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2020-07
Springer
http://hdl.handle.net/10138/318388
Hassan, A A, Mohamed, N K, Aly, A A, Tawfeek, H N, Bräse, S & Nieger, M 2020, 'Synthesis and structure confirmation of 2,4-disubstituted thiazole and 2,3,4-trisubstituted thiazole as thiazolium bromide salts', Monatshefte für Chemie, vol. 151, no. 7, pp. 1143-1152. https://doi.org/10.1007/s00706-020-02640-3

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Monatshefte für Chemie - Chemical Monthly
https://doi.org/10.1007/s00706-020-02640-3

ORIGINAL PAPER

Synthesis and structure confirmation of 2,4-disubstituted thiazole and 2,3,4-trisubstituted thiazole as thiazolium bromide salts

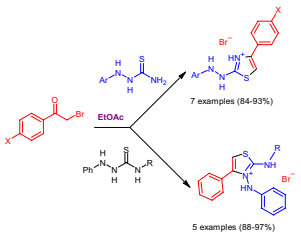
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Received: 18 December 2019 / Accepted: 8 June 2020
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Abstract

The synthesis of 4-substituted 2-(2-arylhydrazinyl)thiazol-3-ium bromides and 4-aryl-2-(substituted amino)-3-(phenylamino)-thiazol-3-ium bromide derivatives in high yields from the interaction of mono- and di-substituted thiosemicarbazides with phenacyl bromide derivatives is reported. The synthesized products have been elucidated using various spectroscopic tools such as IR, NMR, and mass spectrometry. Also the structure of three of the obtained compounds have been confirmed using X-ray crystallographic analyses, which showed that compounds 2-[2-(2,4-dinitrophenyl)hydrazinyl]-4-phenylthiazol-3-ium bromide and 4-phenyl-2,3-bis(phenylamino)thiazol-3-ium bromide crystals have a monoclinic shape and belonged to space group $P2_1/c$, whereas the crystals of 4-phenyl-2-(2-tosylhydrazinyl)thiazol-3-ium bromide show an orthorhombic shape with the space group *Pbca*

Graphic abstract



Keywords Carbonyl compounds · Crystal structure · Cyclizations · Eliminations · Thiazolium bromide derivatives · Thiosemicarbazides

Introduction

Generally the thiazole core occurs in variety of pharmaceutical drugs [1]. For example, the water-soluble vitamin B1 thiamine possesses a thiazole ring within its structure [2]. In addition, the thiazole ring system appears in the bacitracin and penicillin antibiotics and plays a great role in the construction of synthetic drugs [1].

Synthetic drugs related to thiazole family recorded as antimicrobial agents acinitrazole and sulfathiazole [3], penicillin which used as antibiotic [4, 5], pexole antidepressant drugs [6], bleomycin antineoplastic agents and tiazofurin [7], ritonavir used as anti-HIV drug [8], cinalukast antiasthmatic drug [9], nizatidine antiulcer agent [10]. The non-steroidal immunomodulatory drug fanetizole was extensively

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00706-020-02640-3) contains supplementary material, which is available to authorized users.

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Published online: 18 June 2020

used as thiazole derivatives [11] and meloxicam used as anti-inflammatory drug [12]. Thiazole derivatives possess polyoxygenated phenyl molecule that showed anti-fungal activity [13]. Thiazolium salts and bis-thiazolium salts have been prepared and examined as antimalarial potent agents [14]. Imidazo[2,1-*b*]thiazolium bromides showed analgesic and anti-inflammatory activities [15].

The synthetic strategies of thiazolium bromide heterocyclic cores were achieved via more than one step reaction, in which the thiazole ring was constructed first, then alkylation of the thiazole ring using alkyl bromide derivatives, for instance *N*-dodecylthiazolium bromide, and *N*-dodecyl-4-methylthiazolium bromide, were observed during the reaction of 1-bromododecane and thiazole/4-methylthiazole, and have been investigated as antimicrobial agents [16]. A few reactions have been reported for the synthesis of thiazolium bromides in one step procedures, such as the reaction between thiosemicarbazide and 2-bromo-1-(4-chlorophenyl)-ethanone affording 1-[5-(4-chlorophenyl)thiazol-2-yl]hydrazine hydrobromide and investigated as antibacterial [17]. Also, (*E*)-2-[2-(2-nitrobenzylidene)hydrazinyl]-4-phenylthiazol-3-ium bromide was synthesized from the reaction of 1-aryl-2-bromoethanones with 2-(1-substituted methylidene)-hydrazinecarbothioamides [18].

Polymethylene-bridged thiazolium and benzothiazolium salts (plus bases) were used as catalysts for the benzoin condensation; bis(thiazolin-2-ylidene) not thiazolin-2-ylidenes, were found to be the catalytic species in the benzoin condensation catalyzed by thiazolium salts plus base [19]. Thiazolium bromide salts have been used as catalyst for the synthesis of 1,4-diketones via hydroacylation of chalcones (α,β-unsaturated ketones) with aldehydes [20].

3-[2-(1-Butyl-1*H*-imidazol-1,3-ium-3-yl)ethyl]-4,5-dimethyl-1,3-thiazol-3-ium was used as an ionic liquid in the conversion of aldehydes to acyloins and benzoins [21]. Thiazolium salts have been synthesized and their properties as ionic liquid catalyst have been studied; thiazolium halide ionic liquids were synthesized by using 4-methylthiazole or 4-methyl-5-thiazolethanol and alkyl halides [22].

Reactions between mono-substituted thiosemicarbazides with phenacyl bromide derivatives in ethanol at refluxing temperature have been reported and gave 2-amino-5-(4-aminophenyl)-4-(phenyl)-1,3-thiazol-3-ium bromide dihydrate derivatives. Also the same reactions have been carried out using Eschenmoser coupling reaction conditions, triethyl amine (base) and triphenylphosphine (thiophile) in acetonitrile resulting in the formation of diazinylthiazole derivatives [23].

Lee et al. reported that the synthesis of 2-amino-5-(*p*-aminophenyl)thiazoles and 5,5′-bis(2-aminothiazole) derivatives via [5.5] sigmatropic shift of *N*-phenyl-*N*′-(2-thiazolyl)-hydrazones and *N*,*N*′-bis(2-thiazolyl)hydrazines in acid catalyzed benzidine type rearrangement [24].

