Synthesis of 9-amino- and 9-sulfanyl-substituted benzo[*b*]quinolizinium derivatives

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This paper is dedicated to Professor Waldemar Adam on the occasion of his 70th birthday

Abstract

Eight substituted *N*-aryl-9-aminoacridizinium and four *N*,*N*-dialkyl-9-aminoacridizinium derivatives have been prepared in moderate yields by the reaction of 9-bromo- or 9-fluoroacridizinium salts with selected amines. In contrast, the reaction with primary alkylamines gives only traces of the substitution product. The reaction of 9-fluoroacridizinium bromide with thiophenol yields 9-(phenylsulfanyl)acridizinium salt. The 9-(methylsulfanyl)-acridizinium salt was prepared by the cyclodehydration of the pyridinium precursor.

Keywords: Nitrogen heterocycles, quinolizinium, *acridizinium*, amination

Introduction

Benzo-annelated quinolizinium salts represent a class of nitrogen heterocycles with a bridgehead quaternary nitrogen atom, which attract much interest in view of their DNA-binding and DNA-photodamaging properties.[1] Although several routes for the synthesis of benzo[*b*]quinolizinium derivatives, commonly referred to as acridizinium derivatives, are known,[2,3,4] most substituents need to be introduced before the formation of the benzoquinolizinium core. Remarkably, only few amino-substituted benzo[*b*]quinolizinium derivatives are known.[5] Recently, the 9-amino-acridizinium (**1a**) was synthesized and its photophysical properties as well as interaction with DNA were investigated in detail. [6,7]

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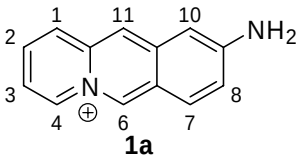
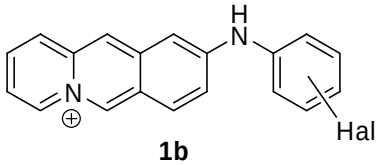


1a



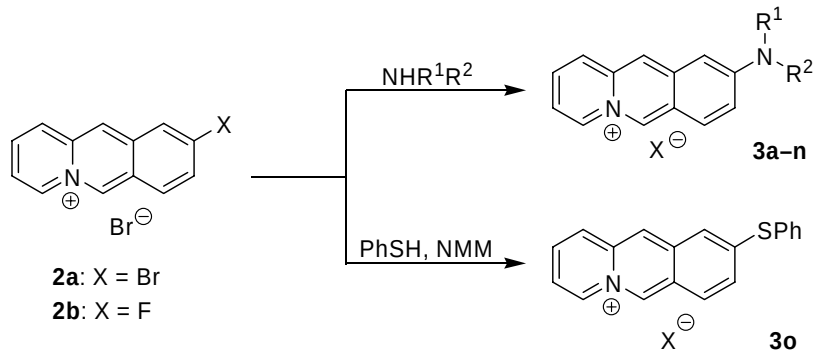
1b

As a part of a project aimed at the development of a novel class of DNA-binding and DNA-photodamaging intercalators based on the acridizinium core, we were interested in the preparation of a wide range of substituted 9-aminoacridizinium derivatives starting from a common and readily available acridizinium precursor. While amination reactions of bromo- and chloro-substituted quinolizinium cations have been described in the literature several decades ago,[8,9] this reaction was shown to deliver substantial amounts of the by-products resulting from the ring-opening and has limited synthetic applicability. Moreover, such amination reactions were unprecedented in the acridizinium system. Our recent studies showed, however, that 9-bromoacridizinium bromide reacts with substituted anilines to give the *N*-aryl-9-aminoacridizinium derivatives **1b**.[10]

In view of the interesting properties of the *N*-aryl-9-aminoacridizinium derivatives, namely, their pronounced fluorescence enhancement upon interaction with double-stranded DNA[10], we wanted to extend the series of substituted aminoacridizinium salts. In this paper we present our investigations of the amination of 9-halogenoacridizinium salts, aimed at the determination of the scope and limitations of this reaction. Beyond the *N*-aryl derivatives with various substituents in the aryl group, we have undertaken the synthesis of *N*-alkyl- or *N*,*N*-dialkyl-substituted derivatives of **1a**, which may serve as reference compounds for the investigation of the effects of the aryl substituent. Moreover, we have prepared sulfur analogues of **1a**, in which the amino group is replaced with a methyl- or phenylsulfanyl substituent. It is proposed that such derivatives could represent a complementary donor–acceptor system, as the sulfanyl group has different electron-donating properties than the amino substituent in the parent system **1a**.

Results and Discussion

Synthesis of 9-aminoacridizinium derivatives and 9-(phenylthio)acridizinium. Similar to the nucleophilic substitution reactions of halogen- and alkoxy-substituted quinolinium[11,12] and quinolizinium salts, the *N*-substituted 9-aminoacridizinium derivatives **3a–ℓ** were synthesized by the reaction of the readily available 9-bromo- or 9-fluoroacridizinium bromides (**2a–b**)[13] with selected amines (Scheme 1; Table 1). Similarly, the 9-(phenylsulfanyl)acridizinium (**3m**) was obtained by the reaction of **2b** with thiophenol in the presence of a mild base (*N*-methylmorpholine, NMM).



Scheme 1. Synthesis of 9-donor-substituted acridizinium derivatives from 9-halogenacridizinium salts. For the experimental details see Table 1.

Table 1. Reaction conditions and yields for the synthesis of acridizinium derivatives **3a–o**

Compound	R^1	R^2	Reaction conditions				Yield / %
			Starting compound	Solvent	Time / h	Temp. / °C	
3a[a]	$-(CH_2)_2O(CH_2)_2-$		**2a**	*i*-PrOH	2	reflux	24
3b[a]	$-(CH_2)_4-$		**2a**	*i*-PrOH	2	reflux	30
3c[a]	C_2H_5	C_2H_5	**2b**	EtOH	1	reflux	71
3d[b,d]	CH_2CH_2OH	CH_3	**2a**	*i*-PrOH	16	reflux	16
3e[b]	$CH(CH_3)_2$	H	**2b**	EtOH	6	reflux	4
3f[b]	$(CH_2)_3CH_3$	H	**2b**	EtOH	6	reflux	1
3g[c]	4-$C_6H_4NMe_2$	H	**2a**	EtOH	48	reflux	14
3h[c]	4-C_6H_4OMe	H	**2a**	*i*-PrOH	48	reflux	18
3i[c]	4-C_6H_4Me	H	**2a**	none	6	130	77
3j[c]	C_6H_5	H	**2a**	none	24	130	23
3k[c]	4-C_6H_4F	H	**2a**	none	22	120	57
3l[c]	4-C_6H_4Br	H	**2a**	none	72	150	11
3m[c]	4-C_6H_4Cl	H	**2a**	none	72	150	15
3n[c]	3-C_6H_4Cl	H	**2a**	none	72	150	20
3o[b]			**2b**	EtOH	1	reflux	42

