Synthesis and Structures of Novel Multi-armed Molecules Involving Benzene as a Core and 4-Phenylthiazole, 4-Pyrazolylthiazole, or Thiadiazole Units as Arms

Mostafa E. Salem, Ahmed F. Darweesh, Ahmad M. Farag, and Ahmed H. M. Elwahy*

Chemistry Department, Faculty of Science, Cairo University, Giza 12613, Egypt
*E-mail: aelwahy@hotmail.com
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A synthesis of novel three-, four-, and sixfold branched 4-phenylthiazolylhydrazones, 4-pyrazolylthiazolylhydrazones, and thiadiazoles which are linked to a benzene core via phenoxy methyl spacers was reported. The synthetic methodology includes initially formation of poly(aldehyde thiosemicarbazones) 9, 14, and 15 by acid catalyzed condensation of thiosemicarbazide (8) with the appropriate poly(aldehydes) 3, 5, and 7, respectively. Subsequent reaction of 9, 14, and 15 with each of 2-bromo-1-phenylethanone (10a) and 2-bromo-1-(4-chlorophenyl)ethanone (10b) in refluxing ethanol in the presence of few drops of TEA afforded 11, 16, and 18, respectively, in good yields. On the other hand, the synthesis of the novel poly(4,5-dihydro-1,3,4-thiadiazolyl) derivatives 20, 21a,b, and 22 was performed by cyclization of 9b, 14a,b, and 15a, respectively, in refluxing acetic anhydride.

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INTRODUCTION

Since the pioneering work of Vögtle and Weber [1] as well as that of MacNicol et al. [2] on multi-armed molecules, much attention have been paid to the synthesis of such compounds for their wide range of applications [3–8]. This class of compounds is considered important hosts for constructing microporous networks possessing selective inclusion properties and their applications in supramolecular host-guest chemistry have been recently reported [9]. Some related compounds have also been used for the formation of discotic mesogens [10], organic electronic and optoelectronic materials [11–13]. They have also been used as building units for dendrimers [14]. Furthermore, thiazole derivatives were reported to exhibit numerous pharmacological and biological applications, such as anti-HIV, anti-inflammatory, antimicrobial, antihypertensive, analgesic, and herbicidal activity [15].

Moreover, pyrazole system is also considered as an important class of heterocyclic compounds not only for being the core unit in a variety of drugs such as celecoxib (Celebrex) [16], sildenafil (Viagra) [17], and rimonabant (Acomplia) [18], but also for possessing a wide range of activities such as antifungal [19], anti-inflammatory [20], antimicrobial [21], antidepressant [22], antiparasitic [23], antiviral [24], and antitumor activities [25].

In addition, 1,3,4-thiadiazole derivatives have also attracted much attention in the last decades for their wide spectrum of biological activities including anti-inflammatory
In connection with these findings, we report herein on the synthesis of novel three-, four-, and sixfold branched 4-phenylthiazolylhydrazones, 4-pyrazolylthiazolylhydrazones,

Scheme 1. Synthesis of tris-(formylphenoxymethyl)benzenes 3a,b.

Scheme 2. Synthesis of tris(aldehyde thiosemicarbazones) 9a and 9b.
and thiazoles which are linked to a benzene core via phenoxyethyl spacers.

RESULTS AND DISCUSSION

We first synthesized the required aldehydes 3a, 3b, 5a, 5b, and 7a, b following reported methods, described by our group or after modification of literature procedure described by other groups. Thus, tris(formylphenoxyethyl)benzenes 3a, b were prepared by reacting the potassium salt of 4-hydroxybenzaldehyde (2a) or salicylaldehyde (2b) with tris(bromomethyl)benzene (1) in refluxing DMF (Scheme 1) [35]. Similarly, the tetrakis(formylphenoxyethyl)benzenes 5a and 5b were prepared, by fourfold substitution of tetrakis

Scheme 3. Reaction of compounds 9a, b with the appropriate 2-bromo-Ethanone derivatives.

Figure 2. Tetrakis- and hexakis (aldehyde thiosemicarbazones) 14a, b and 15a, b.
(bromomethyl)benzenes (4) with four equivalents of the potassium salt of 4-hydroxybenzaldehyde (2a) or salicylaldehyde (2b), respectively. With the same reaction sequence, the hexakis(formylphenoxymethyl)benzenes 7a and 7b were prepared, by sixfold substitution of hexakis(bromomethyl)benzenes (6) with six equivalents of the potassium salt of 4-hydroxybenzaldehyde or salicylaldehyde, respectively (Fig. 1) [35].