Results and discussion

Reaction between 4-substituted thiosemicarbazides and phenacyl bromides

Herein, we investigate the reactions between 4-substituted thiosemicarbazides **1a**–**1d** with phenacyl bromide derivatives (as α-halocarbonyl compounds) **2a** and **2b** in ethyl acetate at room temperature that resulted in the formation of 4-substituted-2-(2-substituted hydrazinyl)thiazol-3-ium bromide **3a**–**3g** in high yields (84–93%) as showed in Scheme 1. The structures of the synthesized compounds **3a**–**3g** were identified using various tools of spectroscopic analyses, and also the structure of **3a** and **3d** were confirmed using X-ray analyses.

In the IR spectrum of compound **3a**, broad bands were observed at 3220 cm^{-1} due to NH, 3102 cm^{-1} because of aromatic-CH, at 1611 cm^{-1} due to C=N, at 1591 cm^{-1} attributed to aromatic C=C, and at 1535 and 1331 cm^{-1} due to NO_2 group.

The ^{1}H NMR spectra of **3a** showed broad signals at $\delta = 10.20$ ppm due to NH-attached directly to 2,4-dinitrophenyl moiety, while NH-attached to C-2 appeared at 10.63 ppm. The two NH-protons show downfield shift, attributed to the high deshielding caused by the di-nitro groups on the aromatic ring and the positive charge on thiazole-ring, respectively, as observed from the X-ray structure analysis of **3a**. The thiazole-H occurred at 7.82 ppm as singlet signal. The aromatic protons appeared at 7.21–7.40 and 7.48–7.55 ppm due to the phenyl protons. The protons appeared at 8.34–8.43 and 8.83–8.92 ppm are of the 2,4-dinitrophenyl protons.

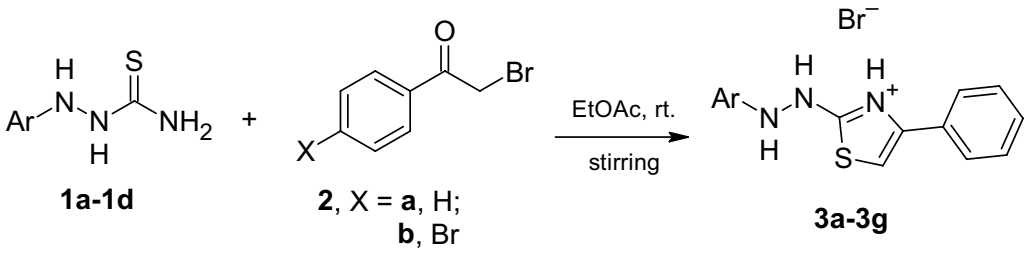
In ^{13}C NMR of **3a**, signals at 115.6, 150.5, and 170.5 ppm due to thiazole C-5, C-4, and C-2 respectively, also the downfield shift attributed to the positive charge on the thiazole ring. The aromatic carbons appeared at the aromatic region as mentioned in the experimental part.

The mass spectrum of **3a** showed that $m/z = 443$ (M^+) confirmed the formation of the thiazolium bromide products via the condensation between thiosemicarbazide **1a** and phenacyl bromide **2a**. The base peak at $m/z = 358$ resulted under liberation of HBr molecule.

X-ray structure of compounds 3a and 3d

The structure of **3a**–**3g** was further confirmed by X-ray diffraction of 4-phenyl-2-[2-(2,4-dinitrophenyl)hydrazinyl]-thiazol-3-ium bromide (**3a**; Fig. 1 and Tables 1–7 in the supplementary data: note that the crystal numbering does not obey the IUPAC numbering rules) and 4-phenyl-2-(2-tosylhydrazinyl)thiazol-3-ium bromide (**3d**; Fig. 2 and

Scheme 1



3a-3d: X = H

a, Ar = 2,4-dinitro-C_6H_3; **b**, Ar = C_6H_5;

c, Ar = 3-Cl-C_6H_4; **d**, Ar = 4-Me-$C_6H_4SO_2$.

3e-3g: X = Br

e, Ar = C_6H_5; **f**, Ar = 3-Cl-C_6H_4;

g, Ar = 4-Me-$C_6H_4SO_2$.

Tables 8–14 in the supplementary data), both showed the planarity of the thiazole ring.

Plausible mechanism for the formation of hydrazinylthiazolium bromide derivatives 3a–3g

The plausible mechanism for the formation of **3a**–**3g** was demonstrated in Scheme 2 as follows: *S*-alkylation takes place via nucleophilic substitution and elimination of HBr molecule to give intermediate **4**. Heterocyclization of **4** through nucleophilic attack of N^4 on the carbonyl-group followed by elimination of H_2O molecule gives **6**. In the presence of HBr the thiazolium bromide derivatives **3a**–**3g** are formed.

Reactions between 1,4-disubstituted thiosemicarbazides 7a–7e and phenacyl bromide 2a

Also, in this paper we investigate the reactions between 1,4-disubstituted thiosemicarbazides **7a**–**7e** and phenacyl bromide (**2a**) in ethyl acetate at room temperature resulting in the formation of 4-aryl-2-(amino)-3-(phenylamino) thiazol-3-ium bromide derivatives **8a**–**8e** in high yields (88–97%) instead of (*Z*)-3-substituted 4-diphenyl-2-(2-phenylhydrazono)-2,3-dihydrothiazoles **9a**–**9e** [23] (Scheme 3). Here, we try to carry out the reaction in a variety of solvents and conditions; we found that the products were formed in high yields and purity when the reactions were carried out in ethyl acetate at room temperature (Table 1).

