32	nd[d]	5.36		7.36	7.21	6.85	
22c	4-CH_3O-Ph	8.57	7.68	7.85	8.16		8.10	6.70	5.32		7.24	6.77		3.66
22d	4-Br-Ph	8.60	7.72	7.90	8.19		8.48	nd	5.36		7.35	7.35		
22e	4-NO_2-Ph	8.57	7.70	7.86	8.17		9.09	7.16	5.37		7.58	8.11		

[a] Measured in $CDCl_3$; [b] δ (CH=); [c] δ (=CH_2); [d] not determined.

Table 2

[13]C chemical shifts of 1-alkyl/aryl-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-(thi)ones **20–21** and 3-(acridin-9-ylmethyl)-1-aryl-ureas **22** (Series I)

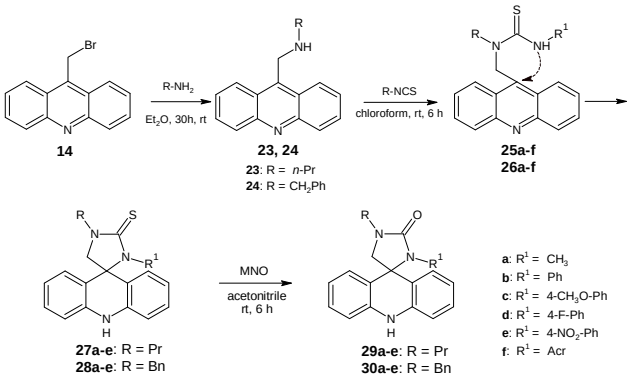
		Dihydroacridine							Spiro ring		1-Me, 1-Ph, or 1-allyl (R)				
	R	1'8'	2'7'	3'6'	4'5'	8'a9'a	4'a10'a	9'	2-C=X	CH_2-4	1''	2''6''	3''5''	4'''	MeO
Imidazolidine-2-thiones (Acr-CH_2-NH-CS-NR-)															
20a[a]	CH_3	126.8	120.5	128.7	114.0	119.0	137.6	67.7	181.4	62.1	29.8				
20a	CH_3	127.0	120.8	129.4	114.7	119.6	138.4	67.4	181.7	62.5	29.9				
20b	Ph	127.9	120.0	129.0	114.0	119.9	137.2	68.8	179.6	62.7	137.3	128.9	127.5	126.4	
20c	4-CH_3O-Ph	128.9	120.0	128.9	114.1	119.9	137.5	69.1	179.8	62.7	130.8	130.6	112.8	157.8	54.9
20d	4-Br-Ph	127.7	120.1	129.1	114.0	119.5	137.3	68.8	179.4	62.5	137.7	130.8	130.6	119.5	
20e	4-NO_2-Ph	127.2	120.4	128.1	114.3	119.3	137.2	69.4	179.7	63.1	144.9	129.3	122.9	144.5	
20f	allyl	127.6	119.9	128.9	113.9	119.6	137.6	66.5	179.8	62.3	46.3	134.1	115.6		
Imidazolidine-2-ones (Acr-CH_2-NH-CO-NR-)															
21a	CH_3	126.2	120.0	128.3	114.0	119.9	138.3	61.7	160.8	58.9	25.5				
21b	Ph	126.4	120.0	128.4	114.0	121.1	137.4	63.0	158.7	59.8	138.0	122.8	127.7	122.9	
21c	4-CH_3O-Ph	127.0	119.9	128.4	113.9	121.2	137.4	63.0	158.8	59.8	130:7	125.6	113.0	155.5	54.8
21d	4-Br-Ph	126.3	120.1	128.6	114.1	119.5	137.5	63.0	158.4	59.6	137.5	124.1	130.6	120.6	
21e	4-NO_2-Ph	125.5	120.3	128.8	113.9	120.1	137.5	63.0	157.9	59.5	144.4	120.2	123.6	141.0	
21f	allyl	127.3	119.7	128.4	113.7	120.7	137.9	61.7	160.1	59.3	43.4	135.2	115.2		
Ureas (Acr-CH_2-NH-CO-NHR)[b]															
22b	Ph	124.9	126.2	130.1	129.6	124.4	148.2	142.1	154.7	34.4	140.0	117.6	128.6	121.2	
22d	4-Br-Ph	125.0	126.3	130.6	128.6	124.4	nd	143.9	154.7	34.5	139.4	119.5	131.3	120.1	
22e	4-NO_2-Ph	125.4	126.8	130.7	130.2	125.0	148.8	142.1	154.6	35.1	147.2	117.4	125.6	141.1	

[a] Measured in $CDCl_3$. [b] The spectrum of **22c** could not be measured due to low concentration.

2.2 1-Alkyl/aryl-3-(*n*-propyl/benzyl)-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones 27a–e and 28a–e and their oxo analogues 29a–e and 30a–e

In continuation, we were interested in whether structural modification of the starting amine could stabilize intermediate thioureas and slow down their transformation to spiroproducts. We therefore carried out a substitution of one amino proton in **15** with a *n*-propyl or benzyl substituent to obtain new starting *sec*-amines, *N*-(acridin-9-ylmethyl)propan-1-amine[24] (**23**) and *N*-(acridin-9-ylmethyl)benzylamine[24] (**24**) (Scheme 5, Series II). For their synthesis, 9-(bromomethyl)acridine was stirred with *n*-propylamine or benzylamine in diethyl ether for 30 h at room temperature to give **23** and **24** in yields after chromatographic purification of 70% and 56%, respectively. The former amine was expected to enhance the lipophilicity of the compounds under study, which could improve their biological accessibility, whereas Bn in the latter one was believed to enhance stacking interactions of our products, which could interact as ligands with the aromatic parts of aminoacids or nucleic acids in target biopolymers. We also hoped that introduction of the donor *n*-propyl substituent to the vicinity of C-9' carbon could diminish its electrophilicity, rendering thus a slower spirocyclization to receive isolable thioureas. To obtain addition products, isothiocyanates **16a−c,e** and 4-fluorophenyl isothiocyanate in chloroform were added to a chloroform solution of the amines **23** or **24**, the reaction mixture was stirred at room temperature for 6 h to give target spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones **27a−e** in yields 40–85% and **28a−e** in yields 49–62% (Scheme 5). NMR monitoring showed that no signals of the intermediate phenyl thiourea **25b** was present in the crude reaction mixture even 5 min after the start of the reaction, thus confirming a much faster spirocyclization than in the series I. This finding may be explained by the enhanced reactivity of

the thiourea moiety due to its increased nucleophilicity induced by the donor *n*-propyl substituent, not by the diminished electrophilicity of the C-9 acridine carbon. In order to prepare the oxo analogues of the spiroproducts, solid MNO was added at once to a solution of spiro products **27a−e, 28a−e**



Scheme 5. Synthesis of *N*-(acridin-9-ylmethyl)propan-1-amine (**23**) and *N*-(acridin-9-ylmethyl)benzylamine **(24)** from the bromide **14** and their reactions with isothiocyanates to give 1,3-disubstituted-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones **27a–f, 28a–f** via non-isolable thioureas **25a−f**, **26a−f** and corresponding 1,3-disubstituted-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-ones **29a–f, 30a–f**.

in dry acetonitrile and the reaction mixture was left to stir for 6 h at room temperature to give spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-ones **29a−e**, **30a−e** in yields 42%–84% and 53%–79%, respectively.

The spiro C-9' carbon signals in the thione products **27a−e**, **28a−e** between 64.8−66.9 ppm and in the oxo products **29a−e**, **30a−e** between 59.4−61.6 ppm were more shielded than those in our previous spiroacridine structures (Table 3).

Table 3

^{13}C chemical shifts of C-9' in our former studies

Compound	R	R1	δ (C-9')	Ref.
3	COOMe, CN	t-Bu	81.2-81.3	13,14
4	COOMe, CN	H	70.3-70.6	15
5	Me	H	74.2	16
5	Ph	H	75.1	16
5	H	Ph	82.2	16
7			69.3	19

Assignments of the chemical shifts of the acridine protons in the thiones **27a−e**, **28a−e** were again based on NOESY correlations between a signal of NH-10' and those of H-4',5' and subsequent COSY or TOCSY correlations with the latter ones. Assignments of benzyl protons started from *ortho* protons which were identified by NOESY cross-peaks with benzyl methylene protons. Concerning the spiroring, the magnetization was transferred from 1''-(*α*)-methylene protons of propyl or benzyl to the imidazolidine 2-C=S and C-4 carbons in the HMBC spectra, whereas transfers to spiro C-9' carbon emerged from acridine H-1',8' and imidazolidine 4-CH_2 protons. The magnetization from the 4-CH_2 protons was transferred also to 2-C=S, C-9', and the acridine bridge C-8'a,9'a carbons (Fig. 3). Replacement of H on N-3 by *n*-Pr or Bn raised the ^{13}C chemical shifts of 4-CH_2 by 4−5 ppm, i.e. less than the usual *β*-effect of carbon (9.4 ppm), and lowered

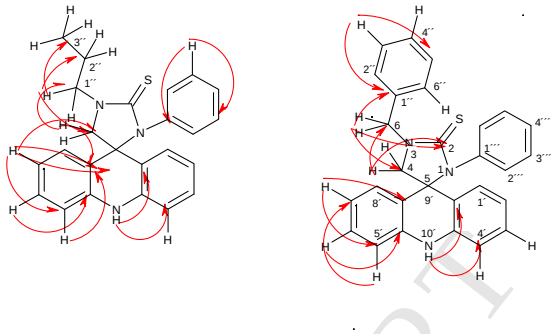


Fig. 3. HMBC transfers in spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones **27b** (Pr) and **28b** (Bn).

these of C-5,9' by 2−3 ppm, as expected for the negative *γ*-effect, but, interestingly, ^{13}C chemical shifts of 2-C=X in the close *β*-position did not change at all (Tables 4, 5). Upon change of the thiones **27**, **28** to the oxo derivatives **29**, **30**, chemical shifts of the C=S carbons between 179.2−181.2 ppm decreased strongly to 156.4−159.9 ppm and this change influenced also the chemical shifts of *α*-protons and carbons of *n*-Pr and Bn

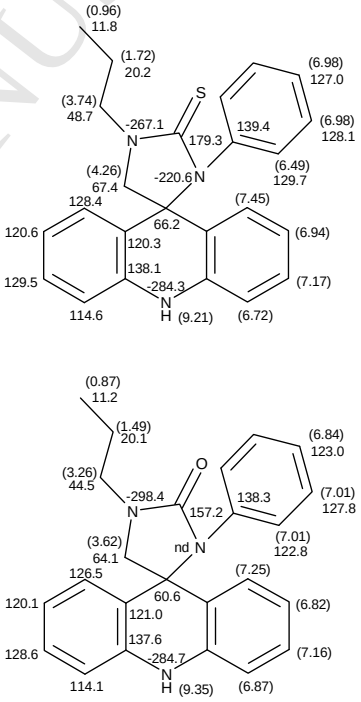


Fig. 4. Chemical shifts of representative compounds **27b** and **29b**.

substituents, which were upfield shifted by about 0.4−0.7 ppm and 3−4 ppm, respectively, in the oxo analogues, in which a similar upfield shift was observed for *α/ipso* and *ortho* phenyl carbons, especially for *p*-nitrophenyl derivatives. Conversely and similarly to Series I, the *ortho* protons of 1-N-Ph were deshielded in **29**, **30**. Definitive assignments are illustrated in Fig. 4 for representative compounds **27b** and **29b**.

Table 4

[1]H chemical shifts of 1-alkyl/aryl-3-(*n*-propyl/benzyl)-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-(thi)ones **27–30** (Series II)

		Dihydroacridine						3-Pr				1-Me, or 1-Ph (R)				
	R	1'8'	2'7'	3'6'	4'5'	NH-10'	CH_2-4	1''	2''	3''		1'''	2'''6'''	3'''5'''	4'''	MeO
Imidazolidine-2-thiones (Acr-CH_2-NPr-CS-NR-)																
27a	CH_3	7.04	6.90	7.22	6.91	9.42	3.73	3.57	1.52	0.83		2.65	-	-	-	
27b	Ph	7.45	6.94	7.17	6.72	9.21	4.26	3.74	1.72	0.96			6.49	6.98	6.98	
27c	4-CH_3O-Ph	7.45	6.95	7.18	6.72	9.19	4.27	3.73	1.70	0.96			6.33	6.53	-	3.57
27d	4-F-Ph	7.46	6.95	7.19	6.73	9.23	4.30	3.74	1.71	0.96			6.44	6.84	-	
27e	4-NO_2-Ph	7.38	6.93	7.21	6.84	9.42	4.23	3.76	1.70	0.95			7.00	7.92	-	
Imidazolidine-2-ones (Acr-CH_2-NPr-CO-NR-)																
29a	CH_3	7.14	6.89	7.19	6.89	9.30	3.36	3.11	1.39	0.80		2.37	-	-	-	
29b	Ph	7.25	6.82	7.16	6.87	9.35	3.62	3.26	1.49	0.87			7.01	7.01	6.84	
29c	4-CH_3O-Ph	7.35	6.86	7.16	6.82	9.27	3.69	3.26	1.52	0.89			6.75	6.59	-	3.57
29d	4-F-Ph	7.29	6.87	7.17	6.87	9.35	3.67	3.27	1.52	0.89			6.95	6.87	-	
29e	4-NO_2-Ph	7.12	6.81	7.20	6.99	9.55	3.60	3.27	1.48	0.84			7.48	7.94	-	
								3-Bn								
	R							CH_2	2'' 6''	3'' 5''	4''					
Imidazolidine-2-thiones (Acr-CH_2-NBn-CS-NR-)																
28a	CH_3	7.01	6.88	7.21	6.90	9.43	3.62	4.89	7.34	7.34	7.24	2.71	-	-	-	
28b	Ph	7.36	6.89	7.16	6.70	9.20	4.15	5.07	7.52	7.44	7.34		6.50	7.03	7.03	
28c	4-CH_3O-Ph	7.34	6.88	7.15	6.68	9.17	4.13	5.04	7.50	7.43	7.32		6.34	6.55	-	3.58
28d	4-F-Ph	7.35	6.87	7.16	6.70	9.21	4.17	5.05	7.51	7.43	7.35		6.44	6.87		
28e	4-NO_2-Ph	7.29	6.86	7.17	6.77	9.36	4.10	5.06	7.49	7.41	7.33		6.96	7.93	-	
Imidazolidine-2-ones (Acr-CH_2-NBn-CO-NR-)																
30a	CH_3	7.11	6.87	7.18	6.88	9.30	3.27	4.38	7.25	7.31	7.23	2.43	-	-	-	
30b	Ph	7.19	6.77	7.12	6.81	9.30	3.50	4.49	7.33	7.33	7.26		7.01	7.01	6.85	
30c	4-CH_3O-Ph	7.29	6.82	7.14	6.79	9.25	3.58	4.52	7.37	7.37	7.29		6.76	6.61	-	3.58
30d	4-F-Ph	7.24	6.80	7.15	6.83	9.32	3.57	4.52	7.36	7.36	7.29		6.95	6.90	-	
30e	4-NO_2-Ph	7.07	6.75	7.15	6.90	9.51	3.48	4.52	7.30	7.30	7.25		7.48	7.94	-	

Table 5

[13]C chemical shifts of 1-alkyl/aryl-3-(*n*-propyl/benzyl)-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-(thi)ones **27–30** (Series II)

	Dihydroacridine							Spiro ring		3-Pr			1-Me or 1-Ph (R)			
	1'8'	2'7'	3'6'	4'5'	8'a 9'a	4'a 10'a	9'	2-C=X	CH_2-4	1''	2''	3''	1'''	2'''6'''	3'''5'''	4'''
Imidazolidine-2-thiones (Acr-CH_2-NPr-CS-NR-)																
27a	126.8	120.9	129.4	114.7	119.5	138.6	64.8	181.2	66.9	48.3	20.2	11.6	31.0			
27b	128.4	120.6	129.5	114.3	120.3	138.1	66.2	179.3	67.4	48.7	20.2	11.8	139.4	129.7	128.1	127.0
27c[a]	128.4	120.4	129.5	114.5	120.5	138.0	66.1	179.6	67.2	48.7	20.2	11.8	132.0	131.1	113.4	158.1
27d	128.3	120.7	129.7	114.6	120.0	138.0	66.2	179.3	67.0	48.7	20.2	11.8	135.6	131.7	115.0	160.1
27e	127.7	120.9	129.8	114.9	119.7	137.9	66.8	179.6	67.8	48.7	20.0	11.7	145.0	128.9	123.5	145.9
Imidazolidine-2-ones (Acr-CH_2-NPr-CO-NR-)																
29a	126.6	120.6	129.0	114.6	120.2	139.0	59.9	159.9	63.8	45.0	20.6	11.6	26.6			
29b	126.5	120.1	128.6	114.1	121.0	137.6	60.6	157.2	64.1	44.5	20.1	11.2	138.3	122.8	127.8	123.0
29c[b]	126.9	119.9	128.5	114.0	121.0	137.6	60.6	157.3	64.0	44.6	20.1	11.2	130.9	125.7	113.1	155.6
29d	126.6	120.1	128.6	114.1	120.6	137.6	60.7	157.1	63.9	44.5	20.0	11.1	134.5	125.1	114.5	158.1
29e	125.6	120.5	129.0	114.4	120.0	137.6	61.0	156.4	63.8	44.4	19.9	11.1	144.6	120.1	123.7	141.1

[a] δ (MeO) = 55.4 ppm; [b] δ (MeO) = 54.8 ppm.