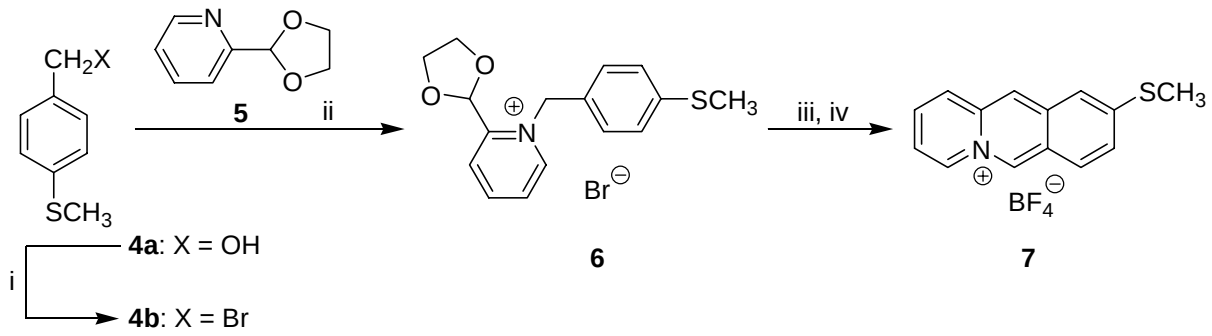
[a–c] Isolated and characterized as: [a] terafluoroborate; [b] hexafluorophosphate; [c] bromide salts. [d] Fully characterized as an *O*-acetyl derivative (**3p**).

The reaction proceeds in refluxing 2-propanol or ethanol in modest to good yields with secondary aliphatic amines, to give the compounds **3a–d**. However, the reactions with selected primary aliphatic amines (isopropylamine, butylamine) gave mostly mixtures of unidentified products, which presumably correspond to the products resulting from the destruction of the

acridizinium core by the nucleophilic addition of amine to position 6, followed by further reactions of the resulting intermediates.[14,15] Only traces of the substitution products (**3e–f**) could be isolated by column chromatography and conversion of the isolated bromides into the corresponding tetrafluoroborates or hexafluorophosphates.

In the case of donor-substituted anilines, the substitution products **3g–h** could be obtained, albeit in low yields (< 20%), when the reaction was performed in refluxing 2-propanol or ethanol. In the cases of aniline, toluidine, or halogen-substituted anilines, the formation of the products **3i–n** required considerably higher temperatures (120–150 ºC). The latter reactions were performed in the absence of the solvent, but in the presence of a Lewis-acid catalyst ($BF_3 \times Et_2O$). The presence of other catalysts such as Lewis acids ($SnCl_4$), Brønsted acids (hydrochloride of the corresponding amine, pyridine hydrochloride) or auxiliary bases, such as DBU or pyridine, did not improve the yield of the desired products. The arylamino-substituted derivatives **3g–n** were isolated as bromides by several subsequent crystallization steps. Unfortunately, attempts to obtain substitution products with several electron-poor aromatic amines, such as 4-aminobenzonitrile, 4-(trifluoromethyl)aniline and 3-aminopyridine, were unsuccessful even at harsh conditions (180–200 °C). The structures of the acridizinium derivatives **3a–p** were confirmed by ^{1}H- and ^{13}C NMR spectroscopy, mass-spectrometric and elemental analysis data.

Synthesis of 9-(Methylsulfanyl)acridizinium. The synthesis of 9-(methylsulfanyl)acridizinium salt **7** followed the general approach for the preparation of substituted acridizinium salts by the cyclodehydration of pyridinium precursors (Scheme 2).[2,6] Thus, 4-(methylsulfanyl)benzyl bromide (**4b**) was prepared from the commercially available 4-(methylsulfanyl)benzyl alcohol (**4a**) following the published procedure[16] and allowed to react with (1,3-dioxolan-2-yl)pyridine (**5**),[17] to give the quaternary salt **6** almost quantitatively. The cyclodehydration of the salt **6** in PPA, which is most widely used as a cyclization medium in such reactions,[2] gave only a moderate yield of the desired product (42%); however, the use of methanesulfonic acid led to an increase of the yield on this stage up to 81%. The 9-(methylsulfanyl)acridizinium **7**, isolated as a tetrafluoroborate, was prepared in 78% overall yield based on the alcohol **4a**; its structure is supported by the spectroscopic and elemental analysis data.



Scheme 2. Synthesis of 9-(methylsulfanyl)acridizinium tetrafluoroborate (**7**). Reagents and conditions: (i) HBr, toluene, 90 °C, 1 h, 98%; (ii) DMSO, rt, 7 days, 98%; (iii) $MeSO_3H$, 90 °C, 2 h; (iv) aq. $NaBF_4$, 81%.

Electron-donor properties of the substituents evaluated by NMR spectroscopy. Due to the strong electron-accepting properties of the quaternary nitrogen atom, 9-substituted acridizinium salts represent a donor–acceptor system which may be useful for the evaluation of the relative electron-donating properties of the substituents in position 9. Numerous studies have been performed aimed at the derivation of the substituent constants from the values of ^1H and ^{13}C chemical shifts of substituted benzenes.[18,19] Along these lines we observed a good correlation ($r^2 = 0.984$) of the chemical shifts of the 6-H proton atom with the Hammett–Brown constants of the substituents, for which the σ_p^+ were known (Figure 1).[20] The correlations of the chemical shifts of other nuclei, such as C9 or C11, were less satisfying.

The correlation may be used for the estimation of the electron-donor properties of the amino substituents, for which the corresponding σ_p^+ values have not been determined, so far. Indeed, the relative electron-donor strength of the arylamino substituents obtained from our data (Figure 1) is agreeable with the expected, considering the values of the Hammett constants of the substituent in the aryl ring. However, it should be noted that the values only reflect a trend and should be considered with caution, since the number of the points used for the regression analysis is too small to establish a firm relationship.