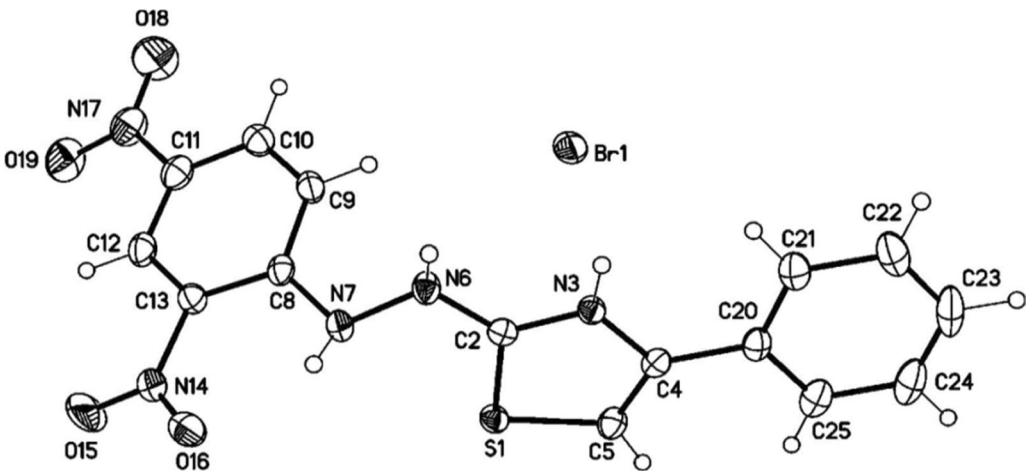


Fig. 1 Molecular X-ray structure of 2-[2-(2,4-dinitrophenyl)hydrazinyl]-4-phenylthiazol-3-ium bromide (**3a**)

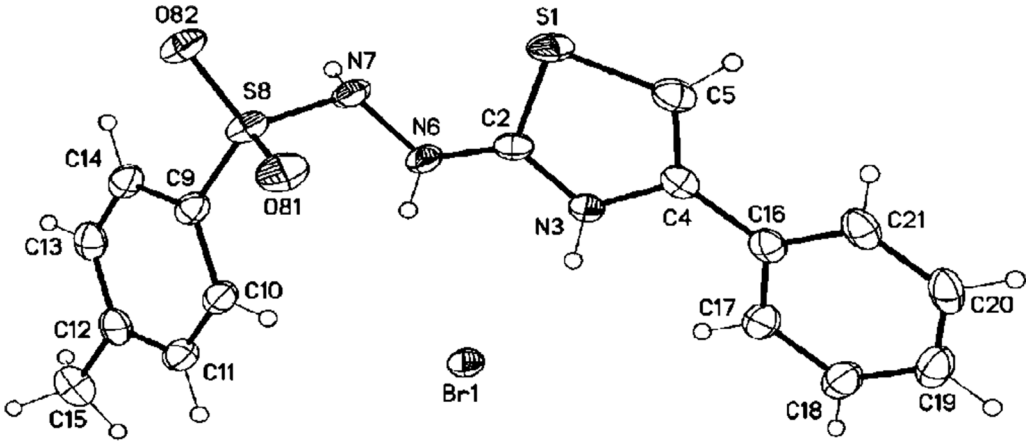
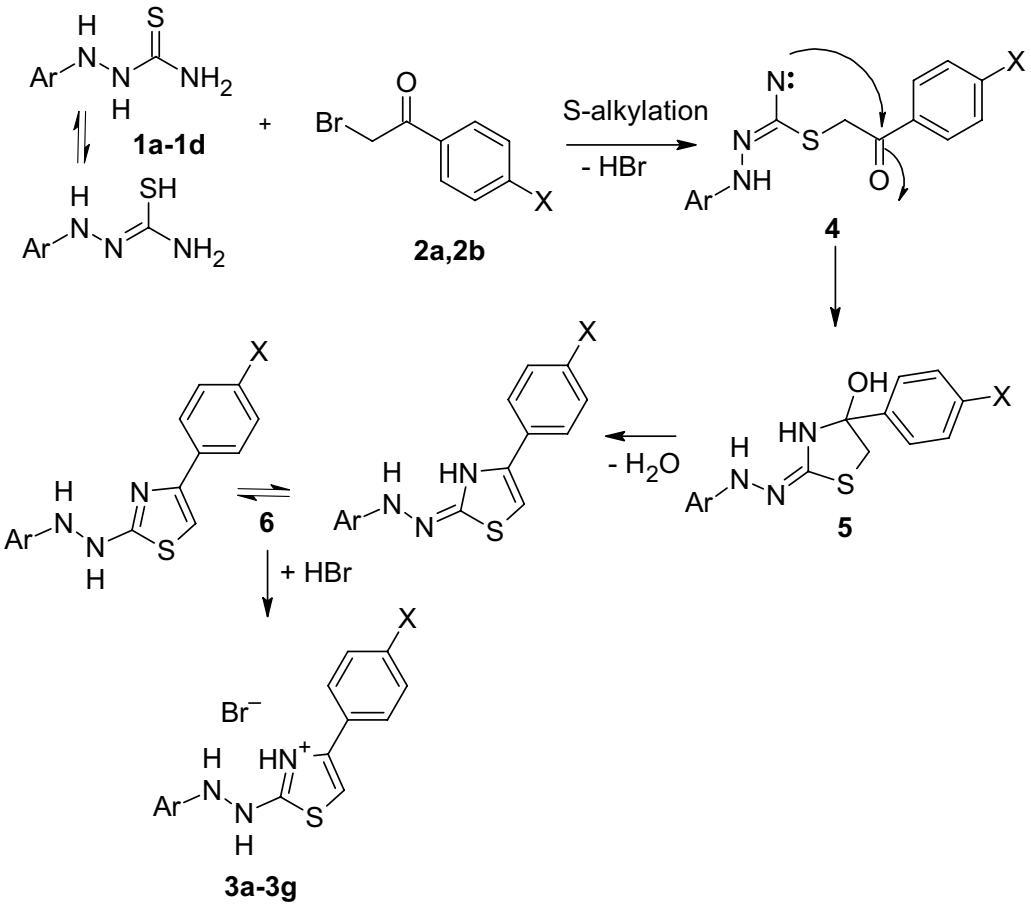


Fig. 2 Molecular X-ray structure of 4-phenyl-2-(2-tosylhydrazinyl)thiazol-3-ium bromide (**3d**)

Scheme 2



The structures of compounds **8a**–**8e** were confirmed using spectroscopic methods, such as IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry as well as X-ray crystallographic analysis.