	Dihydroacridine							Spiro ring		3-Bn					1-Me or 1-Ph (R)			
	1'8'	2'7'	3'6'	4'5'	8'a 9'a	4'a 10'a	9'	2-C=X	CH_2-4	CH_2	1''	2'' 6''	3'' 5''	4''	1'''	2'''6'''	3'''5'''	4'''
Imidazolidine-2-thiones (Acr-CH_2-NBn-CS-NR-)																		
28a	126.8	120.8	129.4	114.7	119.3	138.5	64.8	181.2	66.3	50.3	137.1	128.3	129.0	127.9	31.3			
28b	128.3	120.5	129.6	114.6	120.1	138.0	66.3	179.4	66.7	50.5	137.0	128.7	129.1	128.2	139.3	129.8	128.2	127.3
28c[a]	128.4	120.5	129.5	114.5	120.1	138.0	66.2	179.6	66.6	50.6	137.1	128.7	129.1	128.1	131.9	131.1	113.5	158.2
28d	128.2	120.6	129.7	114.6	119.8	138.0	66.2	179.3	66.3	50.6	136.9	128.7	129.1	128.2	135.5	131.8	115.1	161.0
28e	127.8	120.9	129.9	114.9	119.5	137.9	66.9	179.2	67.1	50.5	136.5	128.7	129.2	128.3	145.8	129.4	123.7	145.4
Imidazolidine-2-ones (Acr-CH_2-NBn-CO-NR-)																		
30a	126.1	120.1	128.5	114.1	119.5	138.4	59.4	159.3	62.9	46.9	137.4	127.8	128.4	127.2	26.2			
30b	127.0	120.5	129.1	114.6	121.3	138.0	61.2	157.6	64.3	47.3	137.5	128.4	129.0	127.9	138.6	123.6	128.4	123.8
30c[b]	127.5	120.4	129.1	114.5	121.3	138.1	61.2	157.7	64.2	47.4	137.7	128.4	129.0	127.8	131.3	126.6	113.7	156.4
30d	127.1	120.6	129.2	114.6	121.0	138.1	61.3	157.5	64.1	47.3	137.5	129.0	128.4	127.9	134.8	126.0	115.2	158.9
30e	126.1	120.3	129.5	114.9	120.3	138.0	61.6	156.9	64.0	47.2	136.9	128.5	129.1	128.0	144.9	120.8	124.2	141.8

[a] δ (MeO) = 55.4 ppm; [b] δ (MeO) = 55.4 ppm.

X-ray single crystal measurement has shown several interesting facts (Fig. 5, Table 6, 7). It confirmed a mutual orthogonal position of the dihydroacridine *versus* imidazolidine ring. It was surprising to find that phenyl was also almost orthogonal toward the imidazolidine ring. This is probably due to its sterical repulsion with the nearby acridine

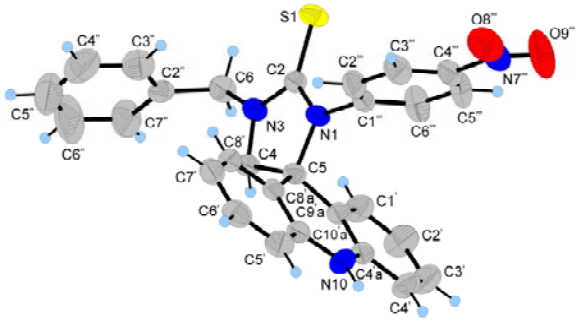


Fig. 5: Structure of 3-benzyl-1-(4'''-nitrophenyl)-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thione (**28e**).

Table 6
Crystal data and structure refinement of the compound **28e**

Compound	**28e**
Empirical formula	$C_{28}H_{22}N_4O_2S$
Formula weight	478.56
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	11.9766(2) Å 15.6048(3) Å 93.680(2)° 13.0091(4) Å
Volume	2426.29(10) Å^3
Z; density (calculated)	4; 1.310 g.cm^{-3}
Absorption coefficient	0.167 mm^{-1}
F(000)	1000
Crystal shape, color	prism, yellow
Crystal size	0.5276 x 0.2386 x 0.2117 mm^3
θ range for data collection	3.05 – 26.00°
Index ranges	$-14 \le h \le 14$, $-19 \le k \le 19$, $-16 \le l \le 15$
Reflections collected/independent	24891/4765 [R(int) = 0.0227]
data/restraints/parameters	4765 / 0 / 316
Goodness-of-fit on F^2	1.055
Final R indices [$I>2\sigma(I)$]	$R1$ = 0.0407, w$R2$ = 0.1105
R indices (all data)	$R1$ = 0.0648, w$R2$ = 0.1187
Largest diff. peak and hole	0.384; -0.314 e.Å^{-3}

ring. Moreover, the angles of the bonds going out from the N1 nitrogen are close to 120° indicating a prevailing sp^2-hybridization of the N1 nitrogen, though formally it should be a sp^3-nitrogen. Consequently, a lone electron pair on N1 is not a sp^3-hybridized orbital known from tertiary amines, but rather a *p*-orbital which can overlap with the orbitals of the C=S double bond. At the same time, this *p*-orbital cannot overlap with the six π-electron system of the 4-nitrophenyl ring, because they are mutually orthogonal. The conjugation effects originating from the *para* substituents of the phenyl, which were observed for carbon as well as nitrogen signals of the phenyl and imidazolidine rings, must thus be transferred to imidazolidine through a connecting σ-bond C1'''−N1. Such an unusual electron arrangement might be responsible for unexpected trends in changes of chemical shifts upon the change of the *para* substituents.

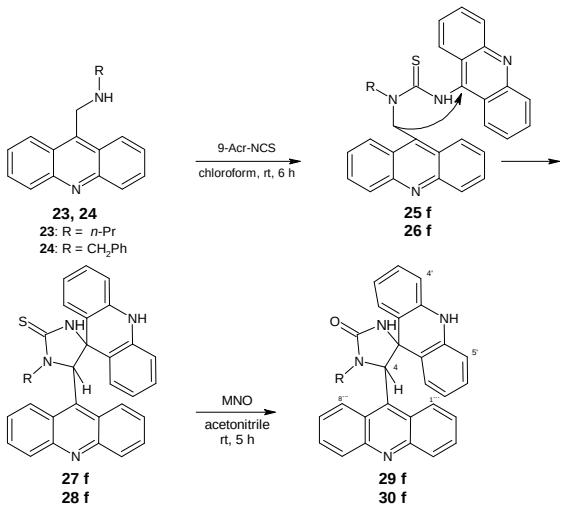
Table 7
Distances and angles in the compound **28e**

Distances (Å)	Angles (°)
C4a–H1', 2.319	N1–C2–N3, 108.50 (14)
C4b–H8', 2.301	N1–C2–S1, 125.83 (12)
S1–C1''', 3.143	N3–C2–S1, 125.66 (12)
S1–C2''', 3.997	C2–N1–C1''', 124.39 (13)
S1–C6''', 3.650	C1'''–N1–C5, 121.90 (12)
C2–N1, 1.347	C2–N1–C5, 113.30 (13)
C2–N3, 1.343	C2–N3–C4, 113.34 (13)
C1'''–N1, 1.432	C2–N3–C6, 126.04 (14)
C6–N3, 1.458	C4–N3–C6, 120.51 (14)
	C2'''–C1'''–N1–C2, 99.9 (2)
	C6'''–C1'''–N1–C2, -80.8 (2)

2.3 4-(Acridin-9'-yl)-3-(*n*-propyl/benzyl)-spiro[dihydroacridine-9'''(10'''*H*),5-imidazolidine]-2-thiones 27f, 28f and their oxo analogues 29f, 30f

An alternative reaction course than in Series II was found for reactions of *N*-(acridin-9-ylmethyl)propan-1-amine (**23**) and *N*-(acridin-9-ylmethyl)benzylamine (**24**) with 9-isothiocyanatoacridine (Series III). The reaction afforded spirocyclic thiones **27f**, **28f** in the isolated yields 66% and 36%, respectively, which were next transformed to their oxo analogues **29f**, **30f** with MNO in acetonitrile, to give isolated yields 27% and 68%, respectively, after crystallization from chloroform/*n*-heptane (Scheme 6). NMR spectra of these four bis-acridine products (Tables 8, 9) showed several differences when compared to the Me and Ph derivatives (**a**−**e**) of the series I and II. First of all, spirocycles **27f**−**30f** displayed only a one-proton methine CH signal (^{1}H: 5.47−6.01 ppm, ^{13}C: 69.8−75.0 ppm) attached to the spiro C-4,9' carbon (61.7−66.4 ppm), instead of the previous two-proton methylene (4-CH$_2$) signal. Second, we have found that spirocycles **27f**−**30f** possessed two unsymmetrical acridine skeletons giving altogether four aromatic spin systems in the NMR spectra, contrary to Me and Ph derivatives (**a**−**e**) in which all corresponding proton and carbon signals of the atom pairs, 1'8', 2'7', 3'6', 4'5', 4'a10'a, and 8'a9'a, in the acridine flanking rings were equivalent.

Regarding this different reaction course, two acridine rings of unstable, non-isolated bis-acridine thiourea intermediates **25f**, **26f** may allow two possible pathways of spirocyclization to come into account (Scheme 6): (a) either an attack of an N-1 nitrogen of thiourea onto a C-9' carbon of the first, 9-methylene-acridine ring as was the case in series I and II, or (b) an attack of a methylene carbon onto a C-9 carbon of the second, 9-amino-acridine ring. As the spectra have shown, the spirocyclization of intermediate, non-isolated thioureas **25f**, **26f**, which reacted very fast, proceeded by the pathway (b), i.e. by the nucleophilic attack of the CH$_2$-carbon of the linker moiety onto the C-9 carbon of the amino-acridine ring despite the fact that no special catalyst for generation of a carbanion had been used. In our former studies,[10,12,13] catalysis by sodium methoxide was necessary to achieve spirocyclization via a methylene carbon in similar types of reactions leading to compounds **1**−**4**.



Scheme 6. Synthesis of 4-(acridin-9'''-yl)-3-(*n*-propyl/benzyl)-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones **27f**, **28f** and their oxo analogues **29f**, **30f**.

To prove the structure of **27f–30f**, we could not employ crystallography, as the products had a powder form and did not afford crystals despite repeated attempts, therefore we relied up on NMR analysis. NOE transfers from the NH-10' proton between 8.35−8.83 ppm allowed to disclose two separate signals of H-4' and H-5' protons of the dihydroacridine cycle (Table 8). Following the COSY and TOCSY transfers allowed assignments of all eight dihydroacridine proton signals and, via HSQC and HMBC spectra, all thirteen carbon signals (Table 9). To corroborate the assignments, we used a new H2BC technique, which enabled easier assignments of the carbons which are two-bonds distant from the source protons. The chemical shifts of NH-1 proton of the imidazolidine, which decreased on going from the thiones **27f/28f** (9.95/10.19 ppm), to the ones **29f**/**30f** (8.19/8.40 ppm), were easily differentiated from those of acridine NH-10' one, because they displayed HMBC transfers to imidazolidine 2-C=S and 4-CH carbons, and to the spirocarbon C-5,9'. The magnetization from the imidazolidine 4-CH proton was transferred to both acridines, namely to carbons C-9''', C-8'''a, 9'''a of the aromatic acridine ring as well as to the spirocarbon C-9' and bridge carbons C-8'a,9'a of the dihydroacridine ring. On the other side, the magnetization transfers from the proton 4-CH to the propyl and benzyl protons were not observed, which prove a high mobility of these substituents.