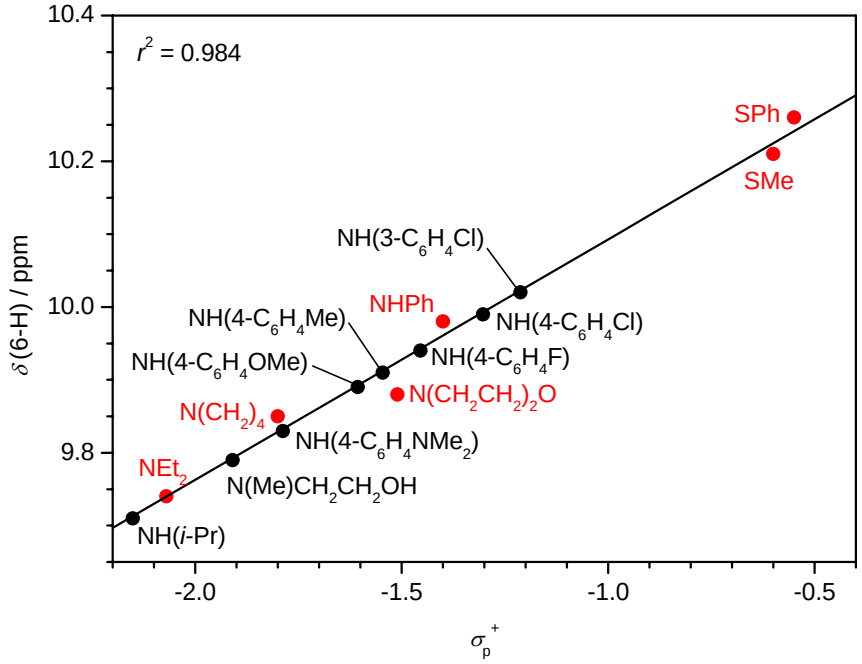


Figure 1. Correlation of the chemical shift of the H-6 atom of 9-amino- and 9-sulfanylacridizinium derivatives (in DMSO-d_6 at 295 K) with the reported σ_p^+ values of the substituents (red points). The black points on the regression curve represent the chemical shifts of the derivatives, for which the σ_p^+ values of the substituent are not known.

Summary

It was shown that the nucleophilic substitution of the halogen atom in 9-bromo- and 9-fluoro-acridizinium salts with amino and sulfur nucleophiles proceeds in low to moderate yields and has practical importance for the synthesis of 9-amino and 9-sulfanyl-substituted acridizinium salts. In general, the reaction with the fluoroacridizinium salt provides better yields of the substitution products, as compared to the bromo-substituted precursor. This observation is in line with the findings that the related fluoro-substituted quinolinium salts easily undergo nucleophilic substitution reaction with amines,[12] and indicates that the key reaction step is the addition of the amino nucleophile to the halogen-substituted position of the acridizinium cation.

A series of such substitution products has been described. The major drawback of the proposed reaction is the difficulty of the isolation and purification of the products. However, the low yields of the substitution products are to some extent compensated by the easy availability of the starting compounds, namely 9-halogenoacridizinium salts. The present amination reaction is limited to the dialkylamines and relatively reactive anilines, since in the case of primary alkylamines only poor yields of the substitution products were obtained and the reaction with acceptor-substituted anilines did not take place. The studies of the photophysical properties of

9-amino and 9-sulfanyl-substituted acridizinium salts, aimed at the establishment of these compounds as a platform for fluorescent probes, are currently underway.

Experimental Section

General Procedures.

All commercially available chemicals were reagent grade and used without further purification. The melting points are uncorrected. Mass-spectra (ESI in the positive-ion mode) were measured at a source voltage 6 kV; only *m*/*z* values in the range of 100–2000 units were analyzed. If not stated otherwise, the NMR spectra were measured in DMSO-d_6 using TMS as internal standard for ^{1}H- and ^{13}C NMR spectroscopy and hexaflurobenzene ($\delta_F = -162.8$ ppm) as external standard for ^{19}F-NMR spectroscopy. The working frequency was 400, 100 and 376 MHz for ^{1}H, ^{13}C and ^{19}F NMR, correspondingly. Unambiguous proton NMR assignments were established by means of {^{1}H, ^{1}H}-COSY experiments. Elemental microanalyses of all new compounds were performed with a HEKAtech EuroEA combustion analyzer by Mr. H. Bodenstedt (Institut für Organische Chemie, Universität Siegen). TLC of acridizinium derivatives was performed on silica gel sheets (Macherey-Nagel Polygram Sil G/UV$_{254}$), eluent: $CHCl_3$–MeOH–AcOH 80:20:1 v/v. 9-Bromo- and 9-fluoroacridizinium bromides were prepared according to the published procedures.[13]

9-(Diethylamino)acridizinium tetrafluoroborate (3c BF_4^-). General procedure for reaction with dialkylamines

A solution of 9-fluoroacridizinium bromide (**2b**, 0.834 g, 3.00 mmol) in EtOH (5 mL) was brought to reflux, and diethylamine (0.461 g, 6.30 mmol) was added. The reaction mixture was heated under reflux for 1 h (monitoring by TLC). After cooling to room temperature, the reaction mixture was evaporated to dryness and the product was isolated by column chromatography (alumina neutral, activity grade I; eluent $CHCl_3$–MeOH, 90:10 v/v). The green-fluorescing fraction was collected. The eluate was evaporated, and the corresponding tetrafluoroborates or hexafluorophosphates were prepared by addition of aqueous HBF_4 (50%) or concentrated aqueous $NaPF_6$ solution to the solution of the isolated product in minimal amount of water, followed by recrystallization of the precipitate from MeCN–AcOEt. The product (0.72 g, 71%) was obtained as orange prisms, mp 197–198 °C; $R_f = 0.58$; ^{1}H NMR δ 1.24 (t, $^3J = 7$ Hz, 6 H, CH_3), 3.65 (q, $^3J = 7$ Hz, 4 H, CH_2), 7.06 (d, $^4J = 2$ Hz, 1 H, 10-H), 7.43 (t, $^3J = 7$ Hz, 1 H, 3-H), 7.64–7.68 (m, 1 H, 2-H), 7.71 (dd, $^3J = 10$ Hz, $^4J = 2$ Hz, 1 H, 8-H), 8.04 (d, $^3J = 9$ Hz, 1 H, 1-H), 8.18 (d, $^3J = 10$ Hz, 1 H, 7-H), 8.30 (s, 1 H, 11-H), 8.75 (d, $^3J = 7$ Hz, 1 H, 4-H), 9.74 (s, 1 H, 6-H); ^{13}C NMR δ 12.4 (CH_3), 44.6 (CH_2), 99.1 (CH), 117.1 (CH), 118.2 (CH), 119.7 (C_q), 122.0 (CH), 125.4 (CH), 129.4 (CH), 130.2 (CH), 133.4 (CH), 137.2 (C_q), 138.0 (CH + C_q), 151.4

(C_q); MS (ESI$^+$): *m*/*z* (%) = 251 (100) $[M]^+$; anal. calcd (%) for $C_{17}H_{19}BF_4N_2$ (338.2): C 60.38, H 5.66, N 8.28; found: C 60.53, H 5.85, N 8.20.

