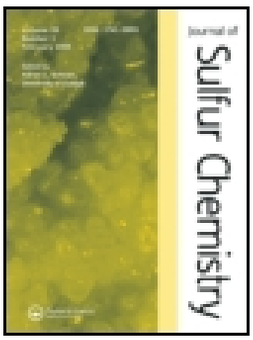

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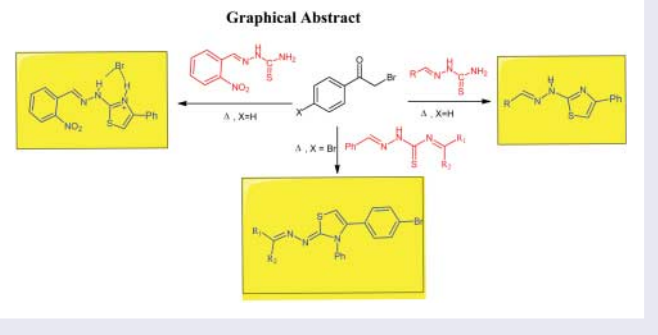
Facile and convenient synthesis of 2,4-disubstituted and 2,3,4-trisubstituted 1,3-thiazoles

Alaa A. Hassan[a], Shaaban K. Mohamed[a,b], Nasr K. Mohamed[a], Kamal M.A. El-Shaieb[a], Ahmed T. Abdel-Aziz[a], Joel T. Mague[c] and Mehmet Akkurt[d]

[a]Chemistry Department, Faculty of Science, Minia University, El-Minia, Egypt; [b]Faculty of Science & Engineering, Metropolitan University, Manchester, England; [c]Department of Chemistry, Tulane University, New Orleans, LA, USA; [d]Department of Physics, Faculty of Sciences, Erciyes University, Kayseri, Turkey

ABSTRACT

An efficient route for the synthesis of (*E*)-2-(2-(2-nitrobenzylidene)-hydrazinyl)-4-phenylthiazol-3-ium bromide, (*E*)-2-(2(substituted benzylidene)hydrazinyl)-4-phenylthiazoles and (*E*)-4-(4-bromophenyl)-2-(cycloalkylidenehydrazono)-3-phenyl-2,3-dihydrothiazoles by reaction of 1-aryl-2-bromoethanones with 2-(1-substituted methylidene)hydrazinecarbothioamides and cycloalkylidene-*N*-phenyl-hydrazinecarbothioamides. The structure of the products has been confirmed by using IR, NMR, mass spectrometry and single-crystal X-ray analyses.



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Aryl-2-bromoethanones; hydrazinecarbothioamides; cyclo-alkylidenehydrazine carbothioamides; Di- and trisubstituted-1,3-thiazoles; thiazolium bromide derivative

Introduction

α-Haloketones are promising synthons for synthesizing carbo- and heterocyclic compounds in preparative organic chemistry.[1] Although the Hantzch method, in which α-haloketone is condensed with a thioamide, has been reported for decades as the method of choice for the synthesis of thiazoles,[2] a great effort has been dedicated for more

CONTACT Alaa A. Hassan alaahassan2001@mu.edu.eg. Chemistry Department, Faculty of Science, Minia University, El-Minia 61519, Egypt

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flexible procedures, and particularly to that of thiazole ring formation. One-pot synthesis via a three-component reaction between aroylisothiocyanates, α-amino acids and α-bromoketones in an ionic liquid was described as a synthesis of thiazole-2(3*H*)imines.[3]

It has been reported that, treatment of freshly prepared differently substituted α-bromoacetophenones with thiourea, afforded the formation of 2-amino-4-phenyl-1,3-thiazole- and 2-amino-4-(4-bromophenyl)-1,3-thiazole in 52% and 47% yields, respectively.[4] Synthetic methods have also been reported for trisubstituted thiazoles.[5–10] Trisubstituted thiazoles were synthesized using ligand-free, palladium-catalyzed, direct 5-arylation of 2,4-disubstituted thiazole and conventional or microwave-assisted heating in low to moderate yields.[11]

In view of the emerging importance of thiazoles and their derivatives, several methods for their synthesis were developed using various catalysts,[12] conditions [13–15] and strategies.[16–19] However, unsatisfactory yields, prolonged reaction times, tedious work up procedures and use of expensive catalysts are still often encountered problems. Therefore, the development of efficient and facile processes is a major challenge for chemists in organic synthesis.

Many natural products [20] containing the thiazole ring have been isolated and most of them exhibited, *e.g.* antimicrobial, antifungal, antihypertensive, anti-inflammatory and antitumor cytotoxic activities.[21–25]

The 2-iminothiazolidine moiety is present in a large variety of physiologically active compounds with applications varying from medicinal to agricultural use.[26] Some 2-iminothiazolidines are useful as schistosomicides [27] and many applications in medicinal chemistry.[28]

2-Imino-4-thiazolidines and 3,4-disubstituted-2-imino-4-thiazolines have been synthesized via condensation α-chloromethyl and α-bromomethyl ketimines with potassium thiocyanate.[29,30]

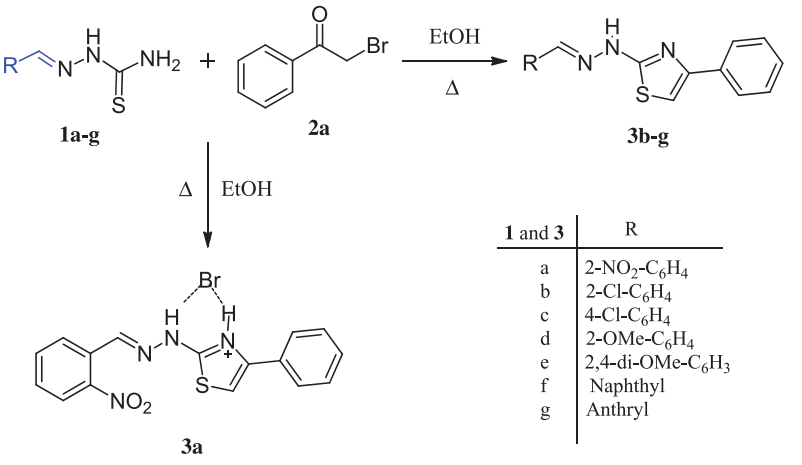
Recently, we have reported the synthesis of 1,3-thiazolylidenehydrazinylidene ethylpyridinum bromide monohydrate, 1,3-thiazolylidenehydrazinum bromide, hemihydrate and 1,3-thiazolylidenehydrazine derivatives by heterocyclization of 2-(1-substituted ethylidene)hydrazinecarbothioamides via reaction with 1-aryl-2-bromoethanones and evaluated their antibacterial activity.[31]