In the aromatic acridine, the inequivalency of both flanking rings was again observed affording altogether eight proton and thirteen carbon signals, which have all been successfully resolved using 2D NMR techniques. Thus, a new stereogenic centre, the C-4 carbon of the imidazolidine renders the asymmetry not only in the close dihydroacridine but also in the more distant aromatic acridine. As we originally did not detect any cross-peaks of the 4-CH proton signal at 6.01 ppm with any of H-1',8' signals of dihydroacridine in the NOESY spectrum of the propyl derivative **27f**, unlike our former observation,[19] we performed a NOESY1D and ROESY1D irradiation of H-4 and found small NOE enhancements of H-1' signal at 7.62 ppm (0.47% and 2.73%, respectively) and signal

Table 8

^{1}H chemical shifts of 4-(acridin-9'''-yl)-3-(*n*-propyl/benzyl)-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-(thi)ones **27f–30f** (Series III)

Series III	Dihydroacridine										3-Pr				4-CH
	1'	2'	3'	4'	5'	6'	7'	8'	NH-10'	NH-1	1''	2''	3''		
27f, 2-C=S	7.62	7.14	7.31	6.81	6.11	6.54	6.20	7.14	8.83	9.95	4.14, 2.38	1.27	0.63		6.01
29f, 2-C=O	7.78	7.12	7.23	6.59	6.02	6.59	6.43	7.31	8.47	8.19	3.48, 2.24	1.14	0.64		5.82
											3-Bn				4-CH
											CH_2	2''6''	3''5''	4''	
28f, 2-C=S	7.53	7.08	7.24	6.70	6.08	6.57	6.27	7.24	8.72	10.19	5.77, 3.41	6.89	7.08	7.13	5.65
30f, 2-C=O	7.63	7.03	7.14	6.45	6.00	6.62	6.52	7.42	8.35	8.40	5.02, 3.22	6.77	7.08	7.14	5.47

	4-Aromatic acridine							
	1'''	2'''	3'''	4'''	5'''	6'''	7'''	8'''
27f	8.13	7.46	7.69	7.97	7.94	7.69	7.31	7.46
29f	8.31	7.31	7.61	7.89	7.97	7.64	7.18	7.31
28f	8.27	7.53	7.73	7.98	7.98	7.63	7.08	6.85
30f	8.48	7.34	7.64	7.92	7.95	7.59	6.94	6.70

Table 9

^{13}C chemical shifts of 4-(acridin-9'''-yl)-3-(*n*-propyl/benzyl)-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-(thi)ones **27f–30f** (Series III)

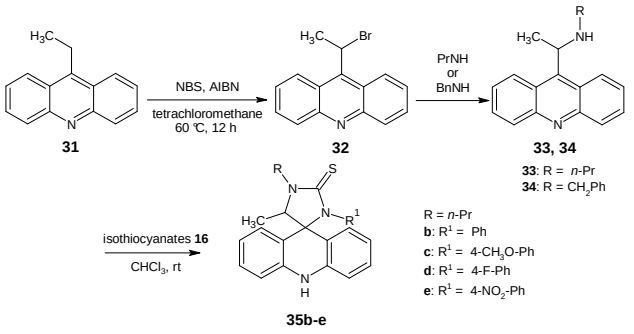
	Dihydroacridine													Spiro ring		3-Pr		
	1'	2'	3'	4'	5'	6'	7'	8'	9'	8'a	9'a	4'a	10'a	2-C=X	CH-4	1''	2''	3''
27f	125.6	121.1	129.3	114.5	113.2	128.5	118.8	127.8	66.4	116.9	122.9	138.6	139.1	183.3	75.0	46.4	20.0	11.4
28f	125.4	120.9	129.2	114.3	113.2	128.4	118.9	127.8	66.3	116.8	122.7	138.6	138.6	183.4	73.9			
29f	125.3	120.9	128.8	114.3	113.0	128.3	119.2	127.7	62.3	118.5	123.1	139.5	139.4	161.5	71.0	43.3	20.1	11.6
30f	124.6	120.2	127.8	113.5	112.4	127.8	118.8	127.2	61.7	118.0	122.0	138.9	138.9	161.0	69.8			

	4-Aromatic acridine													3-Bn				
	1'''	2'''	3'''	4'''	5'''	6'''	7'''	8'''	9'''	8'''a	9'''a	4'''a	10'''a	CH_2	1''	2''6''	3''5''	4''
27f	125.4	126.2	129.9	130.3	130.3	129.9	126.4	123.2	136.3	125.8	124.8	148.2	147.8					
28f	125.4	126.3	129.9	130.3	130.2	129.8	126.0	122.8	135.8	125.6	124.6	147.5	147.3	48.5	135.7	128.5	128.7	128.1
29f	126.3	125.1	129.6	129.8	130.2	129.7	125.9	123.1	136.7	126.2	125.2	148.1	147.8					
30f	125.7	124.7	129.1	129.2	129.5	128.9	124.7	122.3	135.5	125.7	124.9	148.2	147.7	45.3	135.6	128.1	128.2	127.3

H-8''' at 7.46 ppm (3.20% and 24.58%, respectively). These magnitudes coincide with interatomic distances obtained from modeling: H-4–H-8''': 1.91 Å and H-4–H-1': 2.22 Å. These facts prove that the both acridines are very close each to other (e.g., the distance H-1'''–H-8': 2.52 Å) and the difference in observed NOE enhancements here is caused by a more compressed molecule in the present case contrary to the structure without Pr (or Bn) substituent on the N-3 in our former study.[19]

2.4 1-Aryl-3-(*n*-propyl)-4-methyl-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones 35b–e

Last modification we made was on the methylene attached to acridine C-9' carbon, in which one methylene proton was replaced with a methyl group (Series IV). We were interested



Scheme 7. Synthesis of *N*-[1-(acridin-9-yl)ethyl]propan-1-amine (**33**) from 9-ethylacridine (**31**) and its reactions with isothiocyanates **16** to 1-aryl-3-(*n*-propyl)-4-methyl-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones **35b–e**.

if such a sterically hindered electrophilic C-9' site would still be able to form a spirocycle. To prepare starting 9-ethylacridine **31**,[25] we have improved the described procedure for the synthesis of 9-methylacridine.[23] To obtain a synthon *N*-[1-(acridin-9-yl)ethyl]propan-1-amine (**33**), the acridine **31** in tetrachloromethane was allowed to react with NBS and AIBN to give oily, so far undescribed, unstable 9-(1-bromoethyl)acridine (**32**) in 73% yield. The bromide **32** and *n*-propylamine afforded 70% of 1-(acridin-9-yl)ethyl]propan-1-amine (**33**) as an oil, to which phenyl isothiocyanates **16b,c,e**, or 4-fluorophenyl isothiocyanate were added to give crude, oily 1-(4'''-substituted phenyl)-3-propyl-4-methyl-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones **35b−e**, which were proven by NMR to be the corresponding spirocompounds (Scheme 7, Table 10). Despite repeated attempts, preparation of desired *N*-[1-(acridin-9-yl)ethyl]benzylamine (**34**) was not successful, because the reactive benzyl fragment could perhaps easily split-off. NMR spectra of the dihydroacridine system of **35b–e** showed an inequivalency of the flanking rings due to the presence of a new stereogenic C-4 centre. As the 1'-position in dihydroacridine, the one closer to the 4-methyl substituent was selected. The NOESY cross-peaks with two multiplets of the 4-CH(CH_3) group enabled to resolve each from other the protons H-8' and H-1': a 4-CH quartet was closer to a signal in the lower field (7.20−7.40 ppm, H-8') and a methyl doublet was closer to one at a higher field (7.02−7.19 ppm, H-1'). Upon that resolution, all remaining protons and carbons were assigned (Table 10, 11). Within the *n*-propyl group, the stereogenic centre caused a great difference of chemical shifts of α-protons (~0.4 ppm) and a smaller inequivalency of β-ones (~0.1 ppm) as well as the close to methyl C-8'a,9'a carbons were also separated each from other (119 ppm *versus* 116 ppm, resp.).

Table 10

^{1}H chemical shifts of 1-(4-X-phenyl)-3-(*n*-propyl)-4-methyl-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones **35b–35e** (Series IV)

		Dihydroacridine									Spiro ring		3-Pr			1-Ph			
	4-X	1'	2'	3'	4'	5'	6'	7'	8'	NH-10'	CH-4	CH_3-4	1''	2''	3''	2'''6'''	3'''5'''	4'''	MeO
35b	H	7.15	6.88	7.23	6.92	6.80	7.10	6.81	7.33	9.31	3.98	0.79	3.89,3.41	1.63,1.56	0.90	7.04	7.04	6.97	
35c	CH_3O	7.19	6.89	7.22	6.89	6.79	7.10	6.83	7.40	9.25	4.00	0.80	3.88,3.41	1.66,1.56	0.91	6.89	6.60		3.59
35d	F	7.16	6.93	7.27	6.93	6.81	7.13	6.84	7.38	9.32	4.01	0.80	3.87,3.41	1.65,1.56	0.90	7.04	6.93	-	
35e	NO_2	7.02	6.90	7.29	7.01	6.91	7.15	6.78	7.20	9.47	3.97	0.78	3.91,3.39	1.63,1.53	0.88	7.45	7.99	-	

Table 11

^{13}C chemical shifts of 1-(4-X-phenyl)-3-(*n*-propyl)-4-methyl-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones **35b–35e** (Series IV)

		Dihydroacridine													Spiro ring		
	4-X	1'	2'	3'	4'	5'	6'	7'	8'	9'	8'a	9'a	4'a	10'a	2-C=X	CH-4	4-CH_3
35b	H	128.7	119.9	129.6	115.1	114.4	129.1	120.2	128.6	71.2	119.1	116.1	138.6	139.0	182.1	70.3	13.5
35c	CH_3O	128.8	119.8	129.6	115.1	114.4	129.1	120.1	129.1	71.2	119.1	115.9	138.6	139.0	182.5	70.3	13.7
35d	F	128.6	120.0	129.8	114.9	114.5	129.2	120.3	128.8	71.2	118.9	115.8	138.6	139.0	182.2	70.3	13.6
35e	NO_2	127.7	120.5	129.9	115.3	114.7	129.4	120.6	127.7	71.4	118.5	115.6	138.7	139.0	181.2	70.3	13.3

		3-Pr			1-Ph				
	4-X	1''	2''	3''	1'''	2'''6'''	3'''5'''	4'''	MeO
35b	H	46.2	20.6	11.8	139.8	128.4	128.1	126.2	
35c	CH_3O	46.3	20.6	11.8	132.6	130.1	113.4	157.5	55.4
35d	F	46.3	20.6	11.8	136.1	130.5	115.1	160.2	
35e	NO_2	46.3	20.5	11.7	145.8	127.3	123.3	144.1	

^{15}N NMR spectra in DMSO-D_6 of 39 compounds **20a**,**c−f**, **21a**,**c**,**d**,**f**, **22d**,**e**, **27a−f**, **28a−f**, **29a−f**, **30a−f**, **35b−e** referenced to the mixture nitromethane : $CDCl_3$ (1:1) provided more interesting information about the structure and electronic effects inside the molecules (Table 12). Chemical shifts of ^{15}N nuclei in all products, which have been detected via inverse ^{1}H,^{15}N-gHMBC magnetization transfers from nearby protons, evidenced convincingly the nitrogen hybridization. In all spirocycles containing one dihydroacridine ring, two signals of (thio)ureido imidazolidine nitrogens ^{15}N-1 and ^{15}N-3, and one dihydroacridine ^{15}NH-10' signal have been observed except for four compounds (**29b**,**e**, **30c**,**e**), where N-1 signals were not detected due to a weak polarization transfer. Moreover, in the nitro compounds (**e**), signals of $^{15}NO_2$ groups have been found around -10 ppm. Chemical shifts of imidazolidine nitrogens correlated well with effects of the substituents in positions 1, 2, 3, 4, and 5 of the imidazolidine ring. In all spectra the signals of N-1 were systematically deshielded compared to the signals of N-3 by about 19−50 ppm, due to substituent effects of the neighbor acridine and N-1 substituents. The change of 2-thio to 2-oxo analogues moved signals of both neighboring N-1 and N-3 nitrogens upfield by ca. 30 ppm to more negative values. So, deshielding of (thio)ureido ^{15}N nuclei is stronger by the C=S group than by the C=O one. This is a similar effect as that found for ^{1}H and ^{13}C NMR spectra of thioureas, whose protons are more acidic and located thus at higher ppm values than the signals of urea protons.

In 2-thione derivatives, the replacement of N-1-methyl (**20a**, **27a**, **28a**) by phenyl (**27b**, **28b**) has shifted ^{15}N-1 signals substantially downfield from ca. -250 to ca. -220 ppm and those of the more distant ^{15}N-3 nitrogen to a much lesser extent from ca. -270 to -267 ppm. A similar drift of about 31 ppm for signals of ^{15}N-1, though with two other sets of chemical shifts, has been found with 3-oxo derivatives, which were again more shielded in N-1-methyl derivatives **21a**, **29a**, **30a** (ca. -284 ppm) than in N-1-phenyl one **30b** (ca. -255 ppm).

Para-substituents on N-1-phenyls influenced the chemical shifts of both nitrogens N-1 (the close one) and N-3 (the distant one), which, however, moved reversely to each other under the effect of these. Upon going from *p*-methoxy to *p*-nitro, the chemical shifts of distant ^{15}N-3 nitrogens became more deshielded (less negative) by 4.9−7.3 ppm, on the other hand, those of nitrogens ^{15}N-1, to which the phenyls are attached, became more shielded (more negative) by 2.4−2.9 ppm. Especially, the *p*-nitro substituent caused the greatest change. All this proves that N-1-phenyls together with the (thio)ureido part of imidazolidine compose a common, wide-spreading conjugated system. As the reverse trends as the size of induced span of the chemical shifts differences, which were found in both thio and oxo series, were surprising: *para*-substituents on the N-1-phenyls affected more distant ^{15}N-3 nitrogens to a greater extent, than those of ^{15}N-1. An explanation of this fact might lie in (a) a cross-conjugation of the N-1 nitrogen electron pair with 1-phenyl as well as the 2-thi(one) double bond, (b) some kind of intermolecular interaction, for example, formation of a dimeric structure mediated by hydrogen bonds between NH-10 protons of one molecule and nitrogens or sulfur lone electron pairs of the other, and (c) a stacking interaction between aromatics in the dimer.

From comparison of the 3-NH, 3-N-Pr, and 3-N-Bn derivatives it follows that substitution of H by *n*-Pr or Bn moved chemical shifts of N-3 downfield by 4-5 ppm and those of N-1 upfield by about 2 ppm, i.e. alkyls elicited only a small change of ^{15}N chemical shifts. Signals of dihydroacridine NH-nitrogens between -284.0 – -284.8 ppm were almost unaffected by structural changes in the spiroring. In $CDCl_3$, a small upfield shift has been observed for all three ^{15}N NMR signals (*e.g.* -286.5 ppm for **35e**).

In bis-acridine derivatives **27f–30f**, the chemical shift of dihydroacridine nitrogen N-10' was slightly moved to -280 ppm reflecting another type of spirocyclization. On the other hand, the chemical shift of nitrogen N-10''' was not dependent on the change of sulfur (-69 – -70 ppm) by oxygen (-71 ppm). Very interesting reversal effects have been observed when we compared how the methyl substituent in position 4 of imidazolidine-thiones **35b−e** influenced the chemical shift of N-1 and N-3, respectively, in comparison to non-methylated **27b–e.** Closer N-3s were deshielded by about 13 ppm due to a

Table 12

^{15}N chemical shifts of the target spirocompounds

	R	N-1	N-3	N-10'	N-10'''	NO_2
Imidazolidine-2-thiones (Acr-CH_2-NH-CS-NR-)						
20a	CH_3	-249.6	-275.6	-284.7		
20c	4-CH_3O-Ph	-220.2	-272.6	-284.3		
20d	4-Br-Ph	-221.4	-270.2	-284.1		
20e	4-NO_2-Ph	-222.6	-266.2	-284.0		-10.3
20f	allyl	-232.9	-275.4	-284.6		
Imidazolidine-2-ones (Acr-CH_2-NH-CO-NR-)						
21a	CH_3	-284.0	-307.1	-284.7		
21c	4-CH_3O-Ph	-255.4	-304.7	-284.6		
21d	4-Br-Ph	-256.6	-302.8	-284.5		
21f	allyl	-266.4	-307.0	-284.8		
Ureas (Acr-CH_2-NH-CO-NHR)						
22d	4-Br-Ph	-275.3	-290.8	nd		
22e	4-NO_2-Ph	-268.3	-287.9	-73.1		-9.9
Imidazolidine-2-thiones (Acr-CH_2-NPr-CS-NR-)						
27a	CH_3	-251.2	-270.6	-284.6		
27b	Ph	-220.6	-267.1	-284.3		
27c	4-CH_3O-Ph	-221.4	-268.2	-284.3		
27d	4-F-Ph	-222.1	-266.7	-284.1		
27e	4-NO_2-Ph	-223.5	-261.5	-284.0		-10.2
27f	Acr	-248.1	-261.8	-280.3	-69.3	
Imidazolidine-2-ones (Acr-CH_2-NPr-CO-NR-)						
29a	CH_3	-284.6	-301.7	-284.4		
29b	Ph	nd	-298.4	-284.7		
29c	4-CH_3O-Ph	-255.5	-299.5	-284.6		
29d	4-F-Ph	-256.1	-298.5	-284.6		
29e	4-NO_2-Ph	nd	-294.6	-284.4		nd
29f	Acr	-280.2	-291.2	-280.0	nd	
Imidazolidine-2-thiones (Acr-CH(CH_3)-NPr-CS-NR-)						
35b	Ph	-231.6	-254.1	-284.1		
35c	4-CH_3O-Ph	-231.9	-255.6	-284.3		
35d	4-F-Ph	-232.9	-254.0	-284.1		
35e	4-NO_2-Ph	-232.9	-248.2	-283.5		-10.3
35e[a]	4-NO_2-Ph	-233.9	-248.7	-286.5		-11.2
Imidazolidine-2-thiones (Acr-CH_2-NBn-CS-NR-)						
28a	CH_3	-250.2	-269.4	-284.5		
28b	Ph	-219.6	-265.6	-284,1		
28c	4-CH_3O-Ph	-220.6	-266.7	-284.3		
28d	4-F-Ph	-221.2	-265.2	-284.1		
28e	4-NO_2-Ph	-222.3	-260.6	-284.0		-10.4
28f	Acr	-247.3	-259.3	-280.3	-70.0	
Imidazolidine-2-ones (Acr-CH_2-NBn-CO-NR-)						
30a	CH_3	-284.0	-299.6	-284.7		
30b	Ph	-255.1	-296.0	-284.7		
30c	4-CH_3O-Ph	nd	-297.3	-284.8		
30d	4-F-Ph	-255.6	-296.2	-284.7		
30e	4-NO_2-Ph	nd	-292.2	-284.3		nd
30f	Acr	-279.0	-287.8	-280.2	-70.6	