9-(Morpholin-4-yl)acridizinium bromide (3a BF_4^-). Yield 24%, orange prisms; R_f = 0.45; m.p. 256–260 °C; ^{1}H NMR δ 3.64 (m, 4 H, CH_2N), 3.81 (m, 4 H, CH_2O), 7.35 (d, ^4J = 2 Hz, 1 H, 10-H), 7.55 (t, ^3J = 7 Hz, 1 H, 3-H), 7.76 (dd, ^3J = 9 Hz, ^3J = 7 Hz, 1 H, 2-H), 7.93 (dd, ^3J = 10 Hz, ^4J = 2 Hz, 1 H, 8-H), 8.20 (d, ^3J = 9 Hz, 1 H, 1-H), 8.25 (d, ^3J = 10 Hz, 1 H, 7-H), 8.45 (s, 1 H, 11-H), 8.88 (d, ^3J = 7 Hz, 1 H, 4-H), 9.88 (s, 1 H, 6-H); ^{13}C NMR δ 46.5 (CH_2), 65.6 (CH_2), 101.8 (CH), 118.5 (CH), 119.0 (CH), 120.6 (C_q), 122.8 (CH), 125.6 (CH), 129.7 (CH), 129.8 (CH), 133.5 (CH), 137.4 (C_q), 137.8 (C_q), 138.3 (CH), 153.5 (C_q); MS (ESI$^+$): *m*/*z* (%) = 265 (100) $[M]^+$; anal. calcd (%) for $C_{17}H_{17}BF_4N_2O \times ½\ H_2O$ (361.2): C 56.54, H 5.02, N 7.76; found C 56.56, H 4.76, N 7.70.

9-(Pyrrolidin-1-yl)acridizinium bromide (3b BF_4^-). Yield 30%, orange needles; R_f = 0.57; m.p. 248–250 °C; ^{1}H NMR δ 2.06 (m, 4 H, CH_2CH_2), 3.54 (br m, 4 H, NCH_2), 6.81 (d, ^4J = 2 Hz, 1 H, 10-H), 7.42 (t, ^3J = 7 Hz, 1 H, 3-H), 7.54 (dd, ^4J = 2 Hz, ^3J = 9 Hz, 1 H, 8-H), 7.65 (dd, ^3J = 9 Hz, ^3J = 7 Hz, 1 H, 2-H), 8.04 (d, ^3J = 9 Hz, 1 H, 1-H), 8.15 (d, ^3J = 9 Hz, 1 H, 7-H), 8.26 (s, 1 H, 11-H), 8.81 (d, ^3J = 7 Hz, 1 H, 4-H), 9.85 (s, 1 H, 6-H); ^{13}C NMR δ 24.8 (CH_2), 48.0 (CH_2), 99.4 (CH), 116.8 (CH), 118.1 (CH), 119.7 (C_q), 122.9 (CH), 125.3 (CH), 129.3 (CH), 129.9 (CH), 133.3 (CH), 137.1 (C_q), 137.6 (C_q), 138.2 (CH), 150.6 (C_q); MS (ESI$^+$): *m*/*z* (%) = 249 (100) $[M]^+$; anal. calcd (%) for $C_{17}H_{17}BF_4N_2$ (329.2): C 60.74, H 5.10, N 8.33; found C 60.40, H 5.08, N 8.26.

9-[(2-Hydroxyethyl)methylamino]acridizinium hexafluorophosphate (3d PF_6^-). Yield 16%, orange amorphous solid; R_f = 0.37; m.p. 132–134 (shrinks at 80) °C (methyl ethyl ketone); ^{1}H NMR δ 3.24 (s, 3 H, NCH_3), 3.69 (m, 2 H, CH_2), 3.75 (m, 2 H, CH_2), 4.91 (br s, 1 H, OH), 7.06 (d, ^4J = 2 Hz, 1 H, 10-H), 7.45 (dt, ^3J = 7 Hz, ^4J = 1 Hz, 1 H, 3-H), 7.68 (dd, ^3J = 9 Hz, ^3J = 7 Hz, 1 H, 2-H), 7.79 (dd, ^3J = 10 Hz, ^4J = 2 Hz, 1 H, 8-H), 8.08 (d, ^3J = 9 Hz, 1 H, 1-H), 8.17 (d, ^3J = 10 Hz, 1 H, 7-H), 8.33 (s, 1 H, 11-H), 8.79 (d, ^3J = 7 Hz, 1 H, 4-H), 9.79 (s, 1 H, 6-H); ^{13}C NMR δ 39.2 (CH_3), 54.0 (CH_2), 58.5 (CH_2), 99.6 (CH), 117.2 (CH), 118.3 (CH), 119.8 (C_q), 122.5 (CH), 125.4 (CH), 129.4 (CH), 129.6 (CH), 133.4 (CH), 137.3 (C_q), 137.9 (C_q), 138.1 (CH), 153.2 (C_q); MS (ESI$^+$): *m*/*z* (%) = 253 (100) $[M]^+$; satisfactory elemental analysis could not be obtained due to HF elimination upon drying in vacuo.