Results and discussion

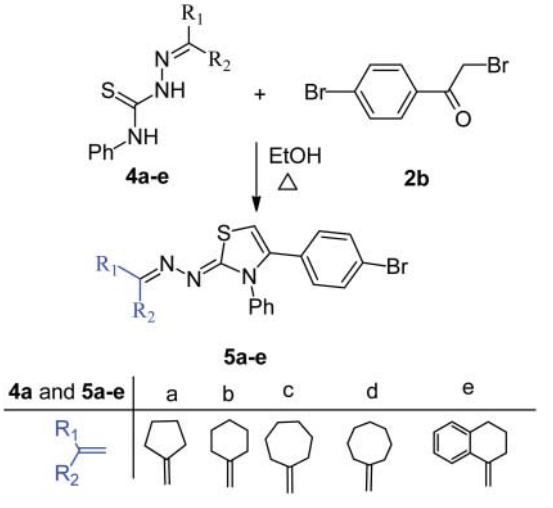
Herein, the behavior of 1-aryl-2-bromoethanones (**2a,b**) towards 2-(1-substituted methylidene) hydrazinecarbothioamides **1a–g** and cycloalkylidene-*N*-phenylhydrazinecarbothio amides **4a–e** will be investigated and compared to the behavior of the same compounds **2a,b** toward 2-(1-substituted ethylidene) hydrazinecarbothioamides.

We also report a facile and efficient preparation of (*E*)-2-(2-(2-nitrobenzylidene) hydrazinyl)-4-phenylthiazol-3-ium bromide **3a**, (*E*)-2-(substituted arylidene)hydrazinyl-4-phenylthiazoles **3b–g** and (*E*)-4-(4-bromophenyl)-2-(cycloalkylidenehydrazono-3-phenyl-2,3-dihydrothiazoles **5a–e** in high yields under mild reaction conditions (Schemes 1 and 2).

Cyclocondensation of 1-aryl-2-bromoethanone (**2a**) with 2(1-substituted methylidene)hydrazinecarbothioamides **1a–g** in absolute ethanol under reflux for 1 h afforded the disubstituted 1,3-thiazoles **3b–g** in 96–98% yields, except in the case of the reaction **2a** with



Scheme 1. The reaction between 2-(1-substituted methylidene)hydrazinecarbonthioamides **1a–g** and 1-aryl-2-bromoethanones (**2a,b**).



Scheme 2. The reaction between cycloalkylidene-N-phenylhydrazinecarbothio amides **4a–e** and 4-bromophenyl-2-bromoethanone (**2b**).

1a, in which (*E*)-2-(2-(2-nitrobenzylidene)hydrazinyl)-4-phenylthiazol-3-ium bromide **3a** (98%) was formed.

A variety of analytical techniques, including IR, NMR, mass spectrometry, elemental analysis and X-ray crystallography, were used to confirm the structural identity of the final products. The target compounds were correctly analyzed for their molecular structure. The infrared spectrum of **3a**, as an example, shows a broad band at 3329 cm^{-1}, which can be attributed to the hydrazine-NH. The IR spectrum of **3a** revealed sharp band at 1616 (C=N), medium band at 1343 (NO_2) and Ar–C=C at 1595 cm^{-1}. A new band at 1033 and 746 cm^{-1} in **3a** was assigned to (C–S–C).[31,32]

The ^{1}H NMR spectrum of **3a** contained two singlets at 7.31 and 8.45 ppm which could be attributed to the thiazole-CH and azomethine CH=N, respectively. A broad exchangeable signal with (D_2O) at 11.18 ppm is attributed to hydrazine-NH. In addition, the presence of multiplets in the range 7.32–8.06 ppm is ascribed to nine aromatic protons. Moreover, the ^{13}C NMR spectrum showed a peak appearing at 167.69 ppm corresponds to thiazole-C2. Signals at 150.42, 147.33 and 104.33 are due to thiazole-C5, azomethine-CH and thiazole-CH, respectively. The aryl-C and aryl-CH were also observed (see experimental design section). In the mass spectra of **3a–g**, molecular ion peaks of all compounds were obtained from EI-MS, but the molecular ion peak abundances were not strong. The mass

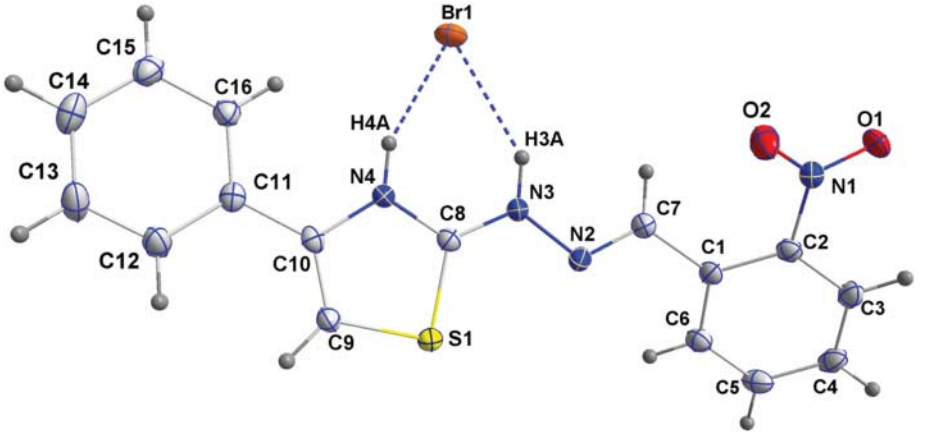


Figure 1. The title compound **3a** with labeling scheme and 50% probability ellipsoids. The N–H . . . Br interactions are shown as dotted lines.