[a] In $CDCl_3$.

positive (deshielding) β-effect of methyl, while more distant N-1 signals were shifted upfield by about 11 ppm because of the negative (shielding) δ-effect of methyl of surprisingly large magnitude when compared with literature.[26]

The chemical shifts of nuclei of the 1-*N*-phenyl substituent nicely reflected different effects of the *para*-substituents as well as an effect coming from the spiro-dihydroacridine skeleton. To evaluate these effects, we calculated ^{13}C NMR increments of the spiro substituent on the carbon chemical shifts of the phenyl nuclei (Table 13), after discounting increment magnitudes of *para* substituents taken from the literature.[27]

We have found an interesting difference between the Z_{ortho} increments in the thiones **20**, **27**, **28** *versus* the ones **21**, **29**, **30**. While the values of Z_{ortho} in the thiones remained almost unchanged for particular *para* substitutents, for the ones we have observed a clear dependence on the Hammett constants σ_p of these substituents: the increments of the spiroskeleton decreased from 4-CH_3O (cca -4 ppm) to 4-NO_2 (-9 ppm) derivatives. This observation can be explained by a push-pull interaction between the spiroskeleton and the *para* substituents present within the molecule. This confirms a different type of cross-conjugation with thioureido *versus* ureido group: in the thiones, the electron pair of nitrogen N-1 is markedly involved in the cross-conjugation with the 2-C=S group, which worsens its interaction with the *para* substituent, thus, the shielding effect on *ortho* and *para* carbons is small and the push-pull effect is minimal, if any, here. This assumption is strongly supported by the above X-ray structure of **28e** with the orthogonal arrangement of imidazolidine *vs*. phenyl ring. The ring-opening of imidazolidin-2-ones **21** to ureas **22** is accompanied by a distinct increase of the shielding effect, especially on the *ortho* carbons.

All these observations elicit the question which is a driving force of spirocyclization in various acridine derivatives possessing the heteroatom moiety in the position 9. The comparison of spirocyclization course of mono- and bis-acridine derivatives, which were studied in this work, showed two different pathways. While mono acridines have only one target, the C-9 carbon of acridine, at which the spirocyclization aims (the classical pathway), bis-acridines possess two types of such carbons C-9 in two different acridine skeletons – one is attached to an amino group and the other to a methylene one.

The experimental result of this and the previous work[19] unequivocally showed that the attacking nucleophile of the bis-acridine substrate was the methylidene carbon and not the amino group, so this pathway can be taken as nonclassical way of spirocyclization, contrary to the classical way of spirocyclization, which was observed for phenyl derivatives **a**−**e**. For starting bis-thioureas **25f**, **26f** we did not observe any product of the classical way of spirocyclization. This indicates that nonclassical pathway of spirocyclization of bis-acridines is considerably faster and passess through a transient state with lower energy.

Moreover, as we have found, the solution of the spiroproduct, which had been prepared from bis-acridine and was let to stand in the NMR sample tube in DMSO-D_6 for a very long time, was not changed or decomposed. We can consider this product to be the most stable thermodynamic product. Another open question is a type of catalysis that stimulates the nonclassical way of spirocyclization. The autocatalysis mediated by a basic nitrogen of acridine seems to

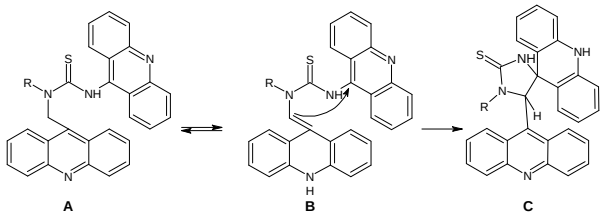
Table 13

Calculated increments Z_i of spiroskeletons on phenyl ^{13}C chemical shifts.

		Z_{ipso}	Z_{ortho}	Z_{meta}	Z_{para}
Imidazolidine-2-thiones (Acr-CH_2-NH-CS-NR-)					
20c	4-CH_3O-Ph	10.0	1.1	-1.3	-4.2
20b	Ph	8.8	0.4	-1.0	-2.1
20d	4-Br-Ph	10.2	0.1	-1.2	-3.6
20e	4-NO_2-Ph	10.3	-0.1	-0.7	-3.9
	Average:	9.8	0.4	-1.1	-3.5
Imidazolidine-2-thiones (Acr-CH_2-NPr-CS-NR-)					
27c	4-CH_3O-Ph	11.2	1.6	-0.7	-3.9
27b	Ph	10.9	1.2	-0.4	-1.5
27d	4-F-Ph	11.5	1.6	-0.5	-2.0
27e	4-NO_2-Ph	10.4	-0.5	-0.1	-2.5
	Average:	11.0	1.0	-0.4	-2.5
Imidazolidine-2-thiones (Acr-CH_2-NBn-CS-NR-)					
28c	4-CH_3O-Ph	11.1	1.6	-0.6	-3.8
28b	Ph	10.8	1.3	-0.3	-1.2
28d	4-F-Ph	11.4	1.7	-0.4	-1.1
28e	4-NO_2-Ph	11.2	0.0	0.1	-3.0
	Average:	11.1	1.2	-0.3	-2.3
Imidazolidine-2-ones (Acr-CH_2-NH-CO-NR-)					
21c	4-CH_3O-Ph	9.9	-3.9	-1.1	-6.5
21b	Ph	9.5	-5.7	-0.8	-5.6
21d	4-Br-Ph	10.0	-6.6	-1.2	-2.5
21e	4-NO_2-Ph	9.8	-9.2	0.0	-7.4
	Average:	9.8	-6.4	-0.8	-5.5
Imidazolidine-2-ones (Acr-CH_2-NPr-CO-NR-)					
29c	4-CH_3O-Ph	10.1	-3.8	-1.0	-6.4
29b	Ph	9.8	-5.7	-0.7	-5.5
29d	4-F-Ph	10.4	-5.0	-1.0	-4.0
29e	4-NO_2-Ph	10.0	-9.3	0.1	-7.3
	Average:	10.1	-6.0	-0.7	-5.8
Imidazolidine-2-ones (Acr-CH_2-NBn-CO-NR-)					
30c	4-CH_3O-Ph	10.5	-2.9	-0.4	-5.6
30b	Ph	10.1	-4.9	-0.1	-4.7
30d	4-F-Ph	10.7	-4.1	-0.3	-3.2
30e	4-NO_2-Ph	10.3	-8.6	0.6	-6.6
	Average:	10.4	-5.1	-0.1	-5.0
Ureas (Acr-CH_2-NH-CO-NR-)					
22b	Ph	11.5	-10.9	0.1	-7.3
22d	4-Br-Ph	11.9	-11.2	-0.5	-3.0
22e	4-NO_2-Ph	12.6	-12.0	2.0	-7.3
	Average:	12.0	-11.4	0.5	-5.9

be the most probable as it can tear off the acidic proton from the methylene group and form a stable carbanion strong enough to attack the aminoacridine C-9 carbon. There are two possibilities that nitrogen, which tears off or accepts a proton from CH_2, comes either from the same molecule or from the other one. In the first case, π-electrons of exocyclic double bond C-9=CH of the dihydrotautomeric form **B** (Scheme 8) attack the C-9 carbon of the aminoacridine to form the spirocycle on aminoacridine. The final step will be the proton transfer from NH-10 from one to other acridine nitrogen and restoration of the aromatic character of the methine-acridine ring. If an intermolecular catalysis is operating, several reaction pathways may come into account. The character of electrophilic C-9 carbon also plays an important role in this reaction. We suppose that C-9 of aminoacridine is a more electron-deficient carbon compared to C-9 of methylene-acridine because of a higher electronegativity of the neighbor nitrogen. Consequently, the CH-group as a stronger

nucleophile attacks the strongly electrophilic C-9 carbon of aminoacridine. The phenyl derivatives **a−e** possessing only the one acridine skeleton have the C-9 carbon electrophilic enough to react with the terminal amino-group of thioureas but the spirocyclization proceeds more slowly, because of lower mutual affinity of both centers.



Scheme 8. Possible tautomeric forms **A**, **B** of intermediate bisacridinyl-thioureas **25f**, **26f**.

The following conclusions can be made from observations in this work:

1. In series I, disubstituted thioureas **17a−f** were formed slowly and their change to spirocycles was finished in ca. two days.
2. Trisubstituted thioureas **25a−e**, **26a−e** of the series II with *n*-Pr and Bn substituents were formed very fast and they changed to spirocycles during 6 h. We did not observe any signals of the thiourea intermediates in the NMR spectra even 5 min after mixing the starting compounds.
3. Trisubstituted bis-acridinyl-thioureas **25f** and **26f** of the series III were formed even faster than **25a−e**, **26a−e**, because 9-isothiocyanatoacridine is more reactive than methyl and phenyl isothiocyanates. The change of thioureas to spiroproducts, in contrast to series II, proceeded through the non-classical way, which can be explained by the higher reactivity of CH-nucleophile and the higher electron dilution on the C-9 centre of aminoacridine.

3. Experimental section

3.1. General information and materials

NMR spectra were recorded at room temperature on a Varian Mercury Plus spectrometer operating at 400.13 MHz for ^{1}H, and 100.61 MHz for ^{13}C, and a spectrometer Varian VNMRS operating at 599.87 MHz for ^{1}H, 150.84 MHz for ^{13}C, and 60.79 MHz for ^{15}N. Spectra were recorded in DMSO-d_6 unless otherwise stated with an internal standard tetramethylsilane (TMS, 0.00 ppm). The 2D gCOSY, TOCSY, NOESY, gHSQC, gHMBC (optimised for a long-range coupling of 8 Hz), gH2BC, and gTOXY-HSQC methods were employed. For ^{15}N NMR measurements, gHSQC and gHMBC (optimised for a long-range coupling of 90 Hz) were used. Melting points were determined on a Boetius hot-stage apparatus and are uncorrected. Elemental analysis was performed on a Perkin-Elmer CHN 2400 elemental analyser. Mass spectra (MS) were measured on a MALDI-TOF IV instrument (Shimadzu, Kratos Analytical, England) in a positive matrix-assisted laser desorption/ionization coupled with in-source decay (ISD) combined with a time-of-flight analyzer. 2,5-Dihydroxybenzoic acid (DHB) was used as a matrix. The sample (1 mg) was dissolved in acetonitrile/water 1:1 (1 mL). For the spot preparation, a mixture of 1 μL of the matrix DHB with 10 pmol/μL analyte solution was used. The sample spots were air-dried at room temperature. Ion acceleration voltage was set to 5 kV. Samples were irradiated by 337 nm photons from a nitrogen laser. Typically, 100 shots were summed into a single mass spectrum. The reactions were monitored on pre-coated TLC-sheets ALUGRAM® SIL G/UV$_{254}$ (Macherey-Nagel, Germany). Preparative column chromatography was performed on silicagel Merck, 230–400 mesh. Quantum chemical calculations were carried out using the *Gaussian03* program. Infrared spectra were taken on an Avatar FT-IR 6700 spectrometer (Thermo Scientific, UK) using an attenuated total reflectance (ATR) method in the range of 4000 - 400 cm^{-1}.

The crystal structure was determined on an Oxford Diffraction Xcalibur2 diffractometer equipped with a Sapphire2 CCD detector. Crysalis CCD was used for data collection while Crysalis RED was used for the cell refinement, data reduction, and absorption correction.[28] The structure was solved by a direct method with SHELXS97 and subsequent Fourier syntheses using SHELXL97.[29] Anisotropic displacement parameters were refined for all non-H atoms. The H atoms were placed in calculated positions and refined riding on their parent C or N atoms with C–H distances of 0.93 and 0.97 Å for aromatic and methylene groups, respectively, and N–H distance of 0.86 Å. A geometric analysis was performed using SHELXL97. DIAMOND[30] was used for molecular graphics.

3.2. General procedure for the synthesis of 3-(acridin-9-ylmethyl)-1-alkyl/arylthioureas 17a–f and 1-alkyl/aryl-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones 20a–f

To an aqueous solution of 1-(acridine-9-yl)methanamine dihydrochloride (**15**.2HCl, 200 mg, 0.71 mmol), an aqueous solution of sodium carbonate (75 mg, 0.71 mmol) was added. The free amine **15** was extracted with dry benzene (3×10 mL), organic layers were combined, dried over magnesium sulfate, filtered, and evaporated to 5 mL. To this well stirred solution, isothiocyanate **16** (0.71 mmol) in 1–2 mL of dry benzene was added at once at room temperature. The mixture turned heterogeneous after a few min and the reaction course was followed by TLC (eluent: cyclohexane/ethyl acetate, 2:1) until completion. The precipitate was filtered off, washed with diethyl ether, dried, and crystallized from a mixture of dimethylformamide/methanol.

*3.2.1. 1-Methyl-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**20a**)*

Yield 138 mg, 69%. Bright yellow solid. Mp 230.0–231.0 °C. [Found: C 68.07; H 5.49; N 14.71; $C_{16}H_{15}N_3S$ (281.38) requires C 68.30; H 5.37; N 14.93%]; EI-MS (70eV): *m/z* (%) = 282 (MH^+, 100), 251 (64), 210 (7). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.98 (1H, s, NH-10'), 7.12 (2H, dd, *J* 8.0, 1.3 Hz, H-1',8'), 7.08 (2H, ddd, *J* 8.0, 7.2, 1.3 Hz, H-3',6'), 6.86 (1H, s, NH-3), 6.79 (2H, ddd, *J* 8.0, 7.2, 1.2 Hz, H-2',7'), 6.77 (2H, dd, *J* 8.0, 1.2 Hz, H-4',5'), 3.68 (2H, s, H-4), 2.71 (3H, s, Me); ^{1}H NMR (600 MHz, DMSO): δ_H = 9.40 (s, 1H, NH-1), 8.39 (s, 1H, NH-3), 7.36 (2H, ddd, *J* 8.4, 7.2, 1.2 Hz, H-3',6'), 7.09 (2H, dd, *J* 8.4, 1.2 Hz, H-1',8'), 6.91 (2H, ddd, *J* 8.4, 6.6, 1.2 Hz, H-2',7'), 6.90 (2H, dd, *J* 8.4, 1.2 Hz, H-4',5'), 3.62 (2H, s, H-4), 2.61 (3H, s, Me).

