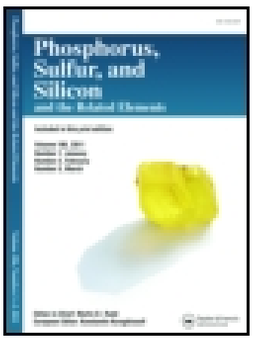

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Synthesis and characterization of new thiadiazole derivatives bearing a pyrazole moiety

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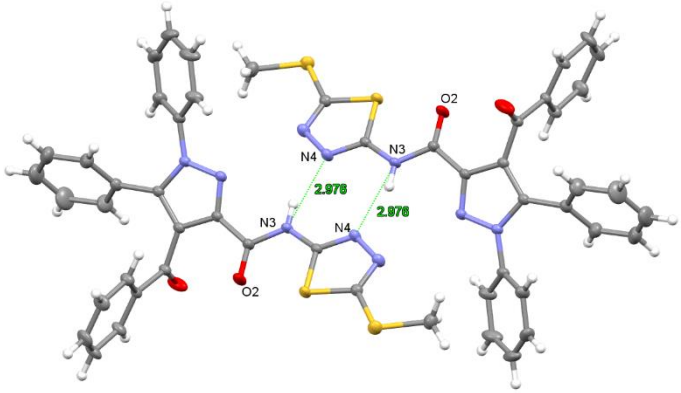
ABSTRACT

A series of thidiazole derivatives (**4**, **7**) from pyrazole-3-carboxylic acid chloride (**2**) and pyrazole-3,4-dicarboxylic acid chloride derivatives (**6**) were synthesized and characterized. The structures of the new compounds were confirmed byelemental analysis, NMR (^{1}H and ^{13}C) and IR spectra. The molecular and crystal structure of 4-benzoyl-*N*-[5-(methylthio)-1,3,4-thiadiazol-2-yl]-1,5-di-phenyl-1*H*-pyrazole-3-carboxamide(**4d**)was determined by single crystal X-ray diffraction method.



KEYWORDS

Thiadiazole**;**pyrazole; X-ray structure

Introduction

Recently, thiadiazole derivatives have received significant attention and have been increasingly investigated due to their diverse range of biological properties. They exhibit, for example, anti-microbial,[1,2]anti-bacterial,[3] anticancer,[4] anti-inflammatory,[5,6] carbonic anhydrase inhibiting effect,[7] antanxiety, anti-depressant,[8] anti-oxidant properties.[9]Five membered heterocyclic compounds exhibit a variety of biological activities, amongst them 2,5-disubstituted 1,3,4-thiadiazoles are associated with diverse biological activities probably by virtue of = N-C-S-group.[10]In addition, some thiadiazole derivatives are pharmacologically active substances such as acetazolamide, methazolamide, sulfamethazole drugs and the derivatives of these drugs exhibit other activities, including anticonvulsant and selective cerebral vasodilation, as well as the anticipated inhibition of carbonic anhydrase.[11]

In continuation to our interest in the chemical and pharmacological properties of thiadiazole derivatives, we reported a facile synthetic strategy for preparation of some new thiadiazole derivatives linked to a pyrazole moiety.

Resultsanddiscussion

Various 2-amino-1,3,4-thiadiazoles (**3**) were reacted with pyrazole carboxylic acid mono and dichloride derivatives (**2**, **6**) to give the corresponding new thiadiazole derivatives (**4**, **7**)as described in Schemes 1-2. In order to synthesize the mono and dithidiazole compounds (**4**, **7**), firstly carboxyl group of pyrazol carboxylic acids (**1**, **5**) were activated by thionyl chloride[12-14]and then 2-amino-1,3,4-thiadiazole derivatives (**3**) with activated pyrazole carboxylic acid

mono and dichloride (**2**, **6**) were reacted in dry acetonitrile by refluxing. The target compounds (**4**, **7**) were obtained in moderate yields.

The structures of the reaction products were characterized from analytical and spectoscopy data (elemental analysis, IR, ^{1}H, ^{13}C NMR and also X-ray diffraction method for compound **4d**). There are different carbonyl groups features in each ofthe compounds**4** and **7**, each of them with a different electronic environment. So, the IR and NMR spectra provide excellent evidence of their structures. For instance, the absorption bands observed at 1675 and 1663, 1668, 1658 cm^{-1} for **4d** and **7a** belong to benzoyl and amide carbonyl groups, respectively. The ^{1}H NMR spectra of **4d** and **7a** forN-H proton signals were observed at 10.65 and12.01 ppm.The ^{13}C NMR spectra of **4d** and **7a** for carbonyl carbons signalswere observed at 191.0, 157.6 and 160.9, 158.6 ppm.Other characteristic peaks appeared at expected regions (see Experimental for details).