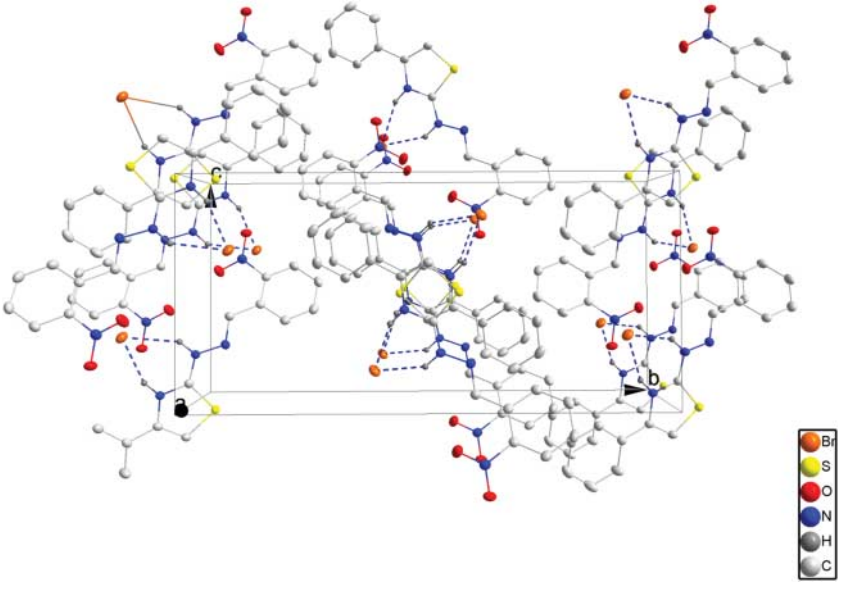


Figure 2. Packing viewed down the *a*-axis. The N–H . . . Br interactions are shown as dotted lines.

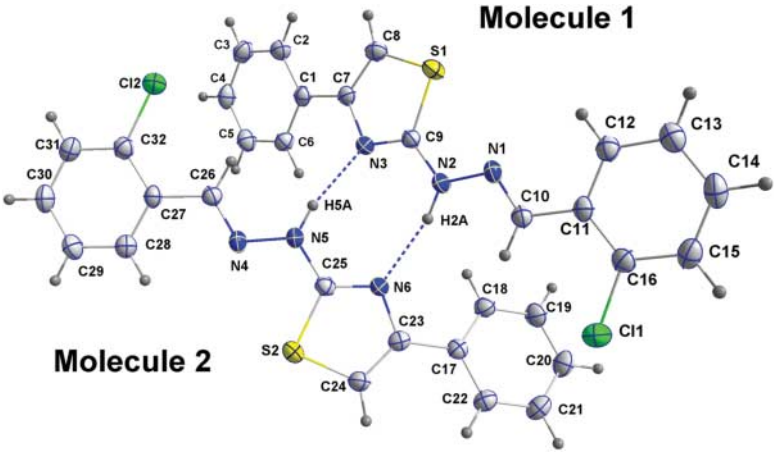


Figure 3. The asymmetric unit of **3b** with the complementary N–H . . . N hydrogen bonds shown as dotted lines. Ellipsoids are drawn at the 50% probability level.

spectrometry fragmentations are characterized by the fragments (M^+-Ar-CH=N) and (M^+-$C_9H_7N_3S$), and have a peak at 102 a.m.u due to [Ar–C≡N]$^+$. The identities of (*E*)-2-(2-substituted benzylidene)hydrazinyl)-4-phenylthiazoles **3a–g** were further confirmed by single-crystal X-ray crystallographic studies for compounds **3a** and **3b**. The ORTEP view of the title compound (*E*)-2-2[2-(2-nitrobenzylidene)hydrazinyl]-4-phenylthiazole **3a** and packing viewed down the *a*-axis are shown in Figures 1 and 2, respectivly. H-atoms attached to carbon were placed in calculated positions (C–H = 0.95—0.98 Å) while those attached to nitrogen were placed in locations derived from a difference map and their parameters adjusted to give N–H = 0.91 Å. All were included as riding contributions with isotropic displacement parameters 1.2–1.5 times those of the attached atoms. Tables 5–7 in the supplementary data show the values of the selected geometric parameters and they are normal. The details of N–H . . . Br intramolecular interactions are given in Table 10 in the supplementary data. The bromide ion is associated with both N–H groups. The cations pack in columns in which adjacent pairs of cations are arranged in an anti-parallel fashion with the thiazolidene rings eclipsed (Figure 2) and the separation of their mean planes is 3.32 (3)°. The distance between the ring centroids is 3.50 (2)°.

The X-ray study of **3b** showed that the asymmetric unit of the title compound 2-[(*E*)-2-[2-chlorobenzylidene]hydrazin-1-yl]-4-phenyl-1,3-thiazole, $C_{16}H_{12}ClN_3S$, contains two independent molecules whose conformations differ primarily in the orientation of the phenyl and chlorobenzene rings with respect to the thiazole ring.

In the crystal, the two independent molecules are associated via complementary N–H . . . ..N hydrogen bands into a dimer. These dimers are associated through weak C–H . . . .Cl and C–H . . . .S interactions into supramolecular chains propagating along the *a*-axis direction (Figure 3).[33]

Compound **3a** contains NO_2 in the aryl group (strong electron withdrawing group). This NO_2 group increased the positive charge on the aromatic ring and consequently on the NH group. This will facilitate the attraction forces between Br^- and delta positive charge on hydrogen atom.

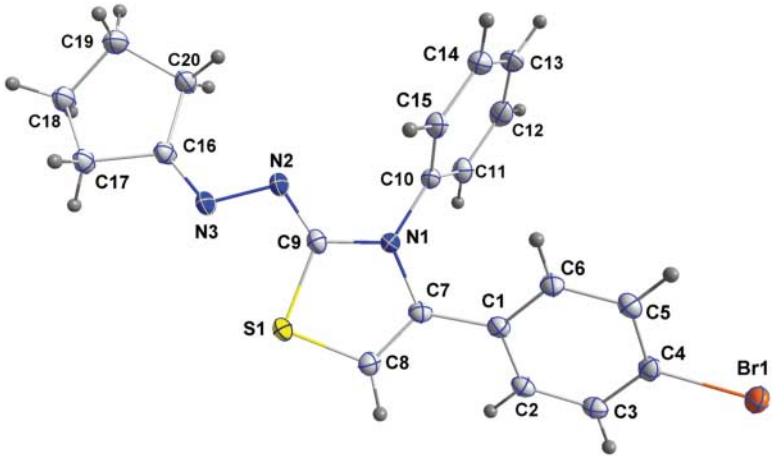


Figure 4. The title compound **5a** with 50% probability displacement ellipsoids for non-hydrogen atoms.