In IR spectrum of **8a** there are characteristic absorption bands that appeared at 3220–3175 cm^{-1} assigned to NH-group vibrations, aromatic-CH vibrations observed in the

region around 3025–3135 cm^{-1}, and absorption band at 1595 cm^{-1} assigned to Ar–C=C vibrations..

From the ^1H NMR spectra of **8a** it was cleared that broad singlet signals appeared downfield at $\delta = 9.88$ ppm due to deshielded NH-proton, the downfield shift caused by the occurrence of the positive charge on the thiazole-ring, and the other NH-proton appeared within the aromatic protons.

The ^{13}C NMR showed signals at $\delta = 112.7$, 138.0, and 168.6 ppm for thiazole C-5, C-4, and C-2, respectively. The aromatic carbons appeared at the characteristic region as illustrated in the experimental part.

The interaction between **7a**–**7e** and **2a** resulted in the formation of 4-aryl-2-(substituted amino)-3-(phenylamino)-thiazol-3-ium bromide derivatives **8a**–**8e** was supported from the mass spectrometry of compound **8a** which showed $m/z = 425$ (M^+) this peak is due to the presence of HBr molecule and formation of the thiazolium salt and base peak $m/z = 343$ support the loss of HBr molecule.

X-ray structure of compound 8a

Also, the structures were unambiguously confirmed from X-ray obtained for the compound 4-phenyl-2,3-bis(phenylamino)thiazol-3-ium bromide (**8a**; Fig. 3 and Tables 15–21; note that the crystallographic numbering does not correspond to the systematic IUPAC numbering rules). The thiazole ring is planar (mean deviation from the L.S.-plane S1, C2, N3 C4, C5 0.0036 Å), while the phenyl substituent and the two NHPh moieties are twisted or orthogonal in respect to the thiazole ring (angle between the L.S. planes 42.44(6)° for C41…C46, 57.92(6)° for N21 and 84.00(5)° for N31).

Plausible mechanism for the formation of 2,3,4-trisubstituted thiazolium bromides 8a–8e

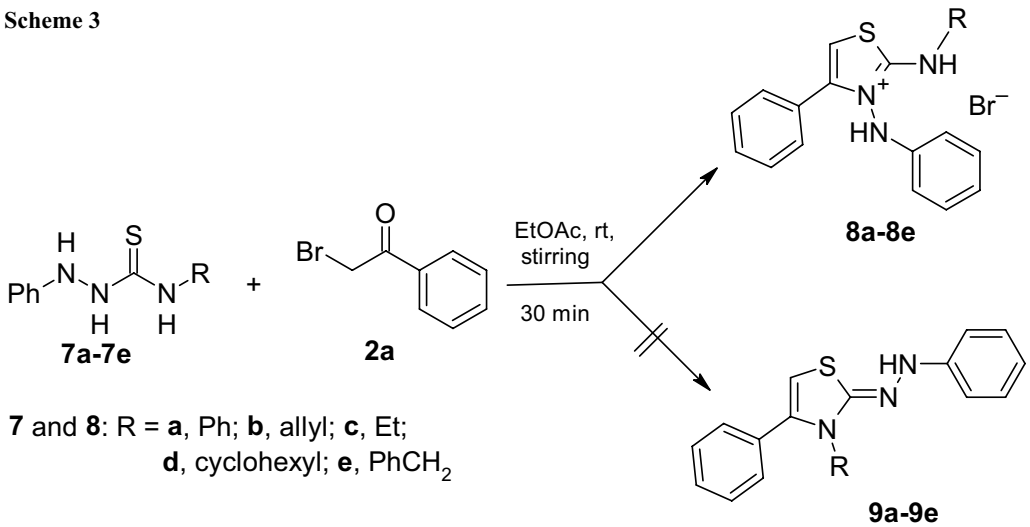
According to the above results, proposed mechanism for the formation of 4-aryl-2-amino-3-(phenylamino)thiazol-3-ium bromide derivatives **8a**–**8e** is illustrated in Scheme 4. This showed that the heterocyclization takes place via sulfur atom and N^2 due to their high nucleophilicity (Scheme 4).

Optimization of the reaction conditions between thiosemicarbazides and phenacyl bromides

Therefore, the optimized reaction conditions involved mixing equimolar amounts of compound **1a**–**1d** or **7a**–**7e** and **2a**, **2b** at room temperature in ethyl acetate (as dipolar aprotic solvent). The solvent, temperature, and the molar ratio of the reactants may all play a critical role on the reaction pathway and these variables were investigated. Different solvents such as tetrahydrofuran (THF), 1,2-dichloroethane, and acetonitrile were studied, but ethyl acetate proved to be the selective solvent. The main factor that controls the process to obtain the target products is to carry out the reactions at room temperature and ethyl acetate was the best solvent chosen to get high yields.

Increasing the amounts of compound **1a**–**1d** or **7a**–**7e** showed that there were no needs to improve the yields of products. The effect of different basic media was investigated, and ethyl acetate without any additive showed high activity.