9-(Isopropylamino)acridizinium hexafluorophosphate (3e PF_6^-). Yield 4%, dark-yellow needles; m.p. 210–213°C (MeOH–AcOEt); ^{1}H NMR δ 1.28 (d, ^3J = 6 Hz, 6 H, CH_3), 3.87 (sept, ^3J = 6 Hz, 1 H, $CHMe_2$), 6.88 (d, ^4J = 1 Hz, 1 H, 10-H), 7.41–7.44 (m, 2 H, 3-H, 8-H), 7.68 (dd, ^3J = 7 Hz, ^3J = 8 Hz, 1 H, 2-H), 7.81 (d, ^3J = 8 Hz, 1 H, NH), 8.04–8.08 (m, 2 H, 1-H, 7-H), 8.27 (s, 1 H, 11-H), 8.77 (d, ^3J = 7 Hz, 1 H, 4-H), 9.70 (s, 1 H, 6-H); ^{13}C NMR δ 21.6 (CH_3), 43.5 (*C*HMe_2), 96.8 (CH), 116.7 (CH), 118.1 (2 CH), 120.4 (C_q), 125.1 (2 CH), 129.5 (CH), 129.6 (CH), 133.3 (CH), 137.4 (C_q), 137.6 (CH), 138.8 (C_q), 152.2 (C_q); MS (ESI$^+$) *m*/*z* (%) = 618 (10) $[2M + PF_6]^+$, 237 (100) $[M]^+$, 195 (34) $[M-C_3H_7]^+$; anal. calcd (%) for $C_{16}H_{17}F_6N_2P$ (382.3): C 50.27, H 4.48, N 7.33; found: C 50.16, H 4.37, N 7.15.

9-(Butylamino)acridizinium hexafluorophosphate (3f PF_6^-). Yield ca 1%, yellow solid; ^{1}H NMR δ 0.96 (t, ^3J = 7 Hz, 3 H, CH_3), 1.40–1.48 (m, 2 H, CH_2), 1.62–1.68 (m, 2 H, CH_2), 3.28–3.31 (m, 2 H, CH_2N), 6.86 (s, 1 H, 10-H), 7.43–7.44 (m, 2 H, 3-H, 8-H), 7.68 (dd, ^3J = 7 Hz, ^3J = 8 Hz, 1 H, 2-H), 7.91 (m, 1 H, NH), 8.05–8.07 (m, 2 H, 1-H, 7-H), 8.28 (s, 1 H, 11-H), 8.77 (d, ^3J = 7 Hz, 1 H, 4-H), 9.71 (s, 1 H, 6-H); ^{13}C NMR δ 13.6 (CH_3), 19.7 (CH_2), 29.8 (CH_2), 42.1 (CH_2), 96.2 (CH), 116.7 (CH), 118.1 (2 CH), 120.5 (C_q), 125.2 (CH), 129.3 (CH), 129.6 (CH), 133.3 (CH), 137.4 (C_q), 137.6 (CH), 138.8 (C_q), 153.2 (C_q).

9-(4-Methoxyphenylamino)acridizinium bromide (3h Br^-). General procedure for the reaction of 9-bromoacridizinium bromide with electron-rich anilines

A solution of salt **2a** (1.36 g, 4.00 mmol) and *p*-anisidine (1.97 g, 16.0 mmol) in *i*-PrOH (25 mL) was stirred under reflux for 48 h. After cooling to room temperature, the reaction mixture was concentrated to approximately one-half of its original volume and poured into Et_2O (300 mL); the red precipitate was separated and recrystallized twice from MeOH, to give 0.27 g (18%) of dark-red needles; R_f = 0.53; m.p. 131–132 °C (MeOH); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.81 (s, 3 H, OCH_3), 7.07 (d, ^3J = 9 Hz, 2 H, 2′-H, 6′-H), 7.20 (d, ^4J = 2 Hz, 1 H, 10-H), 7.35 (d, ^3J = 9 Hz, 2 H, 3′-H, 5′-H), 7.53 (t, ^3J = 7 Hz, 1 H, 3-H), 7.63 (dd, ^3J = 9 Hz, ^4J = 2 Hz, 1 H, 8-H), 7.74 (dd, ^3J = 7 Hz, ^3J = 9 Hz, 1 H, 2-H), 8.06 (d, ^3J = 9 Hz, 1 H, 1-H), 8.22 (d, ^3J = 9 Hz, 1 H, 7-H), 8.43 (s, 1 H, 11-H), 8.88 (d, ^3J = 7 Hz, 1 H, 4-H), 9.74 (s, 1 H, NH), 9.89 (s, 1 H, 6-H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 55.4, 98.9, 114.9 (2 C), 118.0, 118.9, 121.1, 124.2 (2 C), 125.3, 125.4, 130.0, 130.1, 131.7, 133.6, 137.5, 138.0, 138.5, 150.9, 156.7; MS (ESI$^+$): *m*/*z* (%) = 301 (100) $[M]^+$; anal. calcd (%) for $C_{20}H_{17}BrN_2O \times H_2O$ (399.3): C 60.16, H 4.80, N 7.02; found: C 60.29, H 5.05, N 7.02.

9-[4-(Dimethylamino)phenylamino]acridizinium bromide (3g Br^-). Yield 14%, black microcrystals; R_f = 0.59; m.p. 218–219 °C (*i*-PrOH); ^{1}H NMR δ 2.94 (s, 6 H, CH_3), 6.83 (d, ^3J = 8 Hz, 2 H, 3′-H, 5′-H), 7.10 (s, 1 H, 10-H), 7.23 (d, ^3J = 8 Hz, 2 H, 2′-H, 6′-H), 7.48 (t, ^3J = 6 Hz, 1 H, 3-H), 7.59 (d, ^3J = 9 Hz, 1 H, 8-H), 7.69 (dd, ^3J = 9 Hz, ^3J = 6 Hz, 1 H, 2-H), 8.01 (d, ^3J = 9 Hz, 1 H, 1-H), 8.16 (d, ^3J = 9 Hz, 1 H, 7-H), 8.35 (s, 1 H, 11-H), 8.84 (d, ^3J = 6 Hz, 1 H, 4-H), 9.65 (s, 1 H, NH), 9.83 (s, 1 H, 6-H); ^{13}C NMR δ 40.3 (2 CH_3), 98.4 (CH), 113.1 (2 C, CH), 117.6 (CH), 118.6 (CH), 121.0 (C_q), 124.1 (2 CH), 125.3 (2 CH), 127.6 (C_q), 129.8 (CH), 129.9 (CH), 133.5 (CH), 137.5 (C_q), 137.8 (CH), 138.5 (C_q), 148.3 (C_q), 151.4 (C_q); MS (ESI$^+$): *m*/*z* (%) = 314 (100) $[M]^+$, 299 (61) $[M - CH_3]^+$; anal. calcd (%) for $C_{21}H_{20}BrN_3 \times$ ½ H_2O (403.3): C 62.54, H 5.25, N 10.42; found C 62.56, H 5.19, N 10.41.