Experimental section

Melting points are uncorrected and recorded on Electrothermal 9200 digital melting point apparatus. Microanalyses were performed on a Leco-932 CHNS-O Elemental Analyser. IR spectra (in the range of 400-4000 cm^{-1} region) of the molecules were recorded by Perkin-Elmer Spectrometer with a resolution of 4 cm^{-1} at room temperature using ATR techniques. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance model using $Si(CH_3)_4$ as a reference in $CDCl_3$ and DMSO-d_6 at 400 MHz, respectively. The reactions were followed by TLC using DC Alufolien Kieselgel 60 F254 Merck and Camag TLC lamp (254/366 nm). Solvents and all other chemical reagents were purchased from Merck, Sigma, Aldrich and Fluka and used directly

without further purification. The Supplemental Materials file contains sample ^{1}H, ^{13}C NMR and IR spectra of products 4 and 7 (Figures S 1 -- S 44).

General procedure for the synthesis of compound 4 derivatives

Previously, 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carbonyl-chloride (**2**), ethyl-3-(chlorocarbonyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (**2**) and 1,5-diphenyl-1*H*-pyrazole-3,4-di carbonyl-dichloride (**6**) were prepared according to the published methods.[12-14]

To a stirred solution of compound (**2**)or(**6**) in acetonitrile (10 mL) was added the solution of 2-amino-1,3,4-thidiazole derivatives (**3**) in acetonitrile (5 mL) dropwise.The mixture were refluxed for 4-5 h. Later, the solvent was evaporated under reduced pressure to give an oily residue which was triturated with anhydrous diethylether and finally recrystallized from the indicated solvents.

4-Benzoyl-1,5-diphenyl-*N*-1,3,4-thiadiazol-2-yl-1*H*-pyrazole-3-carboxamide (4a)

Compound **4a** wassynthesized from **2** (0.38 g, 1.0 mmol) and **3a** (0.10 g, 1.0 mmol) according to the general procedure. The crude product was purified by recrystallization from ethanol. Yield: 78%; m.p.: 168-169°C. IR (ATR, cm^{-1}): 3330 (N-H), 1682, 1667(C = O), 1596 (C = C), 1496 (C = N), 1210 (C = S). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 10.81 (s, 1H, N-H), 7.85-7.14 (m, 15H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 191.4, 159.9 (C = O), 157.9, 157.8, 147.9, 144.6, 142.3, 138.4, 137.2, 133.6, 129.7, 129.6, 129.6, 129.2, 128.9, 128.6, 128.4, 127.4, 125.2, 122.6, (C = C). *Anal. calcd. for* $C_{25}H_{17}N_5O_2S$ (451 g/mol): C, 66.50; H, 3.80; N, 15.51, S, 7.10. Found: C, 66.81; H, 3.96; N, 15.65, S, 6.90.

4-Benzoyl-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)-1,5-di-phenyl-1*H*-pyrazole-3-carboxamide (4b)

Compound **4b** wassynthesized from **2** (0.38 g, 1.0 mmol) and **3b** (0.12 g, 1.0 mmol) according to the general procedure. The crude product was purified by recrystallization from ethanol. Yield: 81%; m.p.: 230-231°C. IR (ATR, cm^{-1}): 3140 (N-H), 1687, 1663(C = O), 1593 (C = C), 1495 (C = N), 1234 (C = S). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 10.81 (s, 1H, N-H), 7.85-7.14 (m, 15H, Ar-H), 2.66 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 191.1, 160.6 (C = O), 158.0, 157.7, 144.4, 142.5, 138.5, 137.3, 133.5, 129.7, 129.6, 129.5, 129.1, 128.8, 128.6, 128.4, 127.5, 125.1, 122.6 (C = C), 15.3 (CH_3). *Anal. calcd. for* $C_{26}H_{19}N_5O_2S$ (465 g/mol): C, 67.08; H, 4.11; N, 15.04, S, 6.89. Found: C, 66.90; H, 4.05; N, 14.90, S, 6.70.