Scheme 3



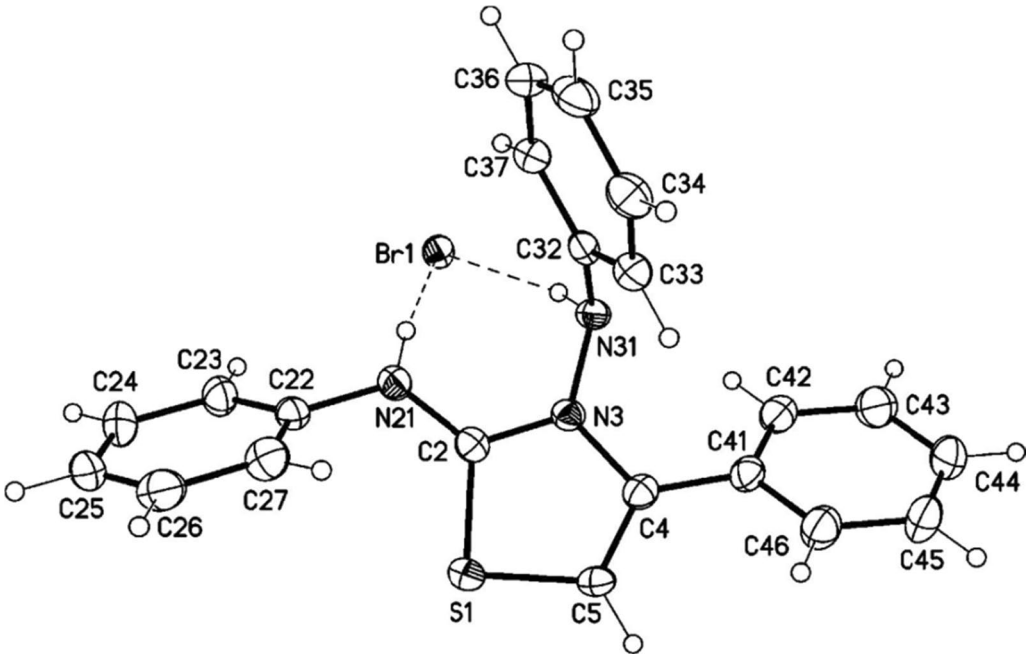
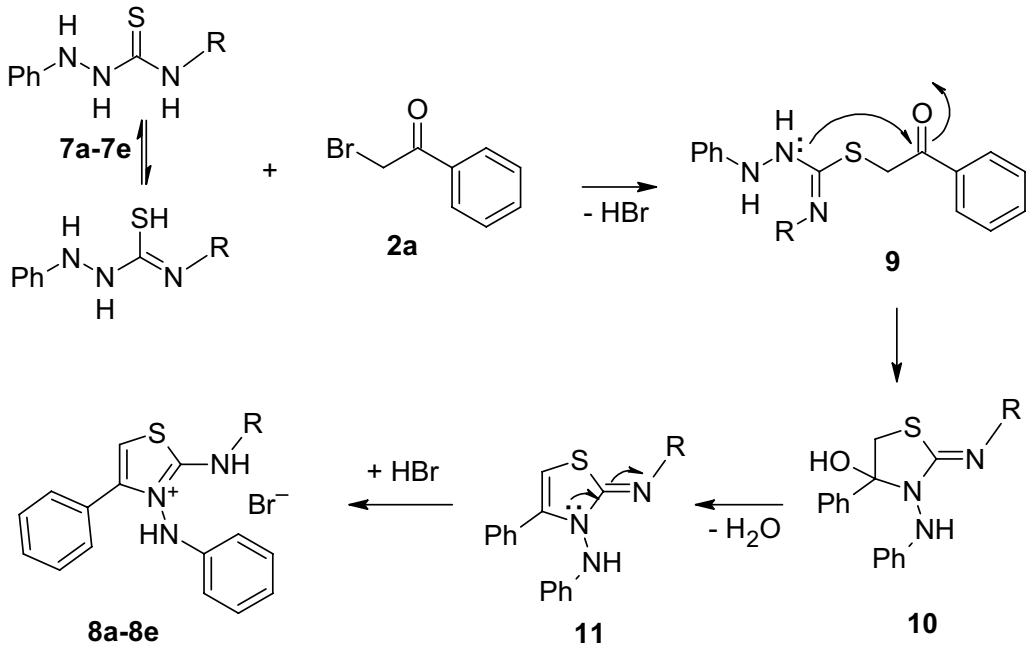


Fig. 3 Molecular X-ray structure of 4-phenyl-2,3-bis(phenylamino)thiazol-3-ium bromide (**8a**)

Scheme 4



Conclusion

Our studies resulted in the construction of novel two groups of substituted thiazolium salts 2,4-disubstituted and 2,3,4-trisubstituted thiazolium bromide derivatives in high yields via one step reaction and at ambient temperature in the presence of ethyl acetate as solvent. Simple and efficient procedures were used to synthesize the thiazolium bromides.

Table 1 Optimization of reaction conditions for the formation of **3a** and **8a**

Entry	Solvent	Yield of **3a**/%	Yield of **8a**/%
1	Tetrahydrofuran	34	29
2	1,2-Dichloroethane	46	36
3	Acetonitrile	39	32
4	Ethyl acetate	90	93

Experimental

Gallenkamp melting point apparatus was used to determine the melting points. IR spectra were recorded with Alpha, Bruker FT-IR instruments using potassium bromide pellets. NMR spectra were recorded for ^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz on a Bruker AM 400 spectrometrer with TMS as internal standard ($\delta = 0$ ppm), and data are reported as follows: chemical shift, multiplicity (s = singlet, t = triplet, q = quartet, m = multiplet, and br = broad). For ^{13}C-NMR, spectra were obtained with complete proton decoupling. Finnigan MAT instrument was used to record the mass spectra (70 eV, EI-mode). Elemental analyses for C, H, N, and S were carried out using an Elmer 306.

Mono and di-substituted thiosemicarbazides were prepared according to literature methods (**1a** [24], **1b** [25], **1c** [26], **1d** [27], **7a**–**7e** [28]). Phenacyl bromides **2a**, **2b** were prepared according to literature [29, 30].

Synthesis of 4-substituted 2-(2-hydrazinyl) thiazol-3-ium bromides 3a–3g

A solution of 1.0 mmol of N-substituted thiosemicarbazides **1a**–**1d** in 15 cm^3 ethyl acetate was added to 1.0 mmol of phenacyl bromides **2a**, **2b** dissolved in 10 cm^3 ethyl acetate. The mixture was stirred for 30 min and allowed to stand overnight, after completion of the reaction; the formed precipitate was filtered, washed several times with ethyl acetate to afford the target products **3a**–**3g** (yields 84–93%).