*3.2.2. 1-Phenyl-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**20b**)*

Yield 139 mg, 57%. Bright yellow solid. Mp 155.0–157.0 °C. [Found: C 73.20; H 5.22; N 12.08; $C_{21}H_{17}N_3S$ (343.45) requires C 73.44; H 4.99; N 12.33 %]; ν_{max} 3261, 1667, 1612, 1583, 1486, 1417, 1342, 1319, 1222, 1191, 1051, 985, 743, 694, 622, 540, 509 cm^{-1}; ^1H NMR (400 MHz) δ_H = 9.22 (1H, s, NH-10'), 8.86 (1H, s, NH-3), 7.54 (2H, d, *J* 8.0 Hz, H-1',8'), 7.19 (2H, ddd, *J* 8.0, 7.4, 0.6 Hz, H-3',6'), 6.98–7.02 (3H, m, H-3",5", and H-4"), 6.96 (2H, ddd, *J* 8.0, 7.6, 0.6 Hz, H-2',7'), 6.75 (2H, d, *J* 8.0 Hz, H-4',5'), 6.50–6.57 (2H, m, H-2",6"), 4.14 (2H, s, H-4).

*3.2.3. 1-(4''-Methoxyphenyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**20c**)*

Yield 170 mg, 64%. Bright yellow solid. Mp 197.0–200.0 °C. [Found: C 70.66; H 4.98; N 11.09; $C_{22}H_{19}N_3OS$ (373.47) requires C 70.75; H 5.13; N 11.25%]; ^1H NMR (400 MHz) δ_H = 8.99 (1H, s, NH-10'), 8.56 (1H, s, NH-3), 7.60 (2H, dd, *J* 7.6, 1.2 Hz, H-1',8'), 7.16 (2H, ddd, *J* 8.4, 7.6, 1.2 Hz, H-3',6'), 6.95 (2H, ddd, *J* 8.4, 7.6, 1.2 Hz, H-2',7'), 6.74 (2H, dd, *J* 8.4, 1.2 Hz, H-4',5'), 6.47–6.50 (2H, m, H-3",5"), 6.40–6.45 (2H, m, H-2",6"), 4.25 (2H, s, H-4), 3.61 (3H, s, MeO).

*3.2.4. 1-(4''-Bromophenyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**20d**)*

Yield 213 mg, 71%. Beige solid. Mp 190.0–191.0 °C. [Found: C 59.53; H 3.90; N 9.78; $C_{21}H_{16}BrN_3S$ (422.34) requires C 59.72; H 3.82; N 9.92%]; EI-MS (70eV): *m/z* (%) = 422 (MH^+, 100), 389 (6), 344 (12), 209 (23), 195 (14); ν_{max} 3399, 3184, 1613, 1583, 1511, 1486, 1407, 1191, 1010, 744, 620, 543, 447 cm^{-1}; ^1H NMR (400 MHz) δ_H = 9.29 (1H, s, NH-10'), 9.00 (1H, s, NH-3), 7.51 (2H, d, *J* 7.8 Hz, H-1',8'), 7.16–7.26 (4H, m, H-3',6',3",5"), 7.00 (2H, t, *J* 7.8 Hz, H-2',7'), 6.77 (2H, d, *J* 8.0 Hz, H-4',5'), 6.48 (2H, d, *J* 8.8 Hz, H-2",6"), 4.15 (2H, s, H-4).

*3.2.5. 1-(4''-Nitrophenyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**20e**)*

Yield 177 mg, 64%. Yellow solid. Mp 185.0–187.0 °C. [Found: C 65.01; H 4.00; N 14.27; $C_{21}H_{16}N_4O_2S$ (388.44) requires C 64.93; H 4.15; N 14.42%]; ν_{max} 3438, 3351, 1555, 1505, 1332, 1256, 846, 755 cm^{-1}; ^1H NMR (400 MHz) δ_H = 9.42 (1H, s, NH-10'), 9.36 (1H, s, NH-3), 7.94 (2H, dd, *J* 8.8, 1.6 Hz, H-3",5"), 7.44 (2H, d, *J* 8.0 Hz, H-1',8'), 7.22 (2H, ddd, *J* 8.0, 7.2, 1.6 Hz, H-3',6'), 7.04 (2H, dd, *J* 8.8, 1.6 Hz, H-2",6"), 6.93 (2H, dd, *J* 7.2, 1.6 Hz, H-2',7'), 6.84 (2H, d, *J* 8.0 Hz, H-4',5'), 4.08 (2H, s, H-4).

*3.2.6. 1-Allyl-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**20f**)*

Yield 140 mg, 64%. Bright yellow solid. Mp 156.0–158.0 °C. [Found: C 70.09; H 5.32; N 13.45; $C_{18}H_{17}N_3S$ (307.41) requires C 70.33; H 5.57; N 13.67%]; ν_{max} 3319, 3241, 1541, 1369, 1245, 914, 734 cm^{-1}; ^1H NMR (400 MHz) δ_H = 9.45 (1H, s, NH-10'), 8.49 (1H, s, NH-3), 7.18–7.28 (4H, m, H-1',8',3',6'), 6.84–6.94 (4H, m, H-2',7',4',5'), 5.31 (1H, ddd, *J* 17.2, 10.4, 6.0 Hz, H-2"), 4.62 (1H, dd, *J* 17.2, 1.6 Hz, H_{trans}-3"), 4.59 (1H, dd, *J* 10.4, 1.6 Hz, H_{cis}-3"), 3.87 (2H, s, H-4), 3.74 (2H, d, *J* 6.0 Hz, H-1").

3.3. General procedure for the synthesis of 1-alkyl/aryl-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-ones 21a–f and 3-(acridin-9-ylmethyl)-1-(4''-X-phenyl)ureas 22b–e

To a solution of 1-alkyl/aryl-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones **20a**–**f** (0.15 mmol) in dry tetrahydrofuran (5 mL), mesitylnitrile oxide (24 mg, 0.15 mmol) was added at once and the reaction mixture was left to stir at room temperature for 6 h under TLC monitoring (cyclohexane/ethyl acetate, 2:1). After completion of the reaction, the precipitated product was filtered off, washed with diethyl ether, dried, and crystallized from a mixture of dimethylformamide/methanol.

*3.3.1. 1-Methyl-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**21a**)*

Yield 25 mg, 63%. Yellow solid. Mp 234.0–236.0 °C. [Found: C 72.68; H 5.90; N 15.49; $C_{16}H_{15}N_3O$ (265.31) requires C 72.43; H 5.70; N 15.84%]; ν_{max} 3335, 1682, 1620, 1580, 1480, 1325, 1250, 755 cm^{-1}; ^1H NMR (400 MHz) δ_H = 9.30 (1H, s, NH-10'), 7.17–7.23 (4H, m, 1',8',3',6'), 6.88–6.95 (4H, m, H-2',7',4',5'), 6.58 (1H, s, NH-3), 3.37 (2H, s, H-4), 2.36 (3H, s, Me).

*3.3.2. 1-Phenyl-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**21b**), 3-(acridin-9-ylmethyl)-1-phenylurea (**22b**)*

Yield 44 mg, 90%. White solid. [Found: C 76.82; H 5.51; N 12.64; $C_{21}H_{17}N_3O$ (327.38) requires C 77.04; H 5.23; N 12.84%]; ν_{max} 3326, 1676, 1615, 1520, 1490, 1445, 1330, 1241, 750 cm^{-1}; ^1H NMR (400 MHz, mixture of products, **21b**/**22b** = 1.12:1.0, for **21b**) δ_H = 9.34 (1H, s, NH-10'), 7.29 (2H, d, *J* 7.6 Hz, H-1',8'), 7.14–7.24 (3H, m, NH-3,3',6'), 7.00–7.06 (4H, m, H-2",6",3",5"), 6.80–6.92 (5H, m, H-4",4',5',2',7'), 3.57 (2H, s, H-4); (for **22b**) 8.59 (2H, d, *J* 8.8 Hz, H-1',8'), 8.32 (1H, s, NH-1), 8.19 (2H, d, *J* 8.8 Hz, H-4',5'), 7.88 (2H, dd, *J* 8.0, 1.2 Hz, H-3',6'), 7.71 (2H, dd, *J* 8.0, 1.2 Hz, H-2',7'), 7.36 (2H, d, *J* 8.0 Hz, H-2",6"), 7.14–7.24 (2H, m, H-3",5"), 6.80–6.92 (1H, m, H-4"), 5.36 (2H, d, *J* 5.6 Hz, H-4).

*3.3.3. 1-(4''-Methoxyphenyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**21c**), 3-(acridin-9-ylmethyl)-1-(4-methoxyphenyl)urea (**22c**)*

Yield 27 mg, 50%. Bright yellow solid. [Found: C 73.77; H 5.44; N 11.74; $C_{22}H_{19}N_3O_2$ (357.41) requires C 73.93; H 5.36; N 11.76%]; ν_{max} 3290, 1671, 1610, 1580, 1485, 1450, 1335, 1242, 750 cm^{-1}; ^1H NMR (400 MHz, mixture of products, **21c**/**22c** = 24.0:1.0, for **21c**) δ_H = 9.27 (1H, s, NH-10'), 7.38 (2H, d, *J* 7.6 Hz, H-1',8'), 7.16 (2H, dd, *J* 8.0, 7.6 Hz, H-3',6'), 7.05 (1H, s, NH-3), 6.86 (2H, t, *J* 7.6 Hz, H-2',7'), 6.82 (2H, d, *J* 8.0 Hz, H-4',5'), 6.76 (2H, d, *J* 8.8 Hz, H-2",6"), 6.59 (2H, d, *J* 8.8 Hz, H-3",5"), 3.64 (2H, s, H-4), 3.57 (3H, s, MeO); (for **22c**) 8.57 (2H, dd, *J* 9.0, 1.2 Hz, H-1',8'), 8.16 (2H, dd, *J* 9.0, 1.8 Hz, H-4',5'), 8.10 (1H, s, NH-1), 7.85 (2H, ddd, *J* 9.0, 6.6, 1.2 Hz, H-3',6'), 7.68 (2H, ddd, *J* 8.4, 6.6, 1.8 Hz, H-2',7'), 7.24 (2H, d, *J* 9.0 Hz, H-2",6"), 6.77 (2H, d, *J* 9.0 Hz, H-3",5"), 6.70 (1H, t, *J* 6.0 Hz, NH-3), 5.32 (2H, d, *J* 6.0 Hz, H-4), 3.66 (3H, s, MeO).

*3.3.4. 1-(4''-Bromophenyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**21d**), 3-(acridin-9-ylmethyl)-1-(4-bromophenyl)urea (**22d**)*

Yield 34 mg, 56%. Yellow solid. [Found: C 62.02; H 3.76; N 10.15; $C_{21}H_{16}BrN_3O$ (406.28) requires C 62.08; H 3.97; N 10.34%]; ν_{max} 3300, 1673, 1615, 1585, 1490, 1450, 1325, 1238, 755 cm^{-1}; ^1H NMR (400 MHz, mixture of products, **21d**/**22d** = 4.9:1.0, for **21d**) δ_H = 9.39 (1H, s, NH-10'), 7.35 (1H, s, NH-3), 7.23 (2H, dd, *J* 7.6, 1.0 Hz, H-1',8'), 7.22 (2H, d, *J* 7.2 Hz, H-3",5"), 7.18 (2H, ddd, *J* 8.2, 6.6, 1.0 Hz, H-3',6'), 7.02 (2H, d, *J* 7.2 Hz, H-2",6"), 6.89 (2H, d, *J* 8.2 Hz, H-4',5'), 6.83 (2H, dd, *J* 7.6, 6.6 Hz, H-2',7'), 3.54 (2H, s, H-4); (for

22d) 8.60 (2H, d, *J* 8.4 Hz, H-1',8'), 8.48 (1H, s, NH-1), 8.19 (2H, d, *J* 8.4 Hz, H-4',5'), 7.90 (2H, dd, *J* 8.4, 7.6 Hz, H-3',6'), 7.72 (2H, dd, *J* 8.4, 7.6 Hz, H-2',7'), 7.32–7.38 (4H, m, H-2'',6'',3'',5''), 5.36 (2H, d, *J* 5.6 Hz, H-4).

*3.3.5. 1-(4''-Nitrophenyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**21e**), 3-(acridin-9-ylmethyl)-1-(4-nitrophenyl)urea (**22e**)*

Yield 33 mg, 59%. Yellow solid. [Found: C 67.81; H 4.39; N 14.81; $C_{21}H_{16}N_4O_3$ (372.38) requires C 67.73; H 4.33, N 15.05 %]; ν_{max} 3290, 1610, 1595, 1480, 1420, 1320, 1249, 750 cm^{-1}; ^1H NMR (400 MHz, mixture of products, **21e**/**22e** = 99.0:1.0, for **21e**) δ_H = 9.53 (1H, s, NH-10'), 7.95 (2H, d, *J* 9.2 Hz, H-3'',5''), 7.76 (1H, s, NH-3), 7.46 (2H, d, *J* 9.2 Hz, H-2'',6''), 7.20 (2H, dd, *J* 8.0, 6.6 Hz, H-3',6'), 7.16 (2H, d, *J* 8.0 Hz, H-1',8'), 6.95 (2H, d, *J* 8.0 Hz, H-4',5'), 6.83 (2H, dd, *J* 8.0, 6.6 Hz, H-2',7'), 3.54 (2H, s, H-4); (for **22e**) 9.09 (1H, s, NH-1), 8.57 (2H, d, *J* 8.4 Hz, H-1',8'), 8.17 (2H, d, *J* 9.0 Hz, H-4',5'), 8.11 (2H, d, *J* 9.0 Hz, H-3'',5''), 7.86 (2H, dd, *J* 9.0, 6.6 Hz, H-3',6'), 7.70 (2H, dd, *J* 8.4, 6.6 Hz, H-2',7'), 7.58 (2H, d, *J* 9.0 Hz, H-2'',6''), 7.16 (1H, t, *J* 6.0 Hz, NH-3), 5.37 (2H, d, *J* 6.0 Hz, H-4).

*3.3.6. 1-Allyl-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**21f**)*

Yield 33 mg, 76%. White solid. Mp 207.0–208.0 °C. [Found: C 74.07; H 6.10; N 14.19; $C_{18}H_{17}N_3O$ (291.35): requires C 74.20; H 5.88; N 14.42%]; ν_{max} 3340, 1625, 1580, 1455, 1245, 755 cm^{-1}; ^1H NMR (400 MHz) δ_H = 9.31 (1H, s, NH-10'), 7.32 (2H, dd, *J* 8.2, 1.2 Hz, H-1',8'), 7.19 (2H, ddd, *J* 8.2, 7.6, 1.2 Hz, H-3',6'), 6.88 (2H, ddd, *J* 8.2, 7.6, 1.2 Hz, H-2',7'), 6.85 (2H, dd, *J* 8.2, 1.2 Hz, H-4',5'), 6.67 (1H, s, NH-3), 5.35 (1H, ddt, *J* 17.2, 10.4, 6.0 Hz, H-2''), 4.71 (1H, ddt, *J* 17.2, 1.6, 1.4 Hz, H_{trans}-3''), 4.66 (1H, ddt, *J* 10.4, 1.6, 1.4 Hz, H_{cis}-3''), 3.55 and 3.57 (2H, AB quartet, *J* 11.2 Hz, H-4), 3.39 (2H, ddd, *J* 6.0, 1.4, 1.4 Hz, H-1'').