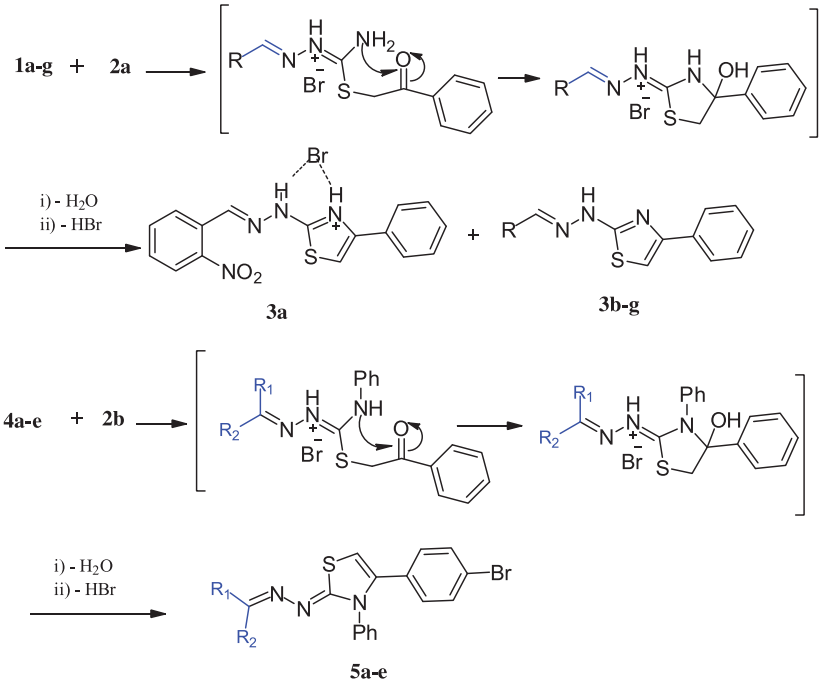
Interestingly, further application of our optimized reaction conditions to *Z*-cycloalkylidene-*N*-phenylhydrazinecarbothioamides **4a–e** and 4-bromophenyl-2-bromoethanone (**2b**) provided the corresponding (*E*)-4-(4-bromophenyl)-2-(cycloalkylidenehydrazono)-3-phenyl-2,3-dihydrothiazoles **5a–e** in 95–97% yields. Cycloalkylidene-*N*-phenylhydrazin ecarbothioamides **4a–e** was prepared according to published procedures.[34,35]

Reaction of **2b** with cycloalkylidene -*N*-phenylhydrazinecarbothioamides **4a–e** in a molar ratio of (1:1) in absolute ethanol has been carried out under reflux with stirring for 1 h. The progress of the reaction was monitored by TLC until completion, and a pale yellow precipitate from **5a–e** was separated (Scheme 2).

The results of combustion analyses and spectroscopic data of **5a–e** suggested the presence of (*E*)-4-(4-bromophenyl)-2-(cycloalkylidenehydrazono)-3-phenyl-2,3-dihydrothia zoles. The gross formula ($C_{20}H_{18}BrN_3S$) of **5a**, as an example, was confirmed by mass spectrometry and exhibited its molecular ion peak at $m/z = 411/413$ (80%) which is in agreement with the proposed structure and clearly shows the addition of one molecule of **2b** to one molecule of **4a** with elimination a molecule of HBr and H_2O.

^{1}H NMR of **5a** showed the appearance of cyclo-pentylidene-CH_2 at $\delta_H = 1.63$ (4H), 2.20 (2H) and 2.32 (2H) as multiplets representing $(CH_2)_2$ and $(CH_2)_2C{=}N$, respectively. A sharp singlet at 6.62 due to thiazole-CH, another multiplets at 7.07–7.45 due to aryl groups. The presence of cyclo-pentylidene-CH_2 is evident from DEPT spectra exhibiting negative signals at 24.08, 24.48, 29.78 and 31.12 ppm. In the ^{13}C NMR spectrum of **5a**, thiazole-C2 and C4 resonate at 165.54 and 137.94 ppm, respectively, further peaks are at $\delta_C = 171.79$ (cyclopentyl-C=N), and 101.78 (thiazole-CH).

Moreover, the structure of **5a** was confirmed unambiguously by the single-crystal X-ray structure analysis (Figure 4).[36] Figure 4 shows the structure of (2*E*)-4-(4-bromophenyl)-2-[2-[(1*E*)-cyclo-pentylidene]hydrazin-1-ylidene]-3-phenyl-2,3-dihydro-1,3-thiazole **5a** in which the cyclopentyl ring adopts a half-chair conformation. The 4-bromophenyl and phenyl rings are twisted out of the plane of the thiazole ring with dihedral angles of 34.6 (1)° and 68.32 (6)°, respectively.[36]



Scheme 3. Mechanistic rationale for the formation of compounds **3a–g** and **5a–e**.

The rational for the formation of **3a–g** and **5a–e** is depicted in scheme 3.

As a result, this synthesis allows much wider substrate scope and provides a general and practical access to the target products. It was found that solvent, temperature and the molar ratio of reactants may all play a critical role on the reaction efficiency. The influence of different solvents has been studied and found that absolute ethanol was a superior solvent compared with benzene, THF, DMF, ethyl acetate and ethylene chloride which gave traces of products.

An increased amount of **2a** as well as **2b** was not necessary to obtain the products in pure and high yields.

Therefore, applying the reactions in absolute ethanol under reflux and using equimolar ratios of **1a–g** with **2a** or **4a–e** with **2b** is chosen as the optimized reaction conditions.

Conclusion

An efficient and facile process for the synthesis of di-and trisubstituted-1,3-thiazoles has been reported. The advantage of this procedure is fast reaction time and high yields without use of expensive catalysts.