9-(4-Toluidino)acridizinium bromide (3i Br^-). General procedure for reaction with electron-poor anilines

9-Bromoacridizinium bromide (**2a**, 1.70 g, 5.0 mmol), *p*-toluidine (2.14 g, 20.0 mmol) and $BF_3 \times Et_2O$ (0.3 mL) were stirred at 130 °C under argon atmosphere for 6 h (monitoring by TLC). After cooling to room temperature, the melt was triturated with Et_2O until a friable powder was obtained. The solid was separated, thoroughly washed with Et_2O and AcOEt, dried

and recrystallized from AcOH (with charcoal) and then from MeOH, to give 1.40 g (77 %) of orange needles, mp 255 °C (dec.); R_f = 0.40; ^{1}H NMR δ 2.35 (s, 3 H, CH_3), 7.28–7.34 (m, 5 H, 4 Ar-H + 10-H), 7.54 (t, ^3J = 7 Hz, 1 H, 3-H), 7.65 (dd, ^3J = 9 Hz, ^4J = 2 Hz, 1 H, 8-H), 7.75 (dd, ^3J = 7 Hz, ^3J = 9 Hz, 1 H, 2-H), 8.08 (d, ^3J = 9 Hz, 1 H, 1-H), 8.22 (d, ^3J = 9 Hz, 1 H, 7-H), 8.47 (s, 1 H, 11-H), 8.89 (d, ^3J = 7 Hz, 1 H, 4-H), 9.80 (s, 1 H, NH), 9.91 (s, 1 H, 6-H); ^{13}C NMR δ 20.6, 99.5, 118.3, 119.0, 121.2, 121.9 (2 C), 125.5 (2 C), 130.0, 130.1 (2 C), 133.5, 133.9, 136.5, 137.5, 138.0, 138.4, 150.2, 153.6; MS (ESI$^+$): *m*/*z* (%) = 285 (100) $[M]^+$; anal. calcd (%) for $C_{20}H_{17}BrN_2$ (365.3): C 65.76, H 4.69, N 7.67; found: C 65.53, H 4.58, N 7.65.

9-(Phenylamino)acridizinium bromide (3j Br$^-$). Yield 23%, orange needles; R_f = 0.33; m.p. (dec.) 110–112 °C (AcOH–H_2O); ^{1}H NMR δ 7.22 (dd, ^3J = 7 Hz, 1 H, Ar-H), 7.43–7.50 (m, 5 H, 4 Ar-H + 10-H), 7.55 (t, ^3J = 7 Hz, 1 H, 3-H), 7.69 (dd, ^3J = 9 Hz, ^4J = 2 Hz, 1 H, 8-H), 7.76 (dd, ^3J = 7 Hz, ^3J = 9 Hz, 1 H, 2-H), 8.10 (d, ^3J = 9 Hz, 1 H, 1-H), 8.26 (d, ^3J = 9 Hz, 1 H, 7-H), 8.52 (s, 1 H, 11-H), 8.94 (d, ^3J = 7 Hz, 1 H, 4-H), 9.87 (s, 1 H, NH); 9.98 (s, 1 H, 6-H); ^{13}C NMR δ 100.0 (CH), 118.6 (CH), 119.1 (CH), 121.3 (C_q), 121.5 (2 CH), 124.4 (CH), 125.5 (CH), 125.6 (CH), 129.6 (2 CH), 130.1 (CH), 133.6 (CH), 137.5 (C_q), 138.2 (C_q), 138.3 (CH), 139.3 (C_q), 149.7 (C_q); MS (ESI$^+$): *m*/*z* (%) = 271 (100) $[M]^+$; anal. calcd (%) for $C_{19}H_{15}BrN_2 \times$ ½ H_2O (360.3): C 63.35, H 4.48, N 7.78; found: C 63.00, H 4.36, N 7.73.

9-(4-Fluorophenylamino)acridizinium bromide (3k Br$^-$). Yield 57%, brick-red needles; R_f = 0.47; m.p. > 250 °C (MeCN–EtOH); ^{1}H NMR δ 7.31–7.35 (m, 3 Ar-H), 7.45–7.49 (m, 2 Ar-H), 7.57 (t, ^3J = 7 Hz, 1 H, 3-H), 7.66 (dd, ^3J = 9 Hz, ^4J = 2 Hz, 1 H, 8-H), 7.77 (dd, ^3J = 7 Hz, ^3J = 9 Hz, 1 H, 2-H), 8.11 (d, ^3J = 9 Hz, 1 H, 1-H), 8.26 (d, ^3J = 9 Hz, 1 H, 7-H), 8.51 (s, 1 H, 11-H), 8.92 (d, ^3J = 7 Hz, 1 H, 4-H), 9.84 (s, 1 H, NH); 9.94 (s, 1 H, 6-H); ^{13}C NMR δ 99.6 (CH), 116.4 (d, 2 CH, $^2J_{C,F}$ = 22.6 Hz), 118.5 (CH), 119.2 (CH), 121.3 (C_q), 124.1 (d, 2 CH, $^3J_{C,F}$ = 8.3 Hz), 125.4 (CH), 125.5 (CH), 130.1 (CH), 133.6 (CH), 135.5 (d, C_q, $^4J_{C,F}$ = 2.6 Hz), 137.4 (C_q), 138.1 (C_q), 138.3 (CH), 150.1 (C_q), 159.0 (d, C_q, $^1J_{C,F}$ = 241.6 Hz); ^{19}F-NMR (376 MHz, DMSO-d_6): δ = −117.6 (sept, J = 4.3 Hz, Ar-F); MS (ESI$^+$): *m*/*z* (%) = 289 (100) $[M]^+$; anal. calcd (%) for $C_{19}H_{14}BrFN_2 \times 0.2\ H_2O$ (372.8): C 61.21, H 3.89, N 7.51; found: C 61.16, H 3.82, N 7.57.