3.4. General procedure for the synthesis of 1-alkyl/aryl-3-(*n*-propyl)-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones 27a–e and 4-(acridin-9'''-yl)-3-(*n*-propyl)-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thione (27f)

To a stirred solution of *N*-(acridin-9-ylmethyl)propan-1-amine (**23**, 200 mg, 0.8 mmol) in chloroform (3 mL), appropriate isothiocyanate (1.2 equiv, 0.96 mmol) in a chloroform solution (3 mL) was added at once. The reaction mixture was stirred at room temperature for 6 h. The reaction mixture turned heterogenous after few min and the spiroproduct that precipitated was filtered off, washed with diethyl ether, dried, and crystallized from the a mixture of chloroform/diethyl ether or from chloroform/*n*-heptane (**f**).

*3.4.1. 1-Methyl-3-(n-propyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**27a**)*

Yield 182 mg, 70%. Yellow solid. Mp 226.0–227.0 °C. [Found: C 70.45; H 6.40; N 13.08; $C_{19}H_{21}N_3S$ (323.46) requires C 70.55; H 6.54; N 12.99%]; ν_{max} 3250, 1612, 1584, 1485, 1330, 1252, 1128, 741, 609, 522 cm^{-1}; ^1H NMR (600 MHz) δ_H = 9.42 (1H, s, NH-10'), 7.22 (2H, ddd, *J* 8.0, 7.2, 1.5 Hz, H-3',6'), 7.04 (2H, dd, *J* 8.1, 1.5 Hz, H-1',8'), 6.89–6.92 (4H, m, H-2',7',4',5'), 3.73 (2H, s, H-4), 3.57 (2H, t, *J* 7.2 Hz, H-1''), 2.65 (1H, s, Me), 1.50–1.54 (2H, m, H-2''), 0.83 (3H, t, *J* 7.2 Hz, H-3'').

*3.4.2. 1-Phenyl-3-(n-propyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**27b**)*

Yield 207 mg, 67%. Light brown solid. Mp 257.0–258.0 °C. [Found: C 74.59; H 6.15; N 11.08; $C_{24}H_{23}N_3S$ (385.54) requires C 74.77; H 6.01; N 10.90%]; ν_{max} 3244, 1615, 1584, 1507, 1486, 1397, 1334, 1248, 1143, 896, 737, 696, 628, 538 cm^{-1}; ^1H NMR (600 MHz) δ_H = 9.21 (1H, s, NH-10'), 7.45 (2H, dd, *J* 7.8, 1.5 Hz, H-1',8'), 7.17 (2H, ddd, *J* 8.1, 7.2, 1.5 Hz, H-3',6'), 6.97–7.00 (3H, m, H- 3''',4''',5'''), 6.94 (2H, ddd, *J* 7.8, 7.2, 0.9 Hz, H-2',7'), 6.72 (2H, dd, *J* 8.1, 0.9 Hz, H-4',5'), 6.48–6.50 (2H, m, H-2''',6'''), 4.26 (2H, s, H-4), 3.74 (2H, t, *J* 7.2 Hz, H-1''), 1.67–1.73 (2H, m, H-2''), 0.96 (3H, t, *J* 7.8 Hz, H-3'').

*3.4.3. 1-(4'''-Methoxyphenyl)-3-(n-propyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**27c**)*

Yield 188 mg, 57%. Light brown solid. Mp 199.0–200.0 °C. [Found: C 72.01; H 6.00; N 10.30; $C_{25}H_{25}N_3OS$ (415.55) requires C 72.26; H 6.06; N 10.11%]; ν_{max} 3244, 1613, 1584, 1509, 1486, 1451, 1374, 1326, 1249, 1128, 1028, 822, 746, 530, 520 cm^{-1}; ^1H NMR (600 MHz) δ_H = 9.19 (1H, s, NH-10'), 7.45 (2H, dd, *J* 8.7, 1.2 Hz, H-1',8'), 7.18 (2H, ddd, *J* 7.8, 7.8, 1.2 Hz, H-3',6′), 6.95 (2H, ddd, *J* 8.7, 7.8, 1.2 Hz, H-2',7'), 6.72 (2H, dd, *J* 7.8, 1.2 Hz, H-4',5'), 6.52–6.54 (2H, m, H-3''',5'''), 6.30–6.34 (2H, m, H-2''',6'''), 4.27 (2H, s, H-4), 3.73 (2H, t, *J* 7.8 Hz, H-1''), 3.57 (3H, s, MeO), 1.69–1.72 (2H, m, H-2''), 0.96 (3H, t, *J* 7.2 Hz, H-3'').

*3.4.4. 1-(4'''-Fluorophenyl)-3-(n-propyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**27d**)*

Yield 135 mg, 42%. White solid. Mp 234.0–235.0 °C. [Found: C 71.24; H 5.77; N 10.38; $C_{24}H_{22}FN_3S$ (403.51) requires C 71.44; H 5.50; N 10.41%]; ν_{max} 3261, 1613, 1584, 1508, 1486, 1386, 1343, 1332, 1250, 1135, 757, 629, 542, 471 cm^{-1}; ^1H NMR (600 MHz) δ_H = 9.23 (1H, s, NH-10'), 7.46 (2H, dd, *J* 8.4, 1.5 Hz, H-1',8'), 7.19 (2H, ddd, *J* 8.1, 6.9, 1.5 Hz, H-3',6'), 6.95 (2H, ddd, *J* 8.4, 6.9, 1.2 Hz, H-2',7'), 6.82–6.86 (2H, m, H-3''',5'''), 6.73 (2H, dd, *J* 8.1, 1.2 Hz, H-4',5'), 6.42–6.45 (2H, m, H-2''',6'''), 4.30 (2H, s, H-4), 3.74 (2H, t, *J* 7.2 Hz, H-1''), 1.69–1.74 (2H, m, H-2''), 0.96 (3H, t, *J* 7.2 Hz, H-3'').

*3.4.5. 1-(4'''-Nitrophenyl)-3-(n-propyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**27e**)*

Yield 293 mg, 85%. Yellow solid. Mp 268.0–269.0 °C. [Found: C 66.94; H 5.07; N 13.14; $C_{24}H_{22}N_4O_2S$ (430.52) requires C 66.96; H 5.15; N 13.01%]; ν_{max} 3290, 1607, 1583, 1501, 1486, 1455, 1342, 1248, 1135, 847, 755, 739, 692, 538 cm^{-1}; ^1H NMR (600 MHz) δ_H = 9.42 (1H, s, NH-10'), 7.90–7.94 (2H, m, H-3''',5'''), 7.38 (2H, dd, *J* 8.4, 1.5 Hz, H-1',8'), 7.21 (2H, ddd, *J* 9.0, 8.4, 1.5 Hz, H-3',6'), 6.99–7.01 (2H, m, H-2''',6'''), 6.93 (2H, ddd, *J* 8.4, 1.2 Hz, H-2',7'), 6.84 (2H, dd, *J* 9.0, 1.2 Hz, H-4',5'), 4.23 (2H, s, H-4), 3.76 (2H, t, *J* 7.8 Hz, H-1''), 1.68–1.72 (2H, m, H-2''), 0.95 (3H, t, *J* 7.8 Hz, H-3'').

*3.4.6. 4-(Acridin-9'''-yl)-3-(n-propyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**27f**)*

Yield 257 mg, 66%. Yellow solid. Mp 252.0–253.0°C. [Found: C 76.20; H 5.25; N 11.32; $C_{31}H_{26}N_4S$ (486.63) requires C 76.51; H 5.39; N 11.51%]; ν_{max} 3263, 1612, 1583, 1474, 1438, 1327, 1206, 1145, 880, 741, 739, 658, 550, 468 cm^{-1}; ^1H NMR

(600 MHz) δ_H = 9.95 (1H, s, NH-1), 8.83 (1H, s, NH-10'), 8.13 (1H, dd, *J* 9.0 Hz, H-1'"), 7.97 (1H, dd, *J* 9.0, 1.8 Hz, H-4'"), 7.94 (1H, dd, *J* 9.0, 0.6 Hz, H-5'"), 7.66–7.70 (2H, m, H-3'",6'"), 7.62 (1H, dd, *J* 7.8, 1.2 Hz, H-1'), 7.44–7.61 (2H, m, H-2'",8'"), 7.29–7.33 (2H, m, H-3',7'"), 7.12–7.15 (2H, m, H-2',8'), 6.81 (1H, dd, *J* 7.8, 1.2 Hz, H-4'), 6.54 (1H, ddd, *J* 8.1, 7.2, 1.2 Hz, H-6'), 6.20 (1H, ddd, *J* 8.1, 7.2, 0.9 Hz, H-7'), 6.11 (1H, dd, *J* 8.1, 0.9 Hz, H-5'), 6.01 (1H, s, H-4), 4.12–4.17 (1H, m, H-1"a), 2.36–2.41 (1H, m, H-1"b), 1.20–1.30 (2H, m, H-2"), 0.63 (3H, t, *J* 7.8 Hz, H-3").

3.5. General procedure for the synthesis of 1-alkyl/aryl-3-benzyl-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones 28a–e and 4-(acridin-9'''-yl)-3-benzyl-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thione (28f)

To a well stirred solution of *N*-(acridin-9-ylmethyl)benzylamine (**24**, 200 mg, 0.67 mmol) in chloroform (3 mL) at room temperature, an appropriate isothiocyanate (1.20 equiv, 0.80 mmol) in dry chloroform (3 mL) was added at once. The reaction mixture turned heterogenous after few min and the spiroproduct that precipitated was filtered off, washed with diethyl ether, dried, and crystallized from a mixture of chloroform/diethyl ether or chloroform/n-heptane (**f**).

*3.5.1. 3-Benzyl-1-methyl-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**28a**)*

Yield 149 mg, 60%. Light yellow solid. Mp 208.0–210.0 °C. [Found: C 74.16; H 5.93; N 11.13; $C_{23}H_{21}N_3S$ (371.50) requires C 74.36; H 5.70; N 11.31%]; ν_{max} 3278, 1612, 1583, 1518, 1483, 1450, 1383, 1320, 1255, 1239, 1155, 1090, 937, 893, 746, 729, 524, 451 cm^{-1}; ^1H NMR (600 MHz) δ_H = 9.43 (1H, s, NH-10'), 7.32–7.36 (4H, m, H-2",6",3",5"), 7.25–7.28 (1H, m, H-4"), 7.21 (2H, ddd, *J* 8.4, 7.8, 1.5 Hz, H-3',6'), 7.01 (2H, dd, *J* 8.7, 1.5 Hz, H-1',8'), 6.90 (2H, dd, *J* 8.4, 1.2 Hz, H-4',5'), 6.88 (2H, ddd, *J* 8.7, 7.8, 1.2 Hz, H-2',7'), 4.89 (2H, s, NCH_2), 3.62 (2H, s, H-4), 2.71 (3H, s, Me).

*3.5.2. 3-Benzyl-1-phenyl-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**28b**)*

Yield 174 mg, 60%. Light brown solid. Mp 223.0–224.0 °C. [Found: C 77.41; H 5.47; N 9.49; $C_{28}H_{23}N_3S$ (433.57) requires C 77.57; H 5.35; N 9.69%]; ν_{max} 3301, 1611, 1582, 1517, 1484, 1432, 1310, 1220, 746, 693, 525 cm^{-1}; ^1H NMR (600 MHz) δ_H = 9.20 (1H, s, NH-10'), 7.52 (2H, d, *J* 7.2 Hz, H-2",6"), 7.42–7.45 (2H, m, H-3",5"), 7.36 (2H, d, *J* 7.8 1.2 Hz, H-1',8'), 7.34 (1H, t, *J* 8.4 Hz, H-4"), 7.16 (2H, dd, *J* 8.1, 1.2 Hz, H-3',6'), 7.00–7.05 (3H, m, H-3'",4'",5'"), 6.89 (2H, ddd, *J* 7.8, 1.2 Hz, H-2',7'), 6.70 (2H, dd, *J* 8.1, 1.2 Hz, H-4',5'), 6.49–6.51 (2H, m, H-2'",6'"), 5.07 (2H, s, NCH_2), 4.15 (2H, s, H-4).

*3.5.3. 3-Benzyl-1-(4'''-methoxyphenyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**28c**)*

Yield 153 mg, 49%. Light brown solid. Mp 262.0–263.0 °C. [Found: C 75.20; H 5.77; N 8.95; $C_{29}H_{25}N_3OS$ (463.59) requires C 75.13; H 5.44; N 9.06%]; ν_{max} 3262, 1610, 1583, 1511, 1485, 1441, 1399, 1329, 1240, 1030, 755, 629, 519, 455 cm^{-1}; ^1H NMR (600 MHz) δ_H = 9.17 (1H, s, NH-10'), 7.50 (2H, d, *J* 7.5 Hz, H-2",6"), 7.43 (2H, m, H-3",5"), 7.34 (2H, dd, *J* 7.8, 1.2 Hz, H-1',8'), 7.32–7.34 (1H, m, H-4"), 7.15 (2H, ddd, *J* 8.4, 7.2, 1.2 Hz, H-3',6'), 6.88 (2H, ddd, *J* 7.8, 7.2, 1.5 Hz, H-2',7'), 6.68 (2H, dd, *J* 8.4, 1.5 Hz, H-4',5'), 6.53–6.56 (2H, m, H-3'",5'"), 6.32–6.35 (2H, m, H-2'",6'"), 5.04 (2H, s, NCH_2), 4.13 (2H, s, H-4), 3.58 (3H, s, MeO).

*3.5.4. 3-Benzyl-1-(4'''-fluorophenyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**28d**)*

Yield 163 mg, 54%. Yellow solid. Mp 272.0–273.0 °C. [Found: C 74.63; H 5.12; N 9.04; $C_{28}H_{22}FN_3S$ (451.56) requires C 74.48; H 4.91; N 9.31%]; ν_{max} 3261, 1614, 1584, 1487, 1450, 1393, 1329, 1260, 1151, 1065, 756, 634, 526, 468 cm^{-1}; ^1H NMR (600 MHz) δ_H = 9.21 (1H, s, NH-10'), 7.50–7.52 (2H, m, H-2",6"), 7.41–7.44 (2H, m, H-3",5"), 7.34–7.36 (3H, m, H-1',8',4"), 7.16 (2H, ddd, *J* 7.8, 7.2, 1.2 Hz, H-3',6'), 6.84–6.90 (4H, m, H-2',7',3'",5'"), 6.70 (2H, dd, *J* 7.8, 1.2 Hz, H-4',5'), 6.42–6.46 (2H, m, H-2'",6'"), 5.05 (2H, s, NCH_2), 4.17 (2H, s, H-4).