The synthetic utility of aldehydes 3, 5, and 7 as building blocks for novel tris-, tetrakis-, and hexakis(thiazoles), in which the 4-phenylthiazoylhydrazone or 4-pyrazolylthiazolylhydrazone is linked to benzene core via phenoxymethyl group, was investigated. Thus, the tris(aldehyde thiosemicarbazones) 9a and 9b were first synthesized in 77 and 72% yields, respectively, by acid catalyzed condensation of thiosemicarbazide (8) with the appropriate tris(aldehydes) 3a and 3b, respectively (Scheme 2).

Reaction of the latter compounds with each of 2-bromo-1-phenylethanone (10a) and 2-bromo-1-(4-chlorophenyl)ethanone (10b) in refluxing ethanol in the presence of few drops of TEA afforded 11a and 11b in 67 and 69% yields, respectively (Scheme 3). In analogy, reaction of compounds 9a,b with 2-bromo-1-(5-methyl-1-phenyl-1H-pyrazol-4-yl)ethanone (12) in refluxing ethanol in the presence of few drops of TEA afforded 13a and 13b in 70 and 64% yields, respectively (Scheme 3). Compound 12 was

![Figure 3. Tetrakis- and hexakis(thiazoles) 16a,b, 17a,b, 18a,b and 19a,b.](image-url)
synthesized by the reaction of phenylhydrazine with ((dimethylamino)methylene)pentane-2,4-dione, obtained upon treatment of acetylacetone with dimethylformamide dimethylacetal (DMFDMA), followed by bromination upon treatment with Br₂ in AcOH [36].

The same methodology was extended to the preparation of tetrakis- and hexakis(thiazoles) 16–19. Thus, compounds 16–19 were successfully prepared, from 5a,b and 7a,b firstly by reaction with thiosemicarbazide (8) in refluxing EtOH containing few drops of AcOH to give 14a,b and 15a,b in 70, 73 and 68, 64% yields, respectively (Fig. 2).

Subsequent reaction of the latter compounds with the appropriate bromoacetyl compounds 10a,b and 12 in refluxing ethanol in the presence of few drops of TEA afforded the corresponding tetrakis(thiazoles) 16a,b and 17a,b in 65, 69 and 66, 68% yields, respectively, as well as hexakis(thiazoles) 18a,b and 19a,b in 63, 65 and 66, 67% yields, respectively (Fig. 3).

Our study was extended to include the synthesis of the novel tris(4,5-dihydro-1,3,4-thiadiazolyl) derivative 20 in which the thiadiazolyl moiety is linked to the benzene core via phenoxyethyl group, in good yield, by cyclization of tris(aldehyde thiosemicarbazone) 9b in refluxing acetic anhydride (Scheme 4).

Encouraged by the above results, we expanded the scope of this reaction to prepare novel fourfold branched (4,5-dihydro-1,3,4-thiadiazolyl) derivatives 21a and 21b and sixfold branched (4,5-dihydro-1,3,4-thiadiazolyl) derivative 22 (Fig. 4) by cyclization of the appropriate tetrakis(aldehyde thiosemicarbazones) 14a and 14b and hexakis(aldehyde thiosemicarbazone) 15a, respectively, with acetic anhydride.

The structures of the new synthesized compounds were confirmed by IR, NMR, and mass spectra as well as elementary analyses. The IR spectrum of tris(thiazolylhydrazone) 11a as a representative example of these class of compounds revealed an absorption band at 3431 cm⁻¹ because of (NH). Its ¹H NMR spectra showed the presence of a characteristic singlet signal at 7.99 ppm because of one methine proton (―N=CH―). Mass spectrum of compound 11a showed the molecular ion peaks at m/z 999 (M⁺) in agreement with its respective molecular formula. The spectra of other bis(thiazoles) 11b, 16a,b,
and 18a,b showed similar spectral data which are listed in the experimental part.

The symmetry of compounds 19a,b is manifested by a single set of signals characteristic of the six equivalent OCH₂ and six methyl groups in the 1H-NMR spectra. Similarly, compounds 21a,b are characterized by a single set of signals characteristic of the four equivalent OCH₂, four acetyl (CH₃CO), four acetamido (NHCOCH₃), and four methine (CH) groups.