9-(4-Bromophenylamino)acridizinium bromide (3ℓ Br$^-$). Yield 11%, yellow-red prisms; R_f = 0.50; m.p. (dec.) 240–242 °C (*i*-PrOH–MeOH); ^{1}H NMR δ 7.41 (d, ^3J = 9 Hz, 2 H, 2′-H, 6′-H), 7.51 (d, ^4J = 1 Hz, 1 H, 10-H), 7.60 (t, ^3J = 7 Hz, 1 H, 3-H), 7.64 (d, ^3J = 9 Hz, 2 H, 3′-H, 5′-H), 7.69 (dd, ^3J = 9 Hz, ^4J = 1 Hz, 1 H, 8-H), 7.80 (dd, ^3J = 9 Hz, ^3J = 7 Hz, 1 H, 2-H), 8.15 (d, ^3J = 9 Hz, 1 H, 1-H), 8.28 (d, ^3J = 9 Hz, 1 H, 7-H), 8.56 (s, 1 H, 11-H), 8.95 (d, ^3J = 7 Hz, 1 H, 4-H), 9.95 (s, 1 H, NH), 9.99 (s, 1 H, 6-H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 100.7, 115.8, 119.0, 119.1, 119.5, 121.5, 121.9, 123.2 (2 C), 125.7, 130.1, 130.3, 132.4 (2 C), 133.7, 137.5, 138.3, 138.9, 149.0; MS (ESI$^+$): *m*/*z* (%) = 349 (100) $[M]^+$, 270 (7) $[M - Br]^+$; anal. calcd (%) for $C_{19}H_{14}Br_2N_2$ (430.1): C 53.05, H 3.28, N 6.51; found: C 52.57, H 3.19, N 6.46.

9-(4-Chlorophenylamino)acridizinium bromide (3m Br$^-$). Yield 15%, fine bright-orange needles; R_f = 0.56; m.p. 149–151 °C; ^{1}H NMR δ 7.45–7.52 (m, 5 H, 10-H + 4 Ar-H), 7.59 (t, ^3J = 7 Hz, 1 H, 3-H), 7.70 (d, ^3J = 9 Hz, 1 H, 8-H), 7.79 (dd, ^3J = 7 Hz, ^3J = 9 Hz, 1 H, 2-H),

8.14 (d, ^3J = 9 Hz, 1 H, 1-H), 8.26 (d, ^3J = 9 Hz, 1 H, 7-H), 8.55 (s, 1 H, 11-H), 8.95 (d, ^3J = 7 Hz, 1 H, 4-H), 9.99 (br s, 2 H, NH + 6-H); ^{13}C NMR δ 100.5, 118.9, 119.4, 121.4, 122.8 (2 C), 125.6 (2 C), 127.8, 129.5 (2 C), 130.0, 130.2, 133.6, 137.5, 138.2, 138.4, 149.1; MS (ESI$^+$): *m*/*z* (%) = 305 (100) $[M]^+$; anal. calcd (%) for $C_{19}H_{14}BrClN_2$ (385.7): C 59.17, H 3.66, N 7.26; found C 59.06, H 3.71, N 7.23.

9-(3-Chlorophenylamino)acridizinium bromide (3n Br$^-$). Yield 20%, yellow prisms; R_f = 0.56; m.p. 277–279 °C; ^{1}H NMR δ 7.23 (d, ^3J = 8 Hz, 1 H, 6′-H), 7.41–7.51 (m, 3 Ar-H), 7.56 (d, ^4J = 2 Hz, 1 H, 10-H), 7.61 (t, ^3J = 7 Hz, 1 H, 3-H), 7.72 (dd, ^3J = 9 Hz, ^4J = 1.7 Hz, 1 H, 8-H), 7.81 (dd, ^3J = 7 Hz, ^3J = 9 Hz, 1 H, 2-H), 8.16 (d, ^3J = 9 Hz, 1 H, 1-H), 8.28 (d, ^3J = 9 Hz, 1 H, 7-H), 8.63 (s, 1 H, 11-H), 8.97 (d, ^3J = 7 Hz, 1 H, 4-H), 10.02 (br s, 2 H, NH + 6-H); ^{13}C NMR δ 101.1, 119.3, 119.4, 119.5, 120.3, 121.5, 123.7, 125.6 (2 C), 130.0, 130.2, 131.2, 133.6, 133.8, 137.4, 138.1, 138.3, 141.1, 148.7; MS (ESI$^+$): *m*/*z* (%) = 305 (100) $[M]^+$; anal. calcd (%) for $C_{19}H_{14}BrClN_2 \times ½\ H_2O$ (394.7): C 57.82, H 3.83, N 7.10; found C 58.04, H 3.61, N 7.13.

9-(Phenylthio)acridizinium hexafluorophosphate (3o Br$^-$). A solution of 9-fluoroacridizinium bromide (0.834 g, 3.00 mmol) in EtOH (5 mL) was brought to reflux, and thiophenol (0.364 g, 3.30 mmol) and *N*-methylmorpholine (0.334 g, 3.30 mmol) were added. The reaction mixture was heated under reflux for 1 h (monitoring by TLC) and then cooled to room temperature. Water (60 mL) was added, and the mixture was extracted with AcOEt (2 × 30 mL), acidified with HBr to pH 1, and again extracted with AcOEt (3 × 30 mL). The yellow aqueous layer was concentrated in vacuo until oily product began to separate. The oil was dissolved by careful heating (~ 60 °C), and concentrated aqueous solution of NH_4PF_6 (3.26 g, 20.0 mmol) was added. The product separated as brown oil, which soon become solid and was triturated until yellow powder was obtained. The product was collected, washed with water and cold MeOH and dried in vacuo / P_2O_5, to give essentially pure product (0.541 g, 42%) as yellow solid. A sample was recrystallized from methyl ethyl ketone–MeCN, to give yellow prisms, mp 209–212 °C; R_f = 0.69; ^{1}H NMR δ 7.62–7.64 (m, 3 H, Ar-H), 7.69 (s, 1 H, 10-H), 7.71–7.73 (m, 2 H, Ar-H), 7.75 (d, ^3J = 9 Hz, 1 H, 8-H), 7.87 (t, ^3J = 7 Hz, 1 H, 3-H), 8.01 (d, ^3J = 7 Hz, ^3J = 8 Hz, 1 H, 2-H), 8.36–8.38 (m, 2 H, 1-H, 7-H), 8.93 (s, 1 H, 11-H), 9.17 (d, ^3J = 7 Hz, 1 H, 4-H), 10.26 (s, 1 H, 6-H); ^{13}C NMR δ 120.3 (CH), 121.8 (CH), 122.5 (CH), 124.0 (C_q), 126.5 (CH), 128.6 (C_q), 128.7 (CH), 129.7 (CH), 130.4 (CH), 130.6 (2 CH), 131.3 (CH), 134.3 (CH), 134.8 (2 CH), 135.2 (C_q), 138.1 (C_q), 139.7 (CH), 148.0 (C_q); MS (ESI$^+$) *m*/*z* (%) = 721 (11) $[2M + PF_6]^+$, 288 (100) $[M]^+$; anal. calcd (%) for $C_{19}H_{14}F_6NPS$ (433.4): C 52.66, H 3.26, N 3.23, S 7.40; found: C 52.78, H 3.18, N 3.24, S 7.51.