*3.5.5. 3-Benzyl-1-(4'''-nitrophenyl)-spiro[dihydroacridine-9´(10'H),5-imidazolidine]-2-thione (**28e**)*

Yield 167 mg, 52%. Yellow solid. Mp 273.0–274.0 °C. [Found: C 70.08; H 4.45; N 11.51; $C_{28}H_{22}N_4O_2S$ (478.56) requires C 70.27; H 4.63; N 11.71%]; ν_{max} 3279, 1607, 1486, 1452, 1388, 1344, 1236, 1192, 1063, 943, 848, 760, 696, 632, 532 cm^{-1}; ^1H NMR (600 MHz) δ_H = 9.36 (1H, s, NH-10'), 7.91–7.94 (2H, m, H-3'",5'"), 7.49 (2H, dd, *J* 8.1, 1.2 Hz, H-2",6"), 7.39–7.42 (2H, m, H-3",5"), 7.31–7.34 (1H, m, H-4"), 7.29 (2H, dd, *J* 8.4, 1.2 Hz, H-1',8'), 7.17 (2H, ddd, *J* 8.4, 7.2, 1.2 Hz, H-3',6'), 6.94–6.96 (2H, m, H-2'",6'"), 6.86 (2H, dd, *J* 8.4, 7.2, 1.2 Hz, H-2',7'), 6.77 (2H, dd, *J* 8.4, 1.2 Hz, H-4',5'), 5.06 (2H, s, NCH_2), 4.10 (2H, s, H-4).

*3.5.6. 4-(Acridin-9'''-yl)-3-benzyl-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**28f**)*

Yield 129 mg, 36%. Yellow solid. Mp 227.0–228.0 °C. [Found: C 78.60; H 4.99; N 10.57; $C_{35}H_{26}N_4S$ (534.67) requires C 78.62; H 4.90; N 10.48%]; ν_{max} 3419, 3269, 1608, 1582, 1474, 1440, 1363, 1330, 1230, 1177, 1050, 759, 741, 513, 459, 420 cm^{-1}; ^1H NMR (600MHz) δ_H = 10.19 (1H, s, NH-1), 8.72 (1H, s, NH-10'), 8.27 (1H, dd, *J* 7.8, 1.2 Hz, H-1'"), 7.95–7.99 (2H, m, H-4'",5'"), 7.73 (1H, ddd, *J* 8.4, 6.6, 1.2 Hz, H-3'"), 7.63 (1H, ddd, *J* 8.4, 6.6, 1.2 Hz, H-6'"), 7.51–7.55 (2H, m, H-1',2'"), 7.22–7.26 (2H, m, H-3',8'), 7.15–7.02 (5H, m, H-2',3",4",5",7'"), 6.89 (2H, d, *J* 7.2 Hz, H-2",6"), 6.85 (1H, d, *J* 9.0 Hz, H-8'"), 6.70 (1H, dd, *J* 8.4, 1.5 Hz, H-4'), 6.57 (1H, ddd, *J* 7.8, 7.5, 1.5 Hz, H-6'), 6.27 (1H, ddd, *J* 8.5, 7.5, 1.5 Hz, H-7'), 6.08 (1H, dd, *J* 7.8, 1.5 Hz, H-5'), 5.77 (1H, d, *J* 15.0 Hz, NCH_a), 5.65 (1H, s, H-4), 3.41 (1H, d, *J* 15.0 Hz, NCH_b).

3.6. General procedure for the synthesis of 1-alkyl/aryl-3-(*n*-propyl)-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-ones 29a–e and 4-(acridin-9'''-yl)-3-(*n*-propyl)-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-one (29f)

To a solution of 1-alkyl/aryl-3-(*n*-propyl)-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones **27a–f** (0.26 mmol) in dry acetonitrile (5 mL), mesitylnitrile oxide (42 mg, 0.26 mmol) was added at once and the reaction mixture was stirred at room temperature for 6 h. The reaction was followed by TLC (petrolether/ethyl acetate, 2:1). After its completion, the product was filtered off, washed with petrolether, dried, and crystallized from a mixture of chloroform/diethyl ether or chloroform/*n*-heptane (**f**).

*3.6.1. 1-Methyl-3-(n-propyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**29a**)*

Yield 64 mg, 80%. Light brown solid. Mp 209.0–210.0 °C. [Found: C 74.03; H 6.72; N 13.45; $C_{19}H_{21}N_3O$ (307.39) requires C 74.24; H 6.89; N 13.67%]; ν_{max} 3283, 1671, 1616, 1585, 1480, 1452, 1335, 1238, 1036, 986, 892, 742, 711, 623, 476, 423 cm^{-1}; ^1H NMR (600 MHz) δ_H = 9.30 (1H, s, NH-10'), 7.19 (2H, ddd, *J* 8.1, 7.2, 1.2 Hz, H-3',6'), 7.14 (2H, dd, *J* 7.8, 1.2 Hz, H-1',8'), 6.87–6.90 (4H, m, H-2',7',4',5'), 3.36 (2H, s, H-4), 3.11 (2H, t, *J* 7.2 Hz, H-1"), 2.37 (3H, s, Me), 1.37–1.42 (2H, m, H-2"), 0.80 (3H, t, *J* 7.2 Hz, H-3").

*3.6.2. 1-Phenyl-3-(n-propyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**29b**)*

Yield 40 mg, 42%. Light brown solid. Mp 182.0–184.0 °C. [Found: C 78.13; H 6.45; N 11.20; $C_{24}H_{23}N_3O$ (369.46) requires C 78.02; H 6.27; N 11.37%]; ^1H NMR (600 MHz) δ_H = 9.35 (1H, s, NH-10'), 7.25 (2H, dd, *J* 8.4, 1.2 Hz, H-1',8'), 7.16 (2H, ddd, *J* 8.4, 7.2, 1.2 Hz, H-3',6'), 6.99–7.03 (4H, m, H-2'",6'",3'",5'"), 6.87 (2H, dd, *J* 8.4, 0.9 Hz, H-4',5'), 6.80–6.85 (1H, m, H-4'"), 6.82 (2H, ddd, *J* 8.4, 7.2, 0.9 Hz, H-2',7'), 3.62 (2H, s, H-4), 3.26 (2H, t, *J* 7.2 Hz, H-1"), 1.48–1.52 (2H, m, H-2"), 0.87 (3H, t, *J* 7.2 Hz, H-3").

*3.6.3. 1-(4'''-Methoxyphenyl)-3-(n-propyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**29c**)*

Yield 72 mg, 69%. Light brown solid. Mp 220.0–221.0 °C. [Found: C 75.08; H 6.20; N 10.32; $C_{25}H_{25}N_3O_2$ (399.48) requires C 75.16; H 6.31; N 10.52%]; ν_{max} 3301, 1674, 1615, 1585, 1510, 1480, 1426, 1342, 1244, 1198, 1034, 825, 749, 628, 588, 528 cm^{-1}; ^1H NMR (600 MHz) δ_H = 9.27 (1H, s, NH-10'), 7.35 (2H, dd, *J* 7.8, 1.2 Hz, H-1',8'), 7.14–7.17 (2H, m, H-3',6'), 6.84–6.87 (2H, m, H-2',7'), 6.82 (2H, dd, *J* 8.4, 1.2 Hz, H-4',5'), 6.74–6.76 (2H, m, H-2'",6'"), 6.57–6.60 (2H, m, H-3'",5'"), 3.69 (2H, s, H-4), 3.57 (3H, s, MeO), 3.26 (2H, t, *J* 7.2 Hz, H-1"), 1.50–1.55 (2H, m, H-2"), 0.89 (3H, t, *J* 7.2 Hz, H-3").

*3.6.4. 1-(4'''-Fluorophenyl)-3-(n-propyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**29d**)*

Yield 85 mg, 84 %. White solid. Mp 231.0–232.0 °C. [Found: C 74.20; H 5.99; N 10.74; $C_{24}H_{22}FN_3O$ (387.45) requires C 74.40; H 5.72; N 10.85%]; ν_{max} 3263, 1667, 1619, 1531, 1485, 1444, 1345, 1256, 1216, 1150, 1088, 831, 742, 696, 521, 499 cm^{-1}; ^1H NMR (600 MHz) δ_H = 9.35 (1H, s, NH-10'), 7.29 (2H, dd, *J* 8.4, 1.5 Hz, H-1',8'), 7.15–7.19 (2H, m, H-3',6'), 6.93–6.96 (2H, m, H-2'",6'"), 6.83–6.90 (6H, m, H-2',7', 4',5',3'",5'"), 3.67 (2H, s, H-4), 3.27 (2H, t, *J* 7.2 Hz, H-1"), 1.49–1.54 (2H, m, H-2"), 0.89 (3H, t, *J* 7.8 Hz, H-3").

*3.6.5. 1-(4'''-Nitrophenyl)-3-(n-propyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**29e**)*

Yield 55 mg, 51%. Yellow solid. Mp 192.0–193.0 °C. [Found: C 69.39; H 5.20; N 13.37; $C_{24}H_{22}N_4O_3$ (414.46) requires C 69.55; H 5.35; N 13.52%]; ^1H NMR (600 MHz) δ_H = 9.55 (1H, s, NH-10'), 7.93–7.95 (2H, m, H-3'",5'"), 7.46–7.49 (2H, m, H-2'",6'"), 7.20 (2H, ddd, *J* 8.1, 7.2, 1.5 Hz, H-3',6'), 7.12 (2H, dd, *J* 8.1, 1.5 Hz, H-1',8'), 6.99 (2H, dd, *J* 8.1, 1.2 Hz, H-4',5'), 6.81 (2H, ddd, *J* 8.1, 7.2, 1.2 Hz, H-2',7'), 3.60 (2H, s, H-4), 3.27 (2H, t, *J* 7.2 Hz, H-1"), 1.47–1.52 (2H, m, H-2"), 0.84 (3H, t, *J* 7.8 Hz, H-3").

*3.6.6. 4-(Acridin-9'''-yl)-3-(n-propyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**29f**)*

Yield 33 mg, 27%. Yellow solid. Mp 263.0–264.0 °C. [Found: C 78.88; H 5.24; N 11.70; $C_{31}H_{26}N_4O$ (470.56) requires C 79.12; H 5.57; N 11.91%]; ν_{max} 3265, 1680, 1615, 1584, 1521, 1474, 1408, 1378, 1329, 1154, 1078, 742, 631, 496 cm^{-1}; ^1H NMR (600 MHz) δ_H = 8.47 (1H, s, NH-10'"), 8.31 (1H, d, *J* 9.0 Hz, H-1'"), 8.19 (1H, s, NH-1), 7.97 (1H, dd, *J* 7.8, 1.5 Hz, H-5'"), 7.89 (1H, dd, *J* 8.4, 1.2 Hz, H-4'"), 7.78 (1H, dd, *J* 7.8, 1.2 Hz, H-1'), 7.64 (1H, ddd, *J* 8.4, 6.6, 1.2 Hz, H-6'"), 7.61 (1H, ddd, *J* 8.4, 6.6, 1.2 Hz, H-3'"), 7.28–7.34 (3H, m, H-8',2'",8'"), 7.23 (1H, ddd, *J* 7.8, 7.2, 1.2 Hz, H-3'), 7.18 (1H, ddd, *J* 8.4, 6.6, 1.5 Hz, H-7'"), 7.12 (1H, ddd, *J* 7.8, 7.2, 1.2 Hz, H-2'), 6.56–6.61 (2H, m, H-4',6'), 6.43 (1H, ddd, *J* 7.8, 7.2, 1.2 Hz, H-7'), 6.02 (1H, dd, *J* 7.2, 1.2 Hz, H-5'), 5.82 (1H, s, H-4), 3.46–3.49 (1H, m, H-1"a), 2.22–2.27 (1H, m, H-1"b), 1.12–1.16 (2H, m, H-2"), 0.64 (3H, t, *J* 7.8 Hz, H-3").

3.7. General procedure for the synthesis of 1-alkyl/aryl-3-benzyl-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-ones 30a–e and 4-(acridin-9'''-yl)-3-benzyl-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-one (30f)

To a solution of 1-alkyl/aryl-3-(*n*-propyl)-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones **28a–f** (0.26 mmol) in dry acetonitrile (5 mL), mesitylnitrile oxide (42 mg, 0.26 mmol) was added at once and the reaction mixture was stirred at room temperature for 6 h. The reaction was followed by TLC (petrolether/ethyl acetate, 2:1). After its completion, the product was filtered off, washed with petrolether, dried, and crystallized from a mixture of chloroform/diethyl ether or chloroform/*n*-heptane (**f**).

*3.7.1. 3-Benzyl-1-methyl-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**30a**)*

Yield 73 mg, 79%. Brown solid. Mp 185.0–189.0 °C. [Found: C 77.83; H 5.95; N 11.57; $C_{23}H_{21}N_3O$ (355.43) requires C 77.72; H 5.96; N 11.82%]; ν_{max} 3291, 1673, 1613, 1584, 1478, 1444, 1401, 1326, 1243, 1038, 876, 849, 748, 699, 612, 566, 480 cm^{-1}; ^1H NMR (600 MHz) δ_H = 9.30 (1H, s, NH-10'), 7.29–7.33 (2H, m, H-3",5"), 7.24–7.25 (2H, m, H-2",6"), 7.21–7.24 (1H, m, H-4"), 7.18 (2H, ddd, *J* 8.4, 7.5, 1.5 Hz, H-3',6'), 7.11 (2H, dd, *J* 7.8, 1.5 Hz, H-1',8'), 6.88 (2H, dd, *J* 8.4, 1.2 Hz, H-4',5'), 6.87 (2H, ddd, *J* 7.8, 7.5, 1.2 Hz, H-2',7'), 4.38 (2H, s, NCH_2), 3.27 (2H, s, H-4), 2.43 (3H, s, Me).

*3.7.2. 3-Benzyl-1-phenyl-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**30b**)*

Yield 67 mg, 62%. Yellow solid. Mp 196.0–197.0 °C. [Found: 80.37; H 5.67; N 10.07; $C_{28}H_{23}N_3O$ (417.50) requires C 80.55; H 5.55; N 10.06%]; ν_{max} 3340, 1678, 1608, 1582, 1477, 1411, 1325, 1265, 1029, 884, 749, 692, 582, 517 cm^{-1}; ^1H NMR (600 MHz) δ_H = 9.30 (1H, s, NH-10'), 7.30–7.35 (4H, m, H-2",6",3",5"), 7.24–7.28 (1H, m, H-4"), 7.19 (2H, dd, *J* 7.5, 1.5 Hz, H-1',8'), 7.12 (2H, ddd, *J* 8.1, 7.2, 1.5 Hz, H-3',6'), 6.99–7.03 (4H, m, H-2'", 6'",3'",5'"), 6.83–6.86 (1H, m, H-4'"), 6.81 (2H, dd, *J* 8.1, 1.2 Hz, H-4',5'), 6.77 (2H, ddd, *J* 7.5, 7.2, 1.2 Hz, H-2',7'), 4.49 (2H, s, NCH_2), 3.50 (2H, s, H-4).

*3.7.3. 3-Benzyl-1-(4'''-methoxyphenyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**30c**)*

Yield 85 mg, 73%. Light brown solid. Mp 264.0–265.0 °C. [Found: C 77.77; H 5.48; N 9.22; $C_{29}H_{25}N_3O_2$ (447.53) requires C 77.83; H 5.63; N 9.39%]; ν_{max} 3285, 1671, 1614,

1585, 1510, 1486, 1436, 1341, 1244, 1026, 828, 748, 695, 656, 543, 509 cm^{-1}; ^1H NMR (600 MHz) δ_H = 9.25 (1H, s, NH-10'), 7.34–7.39 (4H, m, H-2",6",3",5"), 7.28–7.30 (3H, m, H-1',8',4"), 7.14 (2H, ddd, *J* 8.4, 7.2, 1.2 Hz, H-3',6'), 6.82 (2H, ddd, *J* 8.4, 7.2, 1.2 Hz, H-2',7'), 6.79 (2H, dd, *J* 8.4, 1.2 Hz, H-4',5'), 6.74–6.77 (2H, m, H-2'",6'"), 6.60–6.62 (2H, m, H-3'",5'"), 4.52 (2H, s, NCH_2), 3.58 (2H, s, H-4), 3.58 (3H, s, MeO).