Experimental design

Instruments

Melting points were determined using open glass capillaries on a Gallenkamp melting point apparatus, and uncorrected. IR spectra were recorded from potassium bromide disks

on Alpha, Bruker FT-IR. ^{1}H- and ^{13}C NMR spectra (300 MHz for ^{1}H, 75 MHz for ^{13}C) were observed in $CDCl_3$ and DMSO-d_6 as a solvent, on Varian mercury plus 300 spectrometer with tetramethylsilane as an internal standard. The ^{13}C NMR signals were assigned with the aid of DEPT experiments. Mass spectra were obtained in Varian MAT 311 doubly focusing instrument using electron impact ionization (70 eV). X-ray diffractions were measured using Bruker SMART APEXCCD diffractometer with Graphite monochromator and five-focus sealed tube as a Radiation source. TLC was performed as analytical merck 9385 silica aluminum sheets (Kieselgel 60) with pf_{254} indicator; TLC's were viewed at $\lambda_{max} = 254$ nm. The elemental analysis was carried out at the Microanalytical Center, Cairo University, Egypt.

X-ray data were collected using a Bruker D8 VENTURE PHOTON 100 CMOS diffractometer using CuKα radiation in the ω-scan mode at 150(2) K. Data have been processed using APEX2 and SAINT softwares.[37] The numerical absorption correction was applied using the SADABS program.[37] The crystal structure was solved by direct methods using SHELXT,[37] and refined by a full-matrix least-squares procedure based on F2 (SHELXL-2014).[38] The molecular graphics were drawn using the DIAMOND [39] and SHELXT programs.[37]

Starting materials

1-Aryl-2-bromoethanones (**2a,b**) were prepared according to Nobuta et al., [40] and Salama and Novák [41] 2-(1-Substituted methylidene)hydrazinecarbonthioamides **1a–g** were prepared by condensation of phenyl thiosemicarbazide with appropriate aldehydes according to the published procedure.[42] Cycloalkylidene-*N*-substituted hydrazinecarbothioamides **4a–e** were prepared according to the published procedures.[34,35]

2-Cycloocytylidene-N-phenyl hydrazinecarbothioamides (4d)

Colorless crystals (0.269 g, 98%), m.p = 100–102°C, IR (KBr): υ = 3080 (Ar–CH), 2927 (Ali-CH), 1617 (C=N), 1593 (Ar-C=C), 1560 (NH def. and C–N str.), 1362, 990 (C=S and C–N). ^{1}H NMR ($CDCl_3$): δ_H = 1.53–1.54 (m, 2H, CH_2), 1.55–1.56 (m, 4H, $2CH_2$), 1.79–1.81 (m, 4H, $2CH_2$), 2.41–2.42 (m, 4H, $2CH_2$), 7.19–7.23 (m, 1H, Ar-H), 7.36–7.40 (m, 2H, Ar–H), 7.68–7.72 (m, 2H, Ar–H), 8.62 (br, s, 1H, NH), 9.32 (br, s, 1H, NHPh); ^{13}C NMR ($CDCl_3$): δ_C = 24.56,24.92, 25.29, 26.55, 27.33, 28.09, 36.36 (CH_2), 124.18, 125.93, 128.77 (Ar–CH), 138.13 (Ar–C), 158.85 (C=N), 176.0 (C=S). Anal. Calcd. for $C_{15}H_{21}N_3S$: C, 65.41; H, 7.69; N, 15.26; S, 11.64. Found: C, 65.27; H, 7.78; N, 15.41; S, 11.49.

(E)-2-(3,4-Dihydronaphthalen-1(2H)-ylidene)-N-phenylhydrazinecarbothioamide (4e)

Colorless crystals (0.286 g, 97%), m.p = 186–188°C, IR (KBr): υ = 3091 (Ar–CH), 2937 (Ali-CH), 1624 (C=N), 1602 (Ar–C=C),1556 (NH def. and C–N str.), 1360, 992 (C=S and C–N). ^{1}H NMR ($CDCl_3$): δ_H = 1.96–2.01 (m, 2H, CH_2), 2.64–2.67 (m, 2H, CH_2) 2.75–2.82 (m, 2H, CH_2), 7.19–7.24 (m, 1H, Ar–H), 7.26–7.32 (m, 1H, Ar–H), 7.38–7.42 (m, 1H, Ar–H), 8.02–8.04 (m, 1H, Ar–H), 8.87 (br, s, 1H, NH), 9.45 (br, s, 1H, NHPh); ^{13}C NMR ($CDCl_3$): δ_C = 21.52, 25.71, 29.44 (CH_2), 124.56, 126.77, 130.02 (Ar–CH), 138.01, 140.59 (Ar–C), 147.24 (C=N), 176.16 (C=S). Anal. Calcd. for $C_{17}H_{17}N_3S$ (295.40): C, 69.12; H, 5.80; N, 14.22; S, 10.85. Found: C, 68.96; H, 5.88; N, 14.36; S, 11.03.

General procedure of synthesis of di-and trisubstituted thiazoles 3a–g and 5a–e

A mixture of (1.0 mmol) 1-aryl-2-bromoethanones (**2a,b**) and (1.0 mmol) from each of 2-(1-substituted methylene)hydrazinecarbothioamides **1a–g** or cycloalkylidene-*N*-substituted hydrazinecarbothioamides (**4a–e**) in absolute ethanol (30 ml) was refluxed for 1 h, then cooled to room temperature. A yellow solid precipitate was filtered and washed with a small amount of ethanol and recrystallized from ethanol to give pure crystals from **3a–g** to **5a–e**.