9-[(2-Acetoxyethyl)methylamino]acridizinium hexafluorophosphate (3p PF$_6^-$). A solution of **3d PF$_6^-$** (80 mg, 0.20 mmol) in pyridine (0.50 mL) was treated with acetic anhydride (0.50 mL) and the reaction mixture was stirred for 18 h at room temperature, while an orange precipitate has formed. Methanol (5 mL) was added carefully, and the mixture was evaporated to dryness in vacuo. The orange solid residue was recrystallized from ethanol, to give analytically pure

product (64 mg, 73%) as maroon prisms, m.p. (dec.) 182–184 °C; R_f = 0.51; ^{1}H NMR δ 1.92 (s, 3 H, CH_3CO), 3.23 (s, 3 H, NCH_3), 3.96 (t, ^3J = 6 Hz, NCH_2), 4.32 (t, ^3J = 6 Hz, 2 H, CH_2OAc), 7.11 (d, ^4J = 2 Hz, 1 H, 10-H), 7.49 (t, ^3J = 7 Hz, 1 H, 3-H), 7.71 (dd, ^3J = 7 Hz, ^3J = 9 Hz, 1 H, 2-H), 7.81 (dd, ^3J = 10 Hz, ^4J = 2 Hz, 1 H, 8-H), 8.12 (d, ^3J = 9 Hz, 1 H, 1-H), 8.23 (d, ^3J = 10 Hz, 1 H, 7-H), 8.38 (s, 1 H, 11-H), 8.82 (d, ^3J = 7 Hz, 1 H, 4-H), 9.82 (s, 1 H, 6-H); ^{13}C NMR δ 20.5 (CH_3), 38.8 (CH_3), 50.2 (CH_2), 61.0 (CH_2), 99.9 (CH), 117.6 (CH), 118.5 (CH), 119.9 (C_q), 122.1 (CH), 125.4 (CH), 129.5 (CH), 129.7 (CH), 133.4 (CH), 137.3 (C_q), 137.8 (C_q), 138.2 (CH), 152.7 (C_q), 170.1 (CO); IR (KBr): $\tilde{\nu}_{max}$ = 839 (PF_6^-), 1510s, 1614m, 1635s, 1731s (CO) cm^{-1}; MS (ESI$^+$): *m*/*z* (%) = 295 (100) $[M]^+$, 235 (6) $[M - CH_3COO]$; anal. calcd (%) for $C_{18}H_{19}F_6N_2O_2P$ (440.3): C 49.10, H 4.35, N 6.36; found C 49.01, H 4.12, N 6.41.

2-(1,3-Dioxolan-2-yl)-1-[4-(methylthio)benzyl]pyridinium bromide (6 Br$^-$). A solution of 4-(methylthio)benzyl bromide[16] (**4b**; 11.9 g, 51.1 mmol) and 2-(1,3-dioxolan-2-yl)pyridine[17] (**5**; 8.50 g, 56.2 mmol) in DMSO (10 mL) was stirred at room temperature under argon atmosphere for 7 days and then poured into AcOEt (250 mL). After stirring for 30 min, the solvent was decanted, and the residual oil was triturated with acetone until a white solid was obtained. It was collected, washed with acetone, Et_2O, and dried in vacuo / P_2O_5 to give 18.5 g (98%) of a white amorphous product, which was used without further purification. An analytically pure sample was obtained by crystallization from *i*-PrOH–AcOEt: large prisms, mp 113–115 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 2.49 (s, 3 H, SCH_3), 4.21 (s, 4 H, OCH_2), 6.00 (s, 2 H, CH_2N^+), 6.46 (s, 1 H, C*H*(OCH_2)$_2$), 7.33 (br s, 4 H, Ar-H), 8.11 (ddd, ^3J = 8 Hz, ^3J = 6 Hz, ^4J = 1 Hz, 1 H, 5′-H), 8.39 (dd, ^3J = 8 Hz, ^4J = 1 Hz, 1 H, 3′-H), 8.68 (dt, ^3J = 8 Hz, ^4J = 1 Hz, 1 H, 4′-H), 8.92 (dd, ^3J = 6 Hz, ^4J = 1 Hz, 1 H, 6′-H); ^{13}C NMR (100 MHz, CD_3OD) δ 15.1, 61.7, 67.4, 99.0, 127.3, 127.7, 129.6, 130.2, 130.5, 142.9, 147.9, 148.2, 154.2; anal. calcd (%) for $C_{16}H_{18}BrNO_2S$ (368.3): C 52.18, H 4.93, N 3.80, S 8.71; found: C 52.25, H 4.92, N 3.87, S 8.99.

9-(Methylthio)acridizinium tetrafluoroborate (7 BF_4^-). Salt **6 Br$^-$** (5.50 g, 15.0 mmol) in methanesulfonic acid (20 mL) was stirred at 80 °C under argon atmosphere for 1 h. After cooling to 40 °C, the reaction mixture was poured onto crushed ice (60 g). After melting, concentrated aqueous solution of $NaBF_4$ (6.60 g, 60.0 mmol) was added. The yellow precipitate was collected, washed with cold water and dried in vacuo / P_2O_5, to give 3.80 g (81%) of the product. A sample was recrystallized from MeCN–AcOEt: yellow prisms; mp (dec.) 204–206 °C; R_f = 0.50; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.73 (s, 3 H, SCH_3), 7.79–7.89 (m, 2 H, 3-H, 8-H), 7.97–8.05 (m, 2 H, 2-H, 10-H), 8.29 (d, ^3J = 9 Hz, 1 H, 7-H), 8.46 (d, ^3J = 9 Hz, 1 H, 1-H), 8.88 (s, 1 H, 11-H), 9.14 (d, ^3J = 7 Hz, 1 H, 4-H), 10.21 (s, 1 H, 6-H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 14.1, 117.9, 121.5, 121.6, 123.8, 126.6, 127.6, 130.2, 131.2, 134.3, 135.6, 138.1, 139.6, 149.4; MS (ESI$^+$): *m*/*z* (%) = 539 (16) $[2M + BF_4]^+$, 226 (100) $[M]^+$, 211 (9) $[M - CH_3]^+$; anal. calcd (%) for $C_{14}H_{12}BF_4NS$ (313.1): C 53.70, H 3.86, N 4.47, S 10.24; found: C 53.56, H 3.84, N 4.62, S 10.37.

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