2-[2-(2,4-Dinitrophenyl)hydrazinyl]-4-phenylthiazol-3-ium bromide ($C_{15}H_{12}BrN_5O_4S$, 3a) Orange crystals (acetonitrile); yield 0.394 g (90%); m.p.: 202–204 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.21$–7.40 (m, 5H, Ar–H), 7.48–7.55 (m, 1H, Ar–H), 7.82 (s, 1H, thiazole-H), 8.34–8.43 (m, 1H, Ar–H), 8.83–8.92 (m, 1H, Ar–H), 10.20 (br, s, 1H, NH), 10.63 (br, s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 115.6$ (C-5), 123.9, 125.5, 127.6, 128.6, 130.0, 130.4 (Ar–CH), 131.3, 134.8, 136.4, 148.6 (Ar–C), 150.5 (C-4), 170.5 (C-2) ppm; IR (KBr): $\bar{\nu} = 3220$ (NH), 3102 (Ar–CH), 1611 (C=N), 1591 (Ar–C=C), 1528 and 1335 (NO_2) cm^{-1}; MS (70 eV): $m/z = 439/441$ (M^+, 6), 357 (M^+-HBr, 28), 257 (10), 191 (15), 168 (46), 153 (100), 105 (18), 91 (25).

4-Phenyl-2-(2-phenylhydrazinyl)thiazol-3-ium bromide ($C_{15}H_{12}BrN_5O_4S$, 3b) Colorless crystals (acetonitrile); yield 0.309 g (89%); m.p.: 152–153 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.36$–7.48 (m, 4H, Ar–H), 7.61–7.70 (m, 3H, Ar–H and thiazole-H), 7.97–8.08 (m, 5H, Ar–H and NH), 8.39 (br, s, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 117.6$ (C-5), 123.5, 125.9, 128.6, 129.0, 129.9, 133.4 (Ar–CH), 133.5, 155.1 (Ar–C), 150.9 (C-4), 175.4 (C-2) ppm; IR (KBr): $\bar{\nu} = 3175$ (NH), 3097 (Ar–CH), 1618 (C=N), 1577 (Ar–C=C) cm^{-1}; MS (70 eV): $m/z = 347/349$ (M^+, 9), 267 (M^+-HBr, 100), 191 (33), 167 (22), 105 (55), 77 (13).

2-[2-(3-Chlorophenyl)hydrazinyl]-4-phenylthiazol-3-ium bromide ($C_{15}H_{13}BrClN_3S$, 3c) Colorless crystals (acetonitrile); yield 0.329 g (86%); m.p.: 163–164 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 6.98$–7.22 (m, 3H, Ar–H and thiazole-H), 7.39–7.52 (m, 2H, Ar–H and NH), 7.64–7.71 (m, 2H, Ar–H), 7.91–8.07 (m, 4H, Ar–H), 8.45 (br, s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 117.9$ (C-5), 122.3, 123.3, 125.5, 128.8, 129.2, 131.5, 132.2 (Ar–CH), 133.6, 134.8, 155.4 (Ar–C), 151.7 (C-4), 175.1 (C-2) ppm; IR (KBr): $\bar{\nu} = 3215$ (NH), 3087 (Ar–CH), 1621 (C=N), 1589 (Ar–C=C) cm^{-1}; MS (70 eV): $m/z = 383/387$ (M^+, 5), 303 (33), 301 (M^+-HBr, 100), 191 (22), 161 (23), 141 (29), 113 (47), 111 (15).

4-Phenyl-2-(2-tosylhydrazinyl)thiazol-3-ium bromide ($C_{16}H_{16}BrN_3O_2S_2$, 3d) Red crystals (acetonitrile); yield 0.396 g (93%); m.p.: 185–186 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.35$ (s, 3H, CH_3), 7.35–7.41 (m, 3H, Ar–H), 7.50–7.62 (m, 5H, Ar–H and thiazole-H), 7.66–7.73 (m, 2H, Ar–H), 10.02 (br, s, 1H, NH), 10.33 (br, s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 20.9$ (CH_3), 114.6 (C-5), 127.5, 128.7, 129.8, 130.0, 130.9 (Ar–CH), 133.3, 134.9, 144.8 (Ar–C), 151.8 (C-4), 174.3 (C-2) ppm; IR (KBr): $\bar{\nu} = 3156$ (NH), 3086 (Ar–CH), 2982 and 2832 (ali-CH), 1597 (Ar–C=C) cm^{-1}; MS (70 eV): $m/z = 425/427$ (M^+, 8), 345 (M^+-HBr, 100), 191 (24), 185 (33), 161 (43), 155 (65), 105 (8), 91 (6).

4-(4-Bromophenyl)-2-(2-phenylhydrazinyl)thiazol-3-ium bromide ($C_{15}H_{13}Br_2N_3S$, 3e) Colorless crystals (acetonitrile); yield 0.371 g (87%); m.p.: 176–177 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.48$–7.52 (m, 3H, Ar–H and NH), 7.62–7.70 (m, 3H, Ar–H and NH), 8.00–8.18 (m, 5H, Ar–H), 8.48 (br, s, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 114.6$ (C-5), 118.3, 122.9, 129.6, 130.7, 132.7 (Ar–CH), 123.5, 127.9, 149.9 (Ar–C), 150.9 (C-4), 175.5 (C-2) ppm; IR (KBr): $\bar{\nu} = 3241$ (NH), 3054 (Ar–CH), 2925 (ali-CH), 1623 (C=N), 1597 (Ar–C=C) cm^{-1}; MS (70 eV): $m/z = 427/431$ (M^+, 3), 347/349 (M^+-HBr, 100), 271/273 (33), 241/243 (46), 181/183 (25), 167 (7), 107 (20), 77 (55).

4-(4-Bromophenyl)-2-[2-(3-chlorophenyl)hydrazinyl]thiazol-3-ium bromide ($C_{15}H_{12}Br_2ClN_3S$, 3f) Colorless crystals (acetonitrile); yield 0.387 g (84%); m.p.: 190–191 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.93–7.10 (m, 4H, Ar–H and thiazol-H), 7.37–7.51 (m, 2H, Ar–H and NH), 7.65–7.73 (m, 1H, Ar–H), 7.94–8.05 (m, 3H, Ar–H), 8.45 (br, s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 119.1 (C-5), 122.2, 124.3, 128.9, 129.6, 130.8, 132.4 (Ar–CH), 123.0, 128.0, 134.5, 149.7 (Ar–C), 151.8 (C-4), 175.6 (C-2) ppm; IR (KBr): $\overline{\nu}$ = 3210 (NH), 3099 (Ar–CH), 1617 (C=N), 1591 (Ar–C=C) cm^{-1}; MS (70 eV): *m/z* = 461/467 (M^+, 6), 381/385 (M^+-HBr, 100), 269/271 (52), 201 (13), 181/183 (41), 111/112 (71), 105 (83).