*3.7.4. 3-Benzyl-1-(4'''-fluorophenyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**30d**)*

Yield 90 mg, 79%. Brown solid. Mp 199.0–200.0 °C. [Found: C 77.07; H 5.34; N 9.41; $C_{28}H_{22}FN_3O$ (435.49) requires C 77.22; H 5.09; N 9.65%]; ^1H NMR (600 MHz) δ_H = 9.32 (1H, s, NH-10'), 7.32–7.38 (4H, m, H-2",6",3",5"), 7.27–7.30 (1H, m, H-4"), 7.24 (2H, dd, *J* 7.8, 1.2 Hz, H-1',8'), 7.15 (2H, ddd, *J* 7.8, 7.5, 1.2 Hz, H-3',6'), 6.93–6.97 (2H, m, H-2'",6'"), 6.88–6.92 (2H, m, H-3'",5'"), 6.83 (2H, dd, *J* 7.8, 0.6 Hz, H-4',5'), 6.80 (2H, ddd, *J* 7.8, 7.5, 0.6 Hz, H-2',7'), 4.52 (2H, s, NCH_2), 3.57 (2H, s, H-4).

*3.7.5. 3-Benzyl-1-(4'''-nitrophenyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**30e**)*

Yield 64 mg, 53%. Yellow solid. Mp 196.0–197.0 °C. [Found: C 72.56; H 4.62; N 12.03; $C_{28}H_{22}N_4O_3$ (462.50) requires C 72.71; H 4.79; N 12.11%]; ν_{max} 3314, 1685, 1614, 1585, 1481, 1429, 1320, 1268, 1112, 844, 745, 701, 468 cm^{-1}; ^1H NMR (600 MHz) δ_H = 9.51 (1H, s, NH-10'), 7.93–7.95 (2H, m, H-3'",5'"), 7.47–7.49 (2H, m, H-2'",6'"), 7.28–7.31 (4H, m, H-2",6",3",5"), 7.24–7.26 (1H, m, H-4"), 7.15 (2H, ddd, *J* 7.5, 7.2, 0.6 Hz, H-3',6'), 7.07 (2H, d, *J* 7.8 Hz, H-1',8'), 6.90 (2H, dd, *J* 7.5, 0.6 Hz, H-4',5'), 6.75 (2H, dd, *J* 7.8, 7.2 Hz, H-2',7'), 4.52 (2H, s, NCH_2), 3.48 (2H, s, H-4).

*3.7.6. 4-(Acridin-9'''-yl)-3-benzyl-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-one (**30f**)*

Yield 92 mg, 68%. Yellow solid. Mp 276.0–277.0 °C. [Found: C 80.91; H 4.95; N 10.60; $C_{35}H_{26}N_4O$ (518.61) requires C 81.06; H 5.05; N 10.80%]; ν_{max} 3273, 1677, 1616, 1586, 1526, 1479, 1453, 1338, 880, 743, 703, 694 cm^{-1}; ^1H NMR (600 MHz) δ_H = 8.48 (1H, dd, *J* 8.4, 1.2 Hz, H-1'"), 8.40 (1H, s, NH-1), 8.35 (1H, s, NH-10'), 7.95 (1H, dd, *J* 8.4, 1.2 Hz, H-5'"), 7.92 (1H, dd, *J* 8.4, 1.2 Hz, H-4'"), 7.65–7.63 (1H, m, H-3'"), 7.64–7.62 (1H, m, H-1'), 7.59 (1H, ddd, *J* 8.4, 6.6, 1.2 Hz, H-6'"), 7.42 (1H, dd, *J* 7.8, 1.2 Hz, H-8'), 7.34 (1H, ddd, *J* 8.4, 6.6, 1.2 Hz, H-2'"), 7.12–7.16 (2H, m, H-3',4"), 7.06–7.09 (2H, m, H-3",5"), 7.03 (1H, ddd, *J* 7.8, 7.2, 1.2 Hz, H-2'), 6.94 (1H, ddd, *J* 8.7, 6.6, 1.2 Hz, H-7'"), 6.76–6.78 (2H, m, H-2",6"), 6.69–6.71 (1H, m, H-8'"), 6.62 (1H, ddd, *J* 8.1, 7.2, 1.2 Hz, H-6'), 6.52 (1H, ddd, *J* 7.8, 7.2, 1.2 Hz, H-7'), 6.45 (1H, dd, *J* 7.8, 1.2 Hz, H-4'), 6.00 (1H, dd, *J* 8.1, 1.2 Hz, H-5'), 5.47 (1H, s, H-4), 5.02 (1H, d, *J* 15.0 Hz, NCH_a), 3.22 (1H, d, *J* 15.0 Hz, NCH_b).

3.8. Synthesis of 9-(1-bromoethyl)acridine (32)

To prepare starting 9-ethylacridine (**31**),[25] we have improved the described procedure for 9-methylacridine.[23] A mixture of diphenylamine (10 g, 59.1 mmol) and propionic acid (13.13 g, 13.2 mL, 177.3 mmol) was heated in the presence of anhydrous zinc chloride (40 g, 293.5 mmol) to 220 °C for 6 h to give a black tarry product. Next day, the reaction mixture was made strongly alkaline with aqueous ammonia (25 mL) and the insoluble residue was extracted three times with boiling *n*-heptane (3×100 mL) for 30 min. The combined heptane layers were dried over magnesium sulfate, the dessicant filtered off, and the crude product, which precipitated on cooling, was purified by crystallization from cyclohexane to give the pure 9-ethylacridine in the yield 93%, whose mp corresponded with the literature.[25]

To a solution of **31** (1.0 g, 4.8 mmol) in tetrachloromethane (20 mL), *N*-bromosuccinimide (2.56 g, 14.40 mmol) and azobisisobutyronitrile (0.12 g, 0.74 mmol) were added. The reaction mixture was heated at 80 °C under irradiation by a 100 W halogen lamp (Philips) for 6 h. The reaction mixture was extracted with a saturated aqueous solution of sodium bicarbonate (3×20 mL) to remove succinimide, the organic layer was dried over magnesium sulfate, filtered, evaporated, and the residual oil was extracted with petrolether (3×15 mL), combined organic layers were concentrated *in vacuo* to give the pure 9-(1-bromoethyl)acridine (**32**). Yield 1.05 g, 73 %. Yellow oil. ^1H NMR (600 MHz) δ_H = 8.90 (1H, broad s) and 8.66 (1H, broad s - H-1',8'), 8.23 (2H, d, *J* 8.5 Hz, H-4',5'), 7.90 (2H, ddd, *J* 8.5, 6.6, 0.9 Hz, H-3',6'), 7.74–7.77 (2H, m, H-2',7'), 7.02 (1H, q, *J* 7.2 Hz, CH), 2.34 (3H, d, *J* 7.2 Hz, CH_3).

3.9. Synthesis of *N*-[1-(acridin-9-yl)ethyl]propan-1-amine (33)

To a solution of *n*-propylamine (310 mg, 0.43 mL, 5.25 mmol) in dry tetrahydrofuran (10 mL), 9-(1-bromoethyl)acridine (**32**, 500 mg, 1.75 mmol) and potassium carbonate (0.266 g, 1.93 mmol) were added. The reaction mixture was refluxed for 56 h, the solvent was evaporated *in vacuo* and the pure product was obtained by column chromatography (petrolether/ethyl acetate, 4:1). Yield 330 mg, 71%. Brown oil. ^1H NMR (600 MHz) δ_H = 8.21 (1H, d, *J* 8.4 Hz, H-5'), 8.11 (1H, d, *J* 9.0 Hz, H-4'), 7.89–7.92 (1H, m, H-8'), 7.88–7.91 (1H, m, H-6'), 7.76–7.79 (2H, m, H-1',3'), 7.68 (1H, ddd, *J* 7.2, 6.6, 1.8 Hz, H-7'), 7.54 (1H, broad, H-2'), 5.39 (1H, q, *J* 6.6 Hz, 4-CH), 2.47–2.51 (1H, m, CH_a), 2.06–2.11 (1H, m, CH_b), 1.65 (3H, d, *J* 6.6 Hz, 4-CH_3), 1.31–1.37 (2H, m, CH_2), 0.74 (3H, t, *J* 7.2 Hz, CH_3); ^{13}C NMR (150 MHz) δ_C = 148.6 (C-10'a), 148.5 (C-4'a), 146.1 (C-9'), 131.2 (C-6'), 130.4 (C-4'), 130.1 (C-1',3'), 130.0 (C-5'), 127.7 (C-7'), 125.7 (C-2', broad), 125.2 (C-8'), 124.8 (C-9'a), 120.6 (C-8'a), 53.5 (4-CH), 50.6 (NCH_2), 23.3 (CH_2), 23.0 (Pr-CH_3), 12.3 (4-CH_3).

3.10. General procedure for the synthesis of 1-aryl-3-(*n*-propyl)-4-methyl-spiro[dihydroacridine-9'(10'*H*),5-imidazolidine]-2-thiones (35b–e)

To a chloroform solution (3 mL) of *N*-[1-(acridin-9-yl)ethyl]propan-1-amine (**33**, 100 mg, 0.38 mmol), a chloroform solution (3 mL) of apropriate isothiocyanate (1.20 equiv, 0.46 mmol) was added. The reaction mixture was stirred at room temperature for 6 h. A small amount of the pure product **35b–e** was obtained by precipitation with diethyl ether and used for NMR characterization. The filtrate was evaporated to give the oil which, however, could not be purified by chromatography as it decomposed on silica gel.

*3.10.1. 4-Methyl-1-phenyl-3-(n-propyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**35b**)*

Yield 101 mg, 67%. Yellow oil. ^1H NMR (600 MHz) δ_H = 9.31 (1H, s, NH-10'), 7.33 (1H, dd, *J* 7.8, 1.2 Hz, H-8'), 7.23 (1H,

ddd, *J* 8.4, 6.6, 1.8 Hz, H-3'), 7.15 (1H, dd, *J* 7.8, 1.8 Hz, H-1'), 7.10 (1H, ddd, *J* 8.4, 6.6, 1.2 Hz, H-6'), 7.02–7.05 (4H, m, H-2'",6'",3'",5'"), 6.95–6.99 (1H, m, H-4'"), 6.92 (1H, dd, *J* 8.4, 1.2 Hz, H-4'), 6.88 (1H, ddd, *J* 7.8, 6.6, 1.2 Hz, H-2'), 6.79–6.82 (1H, m, H-7'), 6.77–6.81 (1H, m, H-5'), 3.98 (1H, q, *J* 6.6 Hz, 4-CH), 3.86–3.91 (1H, m, H-1"a), 3.38–3.42 (1H, m, H-1"b), 1.60–1.66 (1H, m, H-2"a), 1.52–1.60 (1H, m, H-2"b), 0.90 (3H, t, *J* 7.8 Hz, H-3"), 0.79 (3H, d, *J* 6.6 Hz, 4-CH_3).

*3.10.2. 4-Methyl-1-(4'''-methoxyphenyl)-3-(n-propyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**35c**)*

Yield 109 mg, 67%. Brown oil. ^{1}H NMR (600 MHz) δ_H = 9.25 (1H, s, NH-10'), 7.40 (1H, dd, *J* 7.8, 1.2 Hz, H-8'), 7.22 (1H, ddd, *J* 8.4, 7.2, 1.2 Hz, H-3'), 7.19 (1H, dd, *J* 8.4, 1.2 Hz, H-1'), 7.10 (1H, ddd, *J* 7.8, 7.2, 1.2 Hz, H-6'), 6.87–6.91 (4H, m, H-2',4',2'",6'"), 6.83 (1H, ddd, *J* 7.8, 7.2, 1.2 Hz, H-7'), 6.79 (1H, dd, *J* 7.8, 1.2 Hz, H-5'), 6.58–6.61 (2H, m, H-3'",5'"), 4.00 (1H, q, *J* 6.6 Hz, 4-CH), 3.85–3.90 (1H, m, H-1"a), 3.59 (3H, s, MeO), 3.39–3.43 (1H, m, H-1"b), 1.59–1.90 (1H, m, H-2"a), 1.53–1.59 (1H, m, H-2"b), 0.91 (3H, t, *J* 7.8 Hz, H-3"), 0.80 (3H, d, *J* 6.6 Hz, 4-CH_3).

*3.10.3. 4-Methyl-1-(4'''-fluorophenyl)-3-(n-propyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**35d**)*

Yield 101 mg, 64%. Light brown oil. ν_{max} 3247, 1608, 1581, 1473, 1318, 1245, 1157, 908, 810, 744, 603, 517, 499 cm^{-1}; ^{1}H NMR (600 MHz) δ_H = 9.32 (1H, s, NH-10'), 7.38 (1H, dd, *J* 7.8, 1.2 Hz, H-8'), 7.27 (1H, ddd, *J* 8.4, 6.6, 1.2 Hz, H-3'), 7.16 (1H, dd, *J* 7.8, 1.2 Hz, H-1'), 7.13 (1H, ddd, *J* 7.8, 7.8, 1.2 Hz, H-6'), 7.00–7.05 (2H, m, H-2'",6'"), 6.91–6.96 (4H, m, H-2',4',3'",5'"), 6.84 (1H, ddd, *J* 7.8, 1.2 Hz, H-7'), 6.81 (1H, dd, *J* 7.8, 1.2 Hz, H-5'), 4.01 (1H, q, *J* 6.6 Hz, 4-CH), 3.85–3.90 (1H, m, H-1"a), 3.38–3.43 (1H, m, H-1"b), 1.61–1.68 (1H, m, H-2"a), 1.53–1.61 (1H, m, H-2"b), 0.90 (3H, t, *J* 7.8 Hz, H-3"), 0.80 (3H, d, *J* 6.6 Hz, 4-CH_3).

*3.10.4. 4-Methyl-1-(4'''-nitrophenyl)-3-(n-propyl)-spiro[dihydroacridine-9'(10'H),5-imidazolidine]-2-thione (**35e**)*

Yield 110 mg, 66%. Brown oil. ν_{max} 3366, 1613, 1581, 1480, 1453, 1417, 1312, 1234, 1110, 844, 743, 531 cm^{-1}; ^{1}H NMR (600 MHz) δ_H = 9.47 (1H, s, NH-10'), 7.97–8.00 (2H, m, H-3'",5'"), 7.44–7.47 (2H, m, H-2'",6'"), 7.29 (1H, ddd, *J* 7.8, 7.2, 1.2 Hz, H-3'), 7.20 (1H, dd, *J* 7.8, 1.5 Hz, H-8'), 7.15 (1H, ddd, *J* 7.8, 7.2, 1.5 Hz, H-6'), 7.02–7.04 (1H, m, H-1'), 7.01–7.02 (1H, m, H-4'), 6.90–6.91 (1H, m, H-5'), 6.90 (1H, ddd, *J* 7.8, 7.2, 1.2 Hz, H-2'), 6.77–6.80 (1H, m, H-7'), 3.97 (1H, q, *J* 6.6 Hz, 4-CH), 3.88–3.93 (1H, m, H-1"a), 3.37–3.42 (1H, m, H-1"b), 1.60–1.66 (1H, m, H-2"a), 1.50–1.56 (1H, m, H-2"b), 0.88 (3H, t, *J* 7.8 Hz, H-3"), 0.78 (3H, d, *J* 6.6 Hz, 4-CH_3).

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Supplementary data

Crystallographic data of **28e** (CCDC 948527) have been deposited at the Cambridge Crystallographic Database Centre. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; e–mail: deposit@ccdc.cam.ac.uk).

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