**CONCLUSIONS**

We developed a simple method for the preparation of novel three-, four-, and sixfold branched 4-phenylthiazolylhydrazones, 4-pyrazolylthiazolylhydrazones, and thiadiazoles which are linked to a benzene core via phenoxymethyl spacers. Full characterization of these compounds is reported. The new synthesized compounds are interesting both in their own right as unusual molecules and for their promising pharmacological and biological activities as well as for their expected inclusion properties. The extension of the scope of this method to cover additional multi-armed heterocyclic compounds is now under study.

**EXPERIMENTAL**

**General.** Melting points were determined in open glass capillaries with a Gallenkamp apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3-300 and Shimazu FTIR 8101 PC infrared spectrometer. NMR spectra were recorded in deuterated dimethyl sulfoxide (DMSO-d₆) with a Varian Mercury 1-310 NMR spectrometer at 300 MHz (1H NMR) and 75 MHz (13C NMR). Mass spectra (EI) were obtained at 70 eV with a type Shimadzu GCMQP 1000 EX spectrometer. NMR spectra were recorded in potassium bromide disks on a Pye Unicam SP 3-300 and Shimadzu FTIR 8101 PC infrared spectrometer.

**Synthesis of poly(thiosemicarbazones) 9a,b, 14a,b, and 15a,b.**

**General procedure.** To a solution of poly(aldehydes) 3a,b or 5a,b or 7a,b (1 mmol) in absolute ethanol (25 mL) containing few drops of acetic acid, thiosemicarbazide 8 (3 or 4 or 6 mmol) was added. The reaction mixture was heated under reflux for 3 h. The solid formed upon cooling was collected and recrystallized from ethanol/DMF to give the corresponding poly(thiosemicarbazones) 9a,b, 14a,b, and 15a,b.

2,2′,2″-(4,4′,4″-(Benzene-1,3,5-triytrils(methylene))tris(oxy)tris(benzene-4,1-diyl)-tris(methan-1-yl-1-ylidene)tris(hydrazinecarbothioamide) 9a. Pale yellow powder, (77% yield), mp. 204–205°C; IR: (potassium bromide) 3421, 3367 (NH₂), 3254 (NH), 1601 (C=N) cm⁻¹; 1H-NMR: δ 5.19 (s, 6H, 3 CH₂O), 7.03–7.99 (m, 21H, ArH + 3 NH₂), 8.07 (s, 3H, 3 CH=N), 11.26 (s, 3H, 2 NH); ms: m/z (%) 699 (9.5, M⁺) 389 (54.2), 151 (100), 135 (29.3), 57 (93.5), 43 (82.6). Anal. Calcd. for C₃₂H₃₂N₁₂O₄S₄: C, 55.61; H, 4.67; N, 18.53; S, 14.14. Found: C, 55.51; H, 4.53; N, 18.39; S, 14.01.

Pale yellow powder, (68% yield), mp. 205°C; IR: (potassium bromide) 3423, 3271 (NH₂), 3159 (NH), 1601 (C=N) cm⁻¹; 1H-NMR: δ 5.26 (s, 6H, 3 CH₂O), 6.96–8.13 (m, 21H, ArH + 3 NH₂), 8.51 (s, 3 CH=N), 11.39 (s, 3H, 3 NH); ms: m/z (%) 699 (10.2, M⁺), 630 (60.2), 321 (100), 310 (47.2), 55 (40.3). Anal. Calcd. for C₃₂H₃₂N₁₂O₄S₄: C, 56.63; H, 4.75; N, 18.01; S, 13.74. Found: C, 56.52; H, 4.69; N, 17.95; S, 13.66.

2,2′,2″-(4,4′,4″-(Benzene-1,2,4,5-tetrayltetrakis(methylene))tetrakis(oxy)-tetrakis(benzene-4,1-diyl)-tetrakis(methan-1-yl-1-ylidene)tris(hydrazinecarbothioamide) 14a. Pale yellow powder, (73% yield), mp. 246–248°C; IR: (potassium bromide) 3425, 3364 (NH₂), 3254 (NH), 1594 (C=N) cm⁻¹; 1H-NMR: δ 5.29 (s, 8H, 4 CH₂O), 7.03–7.98 (m, 26H, ArH + 4 NH₂), 8.07 (s, 4H, 4 CH=N), 11.29 (s, 4H, 4 NH); ms: m/z (%) 906 (24.9, M⁺), 815 (100), 801 (31.3), 481 (21.9), 249 (12.2), 57 (11.8). Anal. Calcd. for C₃₅H₃₅N₁₉O₉S₄: C, 55.61; H, 4.67; N, 18.53; S, 14.14. Found: C, 55.51; H, 4.53; N, 18.39; S, 14.01.