(E)-2-2[2-(2-Nitrobenzylidene)hydrazinyl]-4-phenylthiazole-3-ium bromide (3a)

Yellow crystals (ethanol) (0.317 g, 98%), m.p = 244–246°C, IR (KBr): υ = 3329 (NH), 1616 (C=N), 1595 (Ar–C=C), 1343 (NO_2), 1033, 746 (C–S–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ_H = 7.31 (s, 1H, thiazole-CH), 7.32–7.34 (m, 1H, Ar–H), 7.41–7.43 (m, 2H, Ar–H), 7.60–7.64 (m, 1H, Ar–H), 7.78–7.87 (m, 1H, Ar–H), 7.87–7.89 (m, 2H, Ar–H), 8.03–8.06 (m, 2H, Ar–H), 8.45 (s, 1H, CH=N), 11.18 (s, br, 1H, NH);^{13}C NMR (DMSO-d_6): δ_C = 104.33 (thiazole-CH), 124.63, 125.47, 127.40, 127.86, 128.56, 129.65 (Ar–CH), 131.26, 133.43, 144.33 (Ar–C), 147.33 (CH = N), 150.42 (thiazole-C5), 167.69 (thiazole-C2), EI-mass, *m/z* (%) 405/407 (M^+,11), 324 (36), 278 (6), 175 (13), 135 (90), 102 (100), 76 (89). Anal. Calcd. for $C_{16}H_{13}BrN_4O_2S$ (405.27): C, 47.42; H, 3.23; Br, 19.72; N, 13.82; S, 7.91 Found: C, 47.58; H, 3.17; Br, 19.60, N, 13.94; S, 8.07.

(E)-2-[2-(2-Chlorobenzylidene)hydrazinyl]-4-phenylthiazole (3b)

Yellow crystals (ethanol, (0.300 g, 96%), m.p = 208–210°C, IR (KBr): υ = 3323 (NH), 1620 (C=N), 1602 (Ar–C=C), 1040, 750 (C–S–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ_H = 7.32 (s, 1H, thiazole-CH), 7.39–7.43 (m, 6H, Ar–H), 7.86–7.88 (m, 3H, Ar–H), 8.41 (s, 1H, CH=N), 11.08 (s, br, NH).^{13}C NMR (DMSO-d_6): δ_C = 104.01 (thiazole-CH), 125.45, 126.10, 127.52, 128.25, 128.55, 129.73 (Ar–CH), 131.91, 133.11, 134.86 (Ar–C), 147.80 (CH=N), 150.38 (thiazole-C5), 167.80 (thiazole-C2), EI-mass, *m/z* (%) 313/315 (M^+, 9), 175 (36), 135 (100), 125 (58), 89 (60), 77 (82). Anal. Calcd. for $C_{16}H_{12}ClN_3S$ (313.80): C, 61.24; H, 3.85; Cl, 11.30; N, 13.39; S, 10.22. Found: C, 61.07; H, 3.91; Cl, 11.42; N, 13.26; S, 10.32.

(E)-2-[2-(4-Chlorobenzylidene)hydrazinyl]-4-phenylthiazole (3c)

Yellow crystals (ethanol), (0.303 g, 97%), m.p = 216–218°C. IR (KBr): υ = 3321 (NH), 1621 (C=N), 1600 (Ar–C = C), 1041, 749 (C–S–C) cm^{-1},^{1}H NMR (DMSO-d_6): δ_H = 7.30 (s, 1H, thiazole-CH), 7.31–7.33 (m, 1H, Ar–H), 7.41–7.45 (m,2H, Ar–H), 7.46–7.51 (m, 2H, Ar–H), 7.86–7.88 (m, 2H, Ar–H), 7.93–7.95 (m, 2H, Ar–H), 8.43 (s,1H, CH=N), 11.12 (s, br, NH), ^{13}C NMR (DMSO-d_6): δ_C = 104.16 (thiazole-CH), 123.59, 127.64, 127.68, 122.89, 128.36 (Ar–CH), 131.21, 133.35, 137.47 (Ar–C), 147.90 (CH=N), 150.30 (thiazole-C5), 167.92 (thiazole-C2), EI-mass, *m/z* (%) 313/315 (M^+,9), 175 (40), 135 (100), 125 (55), 89 (65), 77 (85). Anal. Calcd. for $C_{16}H_{12}ClN_3S$ (313.80): C, 61.24; H, 3.85; Cl, 11.30; N, 13.39; S, 10.22. Found: C, 61.13; H, 3.94; Cl, 11.46; N, 13.22; S, 10.09.

(E)-2-[2-(2-Methoxybenzylidene)hydrazinyl]-4-phenylthiazole (3d)

Yellow crystals (ethanol), (0.302 g, 98%), m.p = 248–250°C, IR (KBr): υ = 3339 (NH), 1617 (C=N),1590 (Ar–C=C), 1032, 744 (C–S–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ_H = 3.86

(s, 3H, OCH_3), 7.01–7.05 (m, H, Ar–H), 7.09–7.11 (m, 1H, Ar–H), 7.33 (s, 1H, thiazole-CH), 7.35–7.41 (m, 2H, Ar–H), 7.43–7.45 (m, 2H, Ar–H), 7.81–7.86 (m, 3H, Ar–H), 8.44 (s, 1H, CH=N), 11.05 (s, br, NH), ^{13}C NMR (DMSO-d_6): δ_C = 55.73 (OCH_3), 103.78 (thiazole-CH), 122.17, 125.02, 125.72, 127.90, 128.36, 128.71 (Ar–CH), 131.06, 133.83 (Ar–C), 148.08 (CH=N), 150.27 (thiazole-C5), 157.30 (Ar–C–O), 168.36 (thiazole-C2). EI-mass, *m/z* (%) 309 (M^+,10), 175 (35), 135 (79), 91 (39), 77 (100). Anal. Calcd. for $C_{17}H_{15}N_3OS$ (309.39): C, 66.00; H, 4.89; N, 13.58; S, 10.36. Found: C, 65.84; H, 4.96; N, 13.66; S, 10.55.