4-(4-Bromophenyl)-2-(2-tosylhydrazinyl)thiazol-3-ium bromide ($C_{16}H_{15}Br_2N_3O_2S_2$, 3g) Violet crystals (acetonitrile); yield 0.439 g (87%); m.p.: 213–215 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.38 (s, 3H, CH_3), 7.38–7.43 (m, 2H, Ar–H), 7.48–7.57 (m, 5H, Ar–H and thiazole-H), 7.69–7.74 (m, 2H, Ar–H), 10.04 (br, s, 1H, NH), 10.31 (br, s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.9 (CH_3), 112.4 (C-5), 127.8, 129.6, 130.2, 130.5 (Ar–CH), 121.9, 133.3, 135.0, 144.8 (Ar–C), 151.8 (C-4), 173.9 (C-2) ppm; IR (KBr): $\overline{\nu}$ = 3225 (NH), 3094 (Ar–CH), 1615 (C=N), 1590 (Ar–C=C) and 1523 and 1333 (NO_2) cm^{-1}; MS (70 eV): *m/z* = 505/509 (M^+, 12), 425/427 (M^+-HBr, 100), 269/271 (15), 241/243 (12), 183 (35), 181 (15), 155 (55), 91 (90), 77 (50).

Synthesis of 4-aryl-2-amino-3-(phenylamino)-thiazol-3-ium bromide derivatives 8a–8e

To a stirred solution of 0.198 g phenacyl bromide **2a** (1.0 mmol) in 10 cm^3 ethyl acetate a solution of appropriate 1-phenyl-4-substituted thiosemicarbazides **7a**–**7e** (1.0 mmol) in 15 cm^3 ethyl acetate was added portion wise and the mixture allowed to stirred at room temperature. During the stirring a precipitate was formed after a few minutes. The reaction mixture was left overnight, and the precipitate was collected through filtration, washed with ethyl acetate several times to obtain the final products **8a**–**8e** in high purity and in good yields (88–97%).

4-Phenyl-2,3-bis(phenylamino)thiazol-3-ium bromide ($C_{21}H_{18}BrN_3S$, 8a) Colorless crystals (acetonitrile); yield 0.394 mg (93%); m.p.: 165–167 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.60–6.68 (m, 2H, Ar–H), 6.78–6.82 (m, 1H, Ar–H), 7.10–7.15 (m, 2H, Ar–H and thiazole-H), 7.28–7.70 (m, 12H, Ar–H and NH), 9.88 (br, s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 112.7 (C-5), 121.5, 123.6, 128.2, 128.5, 128.8, 129.0, 129.2, 129.9, 130.2 (Ar–CH), 138.0 (C-4), 127.3, 141.1, 144.0 (Ar–C), 168.6 (C-2) ppm; IR (KBr): $\overline{\nu}$ = 3276 (NH), 3020–3110 (Ar–CH), 1595 (Ar–C=C) cm^{-1}; MS (70 eV): *m/z* = 425/427 (M^+, 4), 343 (M^+-HBr, 100), 253 (40), 209 (3), 135 (18), 93 (5), 77 (57).

2-(Allylamino)-4-phenyl-3-(phenylamino)thiazol-3-ium bromide ($C_{18}H_{18}BrN_3S$, 8b) Colorless crystals (acetonitrile); yield 0.376 g (97%); m.p.: 182–183 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.08–5.12 (m, 4H, allyl-CH_2N), 5.15–5.22 (allyl-CH_2=), 5.72–5.82 (m, 1H, allyl-CH=), 6.80–6.86 (m, 2H, Ar–H and thiazole-H), 6.92–6.98 (m, 3H, Ar–H), 7.12–7.15 (m, 3H, Ar–H), 7.42–7.52 (m, 4H, Ar–H and NH), 9.42 (br, s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 64.6 (allyl-CH_2N), 113.6 (C-5), 118.8 (allyl-CH_2=), 122.5, 127.2, 129., 129.4, 129.8, 130.7 (Ar–CH), 134.7 (allyl-CH=), 139.6 (C-4), 142.3, 145.0 (Ar–C), 172.9 (C-2) ppm; IR (KBr): $\overline{\nu}$ = 3280 (NH), 3025–3115 (Ar–CH), 2990 and 2946 (ali-CH), 1598 (Ar–C=C) cm^{-1}; MS (70 eV): *m/z* = 387/389 (M^+, 9), 307 (M^+-HBr, 100), 253 (38), 209 (36), 99 (51), 93 (58).

2-(Ethylamino)-4-phenyl-3-(phenylamino)thiazol-3-ium bromide ($C_{17}H_{18}BrN_3S$, 8c) Colorless crystals (acetonitrile); yield 0.353 g (94%); m.p.: 157–158 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.12–1.18 (t, 3H, J = 6.77 Hz, CH_3), 3.96–4.08 (q, 2H, J = 6.77 Hz, CH_2), 6.90–7.00 (m, 3H, Ar–H and thiazole-H), 7.12 (br, s, 1H, NH), 7.25–7.33 (m, 3H, Ar–H), 7.50–7.68 (m, 5H, Ar–H), 9.32 (br, s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.0 (CH_3), 42.7 (CH_2), 113.4 (C-5), 121.4, 126.5, 127.4, 129.2, 129.8, 130.4 (Ar–CH), 139.6 (C-4), 142.0, 145.9 (Ar–C), 172.8 (C-2) ppm; IR (KBr): $\overline{\nu}$ = 3265 (NH), 3023–3112 (Ar–CH), 2989 and 2940 (ali-CH), 1597 (Ar–C=C) cm^{-1}; MS (70 eV): *m/z* = 375/377 (M^+, 11), 295 (100), 253 (45), 209 (88), 195 (52), 102 (25), 93 (41), 87 (29).