2,2′,2″,2″″,2″″″-(2,2′,2″,2″″,2″″″-(Benzene-1,2,4,5-tetrayltetrakis(methylene))tetrakis(oxy)-tetrakis(benzene-2,1-diyl)-tetrakis(methan-1-yl-1-ylidene)tris(hydrazinecarbothioamide) 14b. Pale yellow powder, (70% yield), mp. 203–205°C; IR: (potassium bromide) 3421, 3364 (NH₂), 3251 (NH), 1595 (C=N) cm⁻¹; 1H-NMR: δ 5.29 (s, 8H, 4 CH₂O), 7.03–7.98 (m, 26H, ArH + 4 NH₂), 8.07 (s, 4H, 4 CH=N), 11.29 (s, 4H, 4 NH); ms: m/z (%) 906 (10.2, M⁺), 815 (100), 801 (31.3), 481 (21.9), 249 (12.2), 57 (11.8). Anal. Calcd. for C₃₅H₃₅N₁₉O₉S₄: C, 55.61; H, 4.67; N, 18.53; S, 14.14. Found: C, 55.54; H, 4.45; N, 18.41; S, 13.88.

β,3,3,4,4″,4‴,4‴″,4‴‴,4‴‴″-Hexahexylhexakis(methylene)hexakis(hydrazinocarbothioamide) 15a. Pale yellow powder, (68% yield), mp. > 300°C; IR: (potassium bromide) 3430, 3275 (NH₂), 3150 (NH), 1595 (C=N) cm⁻¹; 1H-NMR: δ 5.41 (s, 8H, 4 CH₂O), 6.93–8.11 (m, 26H, ArH + 4 NH₂), 8.51 (s, 4H, 4 CH=N), 11.42 (s, 4H, 4 NH); ms: m/z (%) 906 (14.9, M⁺), 816 (47.6), 814 (100), 801 (31.3), 481 (21.9), 250 (12.2), 59 (12.8). Anal. Calcd. for C₄₀H₄₀N₁₉O₉S₄: C, 55.61; H, 4.67; N, 18.53; S, 14.14. Found: C, 55.44; H, 4.45; N, 18.41; S, 13.88.

β,3,3,4,4″,4‴,4‴″,4‴‴,4‴‴″-Hexahexylhexakis(methylene)hexakis(hydrazinocarbothioamide) 15b. Pale yellow powder, (64% yield), mp. 240–242°C; IR: (potassium bromide) 3418, 3260 (NH₂), 3145 (NH), 1600 cm⁻¹; 1H-NMR: δ 5.26 (s, 6H, 3 CH₂O), 6.98–8.13 (m, 21H, ArH + 3 NH₂), 8.07 (s, 3H, 3 CH=N), 11.26 (s, 3H, 2 NH); ms: m/z (%) 699 (10.2, M⁺), 630 (60.2), 321 (100), 310 (47.2), 55 (40.3). Anal. Calcd. for C₃₂H₃₂N₁₂O₄S₄: C, 55.61; H, 4.75; N, 18.01; S, 13.74. Found: C, 56.52; H, 4.69; N, 17.95; S, 13.66.
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1,2,3,4,5,6-Hexakis[(4-(2-(4-phenylthiazol-2-yl)hydrazono)methyl)phenoxy)methyl]benzene 18a. Orange powder, (63% yield), mp. > 300°C; IR: (potassium bromide) 3428 (NH), 1602 (C=N) cm\(^{-1}\); \(^1\)H-NMR: \(\delta\) 5.32 (s, 12H, 6 CH\(_2\)O), 3.50 (s, 6H, 3 CH=CH), 2.52 (s, 6H, 3 CH=CH). 

1,2,3,4,5,6-Hexakis[(2-(2-(4-(4-chlorophenylthiazol-2-yl)hydrazono)methyl)phenoxy)methyl]benzene 18b. Yellow powder, (65% yield), mp. 208–210°C; IR: (potassium bromide) 3433 (NH), 1599 (C=N) cm\(^{-1}\); \(^1\)H-NMR: \(\delta\) 5.55 (s, 12H, 6 CH\(_2\)O), 6.94–7.77 (m, 54H, ArH + 6 thiazole-H), 8.35 (s, 6H, 6 CH=CH), 11.88 (s, 6H, NH); \(^1^\)C-NMR: \(\delta\) 64.3, 104.2, 112.8, 120.5, 120.7, 123.0, 127.0, 128.3, 129.3, 130.3, 131.7, 133.4, 149.2, 155.8, 162.2, 168.0. Anal. Calcd. For C\(_{108}\)H\(_{76}\)Cl\(_6\)N\(_{18}\)O\(_6\)S\(_6\): C, 66.9; H, 4.63; N, 16.94; S, 7.75. Found: C, 66.69; H, 4.52; N, 16.85; S, 7.58.