(E)-2-[2-(3,4-Dimethoxybenzylidene)hydrazinyl]-4-phenylthiazole (3e)

Yellow crystals (ethanol), (0.328 g, 97%), m.p = 256–258°C. IR (KBr): υ = 3317 (NH), 1613 (C=N), 1585 (Ar–C=C), 1035,748 (C–S–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ_H = 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 7.00–7.03 (m,1H, Ar–H), 7.18–7.20 (m, 1H, Ar–H), 7.28–7.31 (m, 2H, Ar–H), 7.32 (s, 1H, thiazole-CH), 7.40–7.45 (m, 2H, Ar–H), 7.84–7.86 (m, 2H, Ar–H), 8.00 (s, 1H, CH=N), 11.03 (s, br, 1H, NH). ^{13}C NMR (DMSO-d_6): δ_c = 55.38, 55.58 (OCH_3), 103.32 (thiazole-CH), 120.39, 125.59, 127.06, 127.69, 128.65 (Ar–CH), 131.22, 133.76 (Ar–C), 147.99 (CH=N), 150.18 (thiazole-C5), 157.49, 158.12 (Ar–C–O), 168.35 (thiazole-C2). EI-mass, *m/z* (%): 339 (M^+, 4), 175 (64), 135 (100), 106 (22), 77 (72). Anal. Calcd. for $C_{18}H_{17}N_3O_2S$ (339.41): C, 63.70; H, 5.05; N, 12.38; S, 9.45. Found: C, 63.86; H, 4.92; N, 12.26; S, 9.61.

(E)-2-[2-(Naphthalene-2-ylmethylene)hydrazinyl]-4-phenylthiazole (3f)

Yellow crystals (ethanol), (0.322 g, 98%),m.p. = 250–252°C, IR (KBr): υ = 3338 (NH), 1619 (C=N), 1608 (Ar–C=C), 1037, 745 (C–S–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ_H = 7.31, 7.34 (m, 1H, Ar–H), 7.39 (s, 1H, thiazole-CH), 7.41–7.43 (m, 1H, Ar–H), 7.44–7.46 (m, 2H, Ar–H), 7.61–7.63 (m, 2H, Ar–H), 7.69–7.72 (m, 2H, Ar–H), 7.88–7.90 (m, 1H, Ar–H), 7.99–8.01 (m, 1H, Ar–H), 8.71 (s, 1H, CH=N), 8.73–8.78 (m, 2H, Ar-H), 11.0 (s, br, 1H, NH).^{13}C NMR (DMSO-d_6): δ_C = 103.84 (thiazole-CH), 125.62, 126.28, 127.29, 127.71, 128.68, 128.89, 129.91 (Ar–CH), 130.83, 132.66, 133.45 (Ar–C), 147.67 (CH=N), 150.67 (thiazole-C5), 168.24 (thiazole-C2). EI-mass, *m/z* (%): 329 (M^+, 8), 175 (87), 135 (100), 82 (76), 77 (46). Anal. Calcd. for $C_{20}H_{15}N_3S$ (329.42): C, 72.92; H, 4.59; N, 12.76; S, 9.73. Found: C, 73.11; H, 4.66; N, 12.69; S, 9.58.

(E)-2-[2-(Anthracen-2-ylmethylene)hydrzinyl]-4-phenylthiazole (3g)

Yellow crystals (ethanol), (0.363 g, 96%), m.p = 264–266°C, IR (KBr): υ = 3336 (NH), 1621 (C=N), 1591 (Ar C=C), 1041, 749 (C–S–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ_H = 7.27–7.30 (m, 4H, Ar–H), 7.33 (s, 1H, thiazole-CH), 7.57–7.60 (m, 2H, Ar–H), 7.68–7.70 (m,2H,Ar–H), 7.89–7.90 (m, 2H, Ar-H), 8.17–8.20 (m, 2H, Ar–H), 8.67 (s, H, CH=N), 8.70–8.74 (m, 2H, Ar-H), 10.97 (s, br, 1H, NH). ^{13}C NMR (DMSO-d_6): δ_C = 103.84 (thiazole-CH), 125.80, 126.42, 127.20, 127.66, 127.88,128.24, 128.68, 128.84, 129.91 (Ar–CH), 130.83, 132.66, 133.45, 135.26 (Ar–C), 148.27 (CH=N), 152.67 (thiazole-C5), 168.88 (thiazole-C2). EI-mass, *m/z* (%): 379 (M^+, 8), 19 (21), 134 (27), 77 (100). Anal. Calcd. for $C_{24}H_{17}N_3S$ (379.48): C, 75.96; H, 4.52; N, 11.07; S, 8.45. Found: C, 76.13; H, 4.49; N, 10.89; S, 8.38.

(E)-4-(4-Bromophenyl)-2-(cyclopentylidenehydrazono)-3-phenyl-2,3-dihydrothiazole (5a)

Yellow crystals (ethanol), (0.332 g, 97%), m.p = 268–270°C, IR (KBr): υ = 3093 (Ar-CH), 2958 (Ali-CH), 1628 (C=N), 1579 (Ar C=C).^{1}H NMR (DMSO-d_6): δ_H = 1063 (m, 4H, 2CH_2), 2.20 (m, 2H, CH_2), 2.32 (m, 2H, CH_2), 6.62 (s, 1H, thiazole-CH), 7.07–7.09 (m, 2H, Ar–H), 7.20–7.22 (m, 2H, Ar-H), 7.26–7.28 (m, 1H, Ar–H), 7.32–7.34 (m, 2H, Ar–H), 7.43–7.45 (m, 2H, Ar–H). ^{13}C NMR (DMSO-d_6): δ_C = 24.08, 24.48, 29.78, 31.12 (CH_2), 101.78 (thiazole-CH), 127.39, 128.29, 128.66, 129.89, 130.27 (Ar–CH), 131.22, 137.81 (Ar–C), 137.94 (thiazole-C4), 165.54 (cyclopenlyl-C=N), 171.79 (thiazole-C2). EI-mass, *m/z* (%) 411/413 (M^+, 80), 331 (22), 257 (12), 135 (26), 77 (100). Anal. Calcd. for $C_{20}H_{18}BrN_3S$ (412.35): C, 58.26; H, 4.40; Br, 19.38; N, 10.19; S, 7.78. Found: C, 58.40; H, 4.32; Br, 19.22; N, 10.32; S, 7.89.