2-(Cyclohexylamino)-4-phenyl-3-(phenylamino)thiazol-3-ium bromide ($C_{21}H_{24}BrN_3S$, 8d) Colorless crystals (acetonitrile); yield 0.387 g (90%); m.p.: 173–174 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.07–2.10 (m, 10H, cyclohexyl-CH_2), 3.75–3.93 (m, 1H, cyclohexyl-CH), 6.60–6.75 (m, 3H, Ar–H and thiazole-H), 6.90–7.06 (m, 3H, Ar–H), 7.32–7.58 (m, 3H, Ar–H), 7.80–7.91 (m, 2H, Ar–H), 8.36 (br, s, 1H, NH), 9.80 (br, s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.8, 31.8, 41.3 (cyclohexyl-CH_2), 58.6 (cyclohexyl-CH), 116.0 (C-5), 122.5, 126.4, 127.7, 128.8, 129.4, 130.7 (Ar–CH), 137.9 (C-4), 143.8, 144.3 (Ar–C), 173.9 (C-2) ppm; IR (KBr): $\overline{\nu}$ = 3269 (NH), 3018–3115 (Ar–CH), 2996 and 2943 (ali-CH), 1591 (Ar–C=C) cm^{-1}; MS (70 eV): *m/z* = 429/431 (M^+, 5), 349 (M^+-HBr, 100), 253 (52), 247 (36), 209 (21), 141 (33), 102 (31), 93 (36), 91 (62).

2-(Benzylamino)-4-phenyl-3-(phenylamino)thiazol-3-ium bromide ($C_{22}H_{20}BrN_3S$, 8e) Colorless crystals (acetonitrile); yield 0.386 mg (88%); m.p.: 194–195 °C; ^{1}H NMR

(400 MHz, DMSO-d_6): $\delta = 5.40$ (s, 2H, CH_2-benzyl), 6.72–6.78 (m, 2H, Ar–H), 6.88–6.92 (m, 1H, Ar–H), 7.02–7.06 (m, 2H, Ar–H), 7.20–7.28 (m, 3H, Ar–H, and thiazole-H), 7.35–7.43 (m, 3H, Ar–H), 7.46–7.60 (m, 6H, Ar–H and NH), 9.20 (br, s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 49.9$ (CH_2-benzyl), 113.4 (C-5), 121.4, 126.2, 128.3, 128.9, 129.0, 129.2, 129.5, 130.3 (Ar–CH), 138.5 (C-4), 173.3 (C-2) ppm; IR (KBr): $\bar{\nu} = 3270$ (NH), 3028–3109 (Ar–CH), 2988 and 2938 (ali-CH), 1598 (Ar–C=C) cm^{-1}; MS (70 eV): $m/z = 437/439$ (M^+, 10), 357 (M^+-HBr, 100), 253 (47), 209 (11), 149 (21), 93 (5), 91 (87), 77 (51).

Single crystal X-ray structure determination of 3a, 3d, and 8a

The single-crystal X-ray diffraction study was carried out on a Bruker D8 Venture diffractometer with Photon II detector at 123(2) K using Cu–Kα radiation ($\lambda = 1.54178$ Å). Dual space methods (SHELXT) [31] were used for structure solution and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F^2) [32]. Hydrogen atoms were refined using a riding model (H(N) free). Semi-empirical absorption corrections were applied.

Compound **3a**: $C_{15}H_{12}N_5O_4S{\cdot}Br$, $M = 438.27$ g mol^{-1}, orange crystals, size $0.18 \times 0.14 \times 0.04$ mm, monoclinic, space group $P2_1/c$ (no.14), $a = 15.2596(8)$ Å, $b = 15.8466(8)$ Å, $c = 7.1347(4)$ Å, $\beta = 94.047(2)°$, $V = 1720.96(16)$ Å^3, $Z = 4$, $D_{calcd} = 1.692$ Mg m^{-3}, F(000) = 880, $\mu = 4.70$ mm^{-1}, $T = 123$ K, 18,164 measured reflections ($2\theta_{max} = 144.2°$), 3383 independent [$R_{int} = 0.027$], 244 parameters, 3 restraints, R_1 [for 3226 $I > 2\sigma(I)$] = 0.024, wR^2 (for all data) = 0.065, $S = 1.05$, largest diff. peak and hole = 0.45 e Å^{-3}/ -0.21 e Å^{-3}.

Compound **3d**: $C_{16}H_{16}N_3O_2S_2{\cdot}Br$, $M = 426.35$ g mol^{-1}, red crystals, size $0.12 \times 0.06 \times 0.04$ mm, orthorhombic, space group *Pbca* (no.62), $a = 12.5822(5)$ Å, $b = 15.4936(6)$ Å, $c = 18.1813(8)$ Å, $V = 3544.3(3)$ Å^3, $Z = 8$, $D_{calcd} = 1.598$ Mg m^{-3}, F(000) = 1728, $\mu = 5.49$ mm^{-1}, $T = 123$ K, 36,334 measured reflections ($2\theta_{max} = 144.4°$), 3499 independent [$R_{int} = 0.032$], 227 parameters, 3 restraints, R_1 [for 3340 $I > 2\sigma(I)$] = 0.024, wR^2 (for all data) = 0.064, $S = 1.04$, largest diff. peak and hole = 0.60 e Å^{-3}/− 0.40 e Å^{-3}.

Compound **8a**: $C_{21}H_{18}N_3S{\cdot}Br$, $M = 424.35$ g mol^{-1}, colourless crystals, size $0.36 \times 0.24 \times 0.16$ mm, monoclinic, space group $P2_1/c$ (no.14), $a = 10.7239(4)$ Å, $b = 10.5069(4)$ Å, $c = 16.6705(7)$ Å, $\beta = 90.611(1)°$, $V = 1878.24(13)$ Å^3, $Z = 4$, $D_{calcd} = 1.501$ Mg m^{-3}, $F(000) = 864$, $\mu = 4.09$ mm^{-1}, $T = 123$ K, 10,503 measured reflections ($2\theta_{max} = 144.4°$), 3660 independent [$R_{int} = 0.026$], 241 parameters, R_1 [for 3633 $I > 2\sigma(I)$] = 0.024, wR^2 (for all data) = 0.066, $S = 1.10$, largest diff. peak and hole = 0.50 e Å^{-3}/− 0.27 e Å^{-3}.

CCDC 1,963,830 (**3a**), 1,963,831 (**3d**), and 1,963,832 (**8a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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