Synthesis of Poly(pyrazolylthiazoles) 13a,b, 17a,b and 19a.b. 

1,3,5-Tris-[2-(2-(4-(4-phenylthiazol-2-yl)hydrazono)methyl)phenoxy]-methyl]benzene 11b. Yellow powder, (66% yield), mp. 180–182°C; IR: (potassium bromide) 3436 (NH), 1599 (C=N) cm\(^{-1}\); \(^1\)H-NMR: \(\delta\) 5.30 (s, 6H, 3 CH=O), 7.01–7.85 (m, 33H, ArH + 3 thiazole-H), 7.89 (s, 3H, 3 CH=CH). 7.09 (b, 3H, 3 NH). 13C-NMR: \(\delta\) 1239 (9.5, M\(^{+}\)), 992 (100), 874 (10.7), 249 (66.9), 13a, 13b, 17a, 17b, 19a, and 19b.

1,3,5-Tris-[2-(2-(4-(4-phenylthiazol-2-yl)hydrazono)methyl)phenoxy]-methyl]benzene 16a. Orange powder, (65% yield), mp. > 300°C; IR: (potassium bromide) 3433 (NH), 1602 (C=N) cm\(^{-1}\); \(^1\)H-NMR: \(\delta\) 5.32 (s, 8H, 4 CH\(_2\)O), 7.08–7.84 (m, 24H, ArH + 3 thiazole-H), 7.98 (s, 4H, 4 CH=CH). 13C-NMR: \(\delta\) 66.9, 104.5, 115.1, 127.9, 128.4, 129.2, 129.3, 130.6, 131.3, 131.6, 134.6, 135.0, 135.3, 155.7, 159.4. Anal. Calcd. For C\(_{74}\)H\(_{57}\)N\(_{15}\)O\(_3\)S\(_3\): C, 66.81; H, 4.63; N, 16.94; S, 7.75. Found: C, 66.69; H, 4.52; N, 16.85; S, 7.58.

1,3,5-Tris-[2-(2-(4-(4-phenylthiazol-2-yl)hydrazono)methyl)phenoxy]-methyl]benzene 16b. Yellow powder, (69% yield), mp. 190–192°C; IR: (potassium bromide) 3438 (NH), 1598 (C=N) cm\(^{-1}\); \(^1\)H-NMR: \(\delta\) 5.45 (s, 8H, 4 CH\(_2\)O), 7.00–7.86 (m, 38H, ArH + 4 thiazole-H). 8.46 (s, 4H, 4 CH=CH). 13C-NMR: \(\delta\) 67.5, 104.2, 112.8, 121.1, 122.7, 125.1, 127.1, 128.0, 130.5, 131.8, 133.4, 135.1, 136.8, 149.2, 155.9, 162.2, 168.2. Anal. Calcd. For C\(_{74}\)H\(_{57}\)Cl\(_3\)N\(_{12}\)O\(_3\)S\(_3\): C, 61.49; H, 3.77; N, 11.63; S, 8.87. Found: C, 61.36; H, 3.65; N, 11.44; S, 8.73.
Orange powder, (66% yield), mp. > 300°C; IR: (potassium bromide) 3444 (NH), 1705 (C=O) cm⁻¹; ¹H-NMR: δ 2.49 (s, 12H, 4 CH₃), 5.45 (s, 8H, 4 CH₂O), 6.74 (s, 4H, 4 thiazone–H), 7.01–7.80 (m, 38H, ArH), 7.89 (s, 6H, 6 NH); 13C-NMR: δ 70.1, 101.4, 115.2, 116.7, 124.5, 127.1, 129.1, 134.5, 138.9, 140.9, 144.3, 150.0, 168.1. Anal. Calcd. for C₂₀H₁₆N₂O₂S₂: C, 66.40; H, 4.34; N, 17.39; S, 7.65.

**REFERENCES AND NOTES**