(E)-4-(4-Bromophenyl)-2-(cyclohexylidenehydrazono)-3-phenyl-2,3-dihydrothiazole (5b)

Yellow crystals (ethanol), (0.330 g, 95%), m.p = 247–249°C, IR (KBr): υ = 3086 (Ar-CH), 2934 (Ali-CH), 1624 (C=N), 1580 (Ar–C=C). ^{1}H NMR ($CDCl_3$): δ_H = 1.57 (m, 4H, 2CH_2), 1.70 (m, 2H, CH_2), 2.38 (m, 2H, CH_2), 2.49 (m, 2H, CH_2), 6.10 (s, 1H, thiazole-CH), 6.95–6.97 (m, 2H, Ar–H), 7.18–7.24 (m, 3H, Ar–H), 7.28–7.32 (m, 4H, Ar–H);^{13}C NMR ($CDCl_3$): δ_C = 26.07, 26.35, 27.44, 28.60, 35.31 (CH_2), 101.37 (thiazole-CH), 122.21, 127.19, 128.22, 118.63, 129.39 (Ar–CH), 131.38, 137.84 (Ar-C), 138.69 (thiazole-C4), 166.42 (cyclohexyl-C=N), 166.56 (thiazole-C2). EI-mass, m/z (%) 425/427 (M^+,72), 401 (12), 271 (28), 135 (32), 77 (100). Anal. Calcd. for $C_{21}H_{20}BrN_3S$ (426.37): C, 59.16; H, 4.73; Br, 18.74; N, 9.86; S, 7.52. Found: C, 58.98; H, 4.81; Br, 18.88; N, 9.73; S, 7.46.

(E)-4-(4-Bromophenyl)-2-(cycloheptylidenehydrazono)-3-phenyl-2,3-dihydrothiazole(5c)

Yellow crystals (ethanol), (0.356 g, 96%), m.p = 240–242°C, IR (KBr): υ = 3080 (Ar-CH), 2919 (Ali-CH), 1611 (C=N), 1573 (Ar–C=C). ^{1}H NMR ($CDCl_3$): δ_H = 1.53–1.56 (m, 4H, 2CH_2), 1.56–1.59 (m, 4H, 2CH_3), 2.53–2.55 (m, 4H, 2CH_2), 6.21 (s, 1H, thiazole-CH), 6.94–6.97 (m, 2H, Ar–H), 7.19–7.22 (m, 3H, Ar–H), 7.27–7.29(m, 2H, Ar–H), 7.30–7.31 (m, 2H, Ar–H); ^{13}C NMR ($CDCl_3$): δ_C = 25.15, 27.63, 30.55, 32.19, 36.91 (CH_2), 101.51 (thiazole-CH), 122.36, 127.29, 128.30, 118.72, 129.52 (Ar–CH), 131.52, 138.02 (Ar–C), 138.82 (thiazole-C4), 165.42 (cycloheptylidene-C=N), 165.58 (thiazole-C2). EI-mass, *m/z* (%): 439/441 (M^+, 64), 411 (29), 385 (12), 329 (33), 258 (17), 135 (24), 77 (100). Anal.Calcd. for $C_{22}H_{22}BrN_3S$ (440.40): C, 60.00; H, 5.04; Br, 18.14; N, 9.54, S, 7.28. Found: 59.84; H, 4.96; Br, 17.98; N, 9.68; S, 7.16.

(E)-4-(4-Bromophenyl)-2-(cyclooctylidenehydrazono)-3-phenyl-2,3-dihydrothiazole(5d)

Yellow crystals (ethanol), (0.369 g, 96%), m.p = 212–214°C, IR (KBr): υ = 3088 (Ar–CH), 2926 (Ali-CH), 1616 (C=N), 1582 (Ar–C=C). ^{1}H NMR ($CDCl_3$): δ_H = 1.54–1.56 (m, 4H, 2CH_2), 1.88–1.90 (m, 2H, CH_2), 2.38–2.41 (m, 4H, 2CH_2), 6.08 (s, 1H, thiazole-CH), 6.98–7.00 (m, 3H, Ar–H), 7.20–7.23 (m, 2H, Ar–H), 7.30–7.32 (m, 4H, Ar–H), 7.30–7.31 (m, 2H,Ar–H); ^{13}C NMR($CDCl_3$): δ_C = 24.37, 25.50, 25.73, 26.31, 27.79, 30.09, 36.40

(CH_2), 101.22 (thiazole-CH), 122.18, 127.06, 128.20, 128.49, 129.36 (Ar–CH), 131.40, 137.97 (Ar–C), 138.64 (thiazole-C4), 164.79 (cyclooctylidene-C=N), 170.45 (thiazole-C2). EI-mass, *m/z*: 453/455 (M^+, 35), 425 (7), 329 (33), 315 (8), 135 (17), 77 (100). Anal. Calcd. for $C_{23}H_{24}BrN_3S$ (454.43): C, 60.79; H, 5.32; Br, 17.58; N, 9.25; S, 7.06. Found: C, 60.91; H, 5.28; Br, 17.46; N, 9.37; S, 6.93.

*(E)-4-(4-Bromophenyl)-2-[(E)-(3,4-dihydronaphthalen-1(2H)-ylidene)hydra-zono]-3-phenyl-2,3-dihydrothiazole (**5e**)*

Yellow crystals (ethanol), (0.399 g, 97%), m.p = 214–216°C, IR (KBr): υ = 3084 (Ar–CH), 2929 (Ali-CH), 1619 (C=N), 1585 (Ar–C=C). ^{1}H NMR ($CDCl_3$): δ_H = 1.82–1.83 (m, 4H, $2CH_2$), 2.73–2.75 (m, 4H, $2CH_2$), 6.17 (thiazole-CH), 6.97–6.99 (m, 1H, Ar–H), 7.09–7.11 (m, 1H, Ar–H), 7.23–7.25 (m, 1H,Ar–H) 7.30–7.32 (m,1H, Ar–H); ^{13}C NMR ($CDCl_3$): δ_c = 22.22, 27.34, 30.14 (CH_2), 102.31 (thiazole-CH), 126.12, 127.34, 128.23, 128.40, 128.48(Ar–CH), 128.68, 129.49, 137.22 (Ar–C), 138.72 (thiazole-C4), 157.32 (dihydronaphthalenylidene-C=N), 168.36 (thiazole-C2). EI-mass, *m/z*: 473/475 (M^+, 13), 135 (12), 130 (41), 77 (100). Anal. Calcd. for $C_{25}H_{20}BrN_3S$ (474.42): C, 63.29; H, 4.25; Br, 16.84; N, 8.86; S, 6.76. Found: C, 63.41; H, 4.19; Br, 17.03; N, 9.02; S, 6.62.

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