4-Benzoyl-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-1,5-diphenyl-1*H*-pyrazole-3-carboxamide (4c)

Compound **4c** wassynthesized from **2** (0.38 g, 1.0 mmol) and **3c** (0.13 g, 1.0 mmol) according to the general procedure. The crude product was purified by recrystallization from ethanol. Yield: 75%; m.p.: 235-236°C. IR (ATR, cm^{-1}): 3137 (N-H), 1677, 1660(C = O), 1595 (C = C), 1498 (C = N), 1196 (C = S). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 10.64 (s, 1H, N-H), 7.86-7.15 (m, 15H, Ar-H), 3.07-3.01 (q, 2H, CH_2), 1.40-1.36 (t, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 191.1, 167.4 (C = O), 157.6, 157.6, 144.4, 142.5, 138.5, 137.3, 133.5, 129.6, 129.6, 129.2 128.9, 128.7, 128.4, 127.5, 125.1, 122.7, (C = C), 25.3 (CH_2), 14.0 (CH_3). *Anal. calcd. for* $C_{27}H_{21}N_5O_2S$ (479 g/mol): C,67.62; H, 4.41; N, 14.60, S, 6.69. Found: C, 67.45; H, 4.20; N, 14.25, S, 6.50.

4-Benzoyl-*N*-[5-(methylthio)-1,3,4-thiadiazol-2-yl]-1,5-di-phenyl-1*H*-pyrazole-3-carbox-amide (4d)

Compound **4d** wassynthesized from **2** (0.38 g, 1 mmol) and **3d** (0.15 g, 1 mmol) according to the general procedure. The crude product was purified by recrystallization from ethanol. Yield: 70%; m.p.: 183-184°C. IR (ATR, cm^{-1}): 3120 (N-H), 1675, 1663(C = O), 1593 (C = C), 1499 (C = N), 1190 (C = S). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 10.65 (s, 1H, NH), 7.85-7.15 (m, 15H, Ar-H), 2.72 (t, 3H, SCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 191.0, 157.7 (C = O), 144.6, 142.3, 138.5, 137.3, 133.5, 129.7, 129.6, 129.6, 129.2, 128.9 128.7, 128.4, 127.4, 125.2, 122.6, (C = C), 16.3 (SCH_3). *Anal. calcd. for* $C_{26}H_{19}N_5O_2S_2$ (497 g/mol): C, 62.76; H, 3.85; N, 14.07, S, 12.89. Found: C, 62.50; H, 3.70; N, 13.90, S, 12.65.

4-Benzoyl-*N*-[5-(ethylthio)-1,3,4-thiadiazol-2-yl]-1,5-di-phenyl-1*H*-pyrazole-3-carbox-amide (4e)

Compound **4e** wassynthesized from **2** (0.38 g, 1.0 mmol) and **3e** (0.16g, 1.0 mmol) according to the general procedure. The crude product was purified by recrystallization from ethanol. Yield: 55%; m.p.: 169-170°C. IR (ATR, cm^{-1}): 3133 (N-H), 1682, 1659(C = O), 1598 (C = C), 1495 (C = N), 1192 (C = S). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 10.64 (s, 1H, N-H), 7.85-7.15 (m, 15H, Ar-H), 3.26-3.21 (q, 2H, SCH_2), 1,45-1.41 (t, 3H, $SCH_2\underline{C}H_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 191.1, 161.0 (C = O), 157.8, 157.6, 144.5, 142.3, 138.4, 137.3, 133.5, 129.7, 129.6, 129.6 129.2, 128.6, 128.4,127.4, 125.2, 122.6, (C = C), 28.7 (SCH_2), 14.7 ($SCH_2\underline{C}H_3$). *Anal. calcd. for* $C_{27}H_{21}N_5O_2S_2$ (511 g/mol): C, 63.38; H, 4.14; N, 13.69; S, 12.54. Found: C, 63.15; H, 4.05; N, 13.50, S, 12.35.

Ethyl-1,5-diphenyl-3-[(1,3,4-thiadiazol-2-yl-amino)-carbonyl]-1*H*-pyrazole-4-carboxy-late (4f)

Compound **4f** wassynthesized from **2** (0.35 g, 1.0 mmol) and **3a** (0.10 g, 1.0 mmol) according to the general procedure. The crude product was purified by recrystallization from i-propanol. Yield: 60%; m.p.: 176-177°C. IR (ATR, cm^{-1}): 3146 (N-H), 1682, 1667(C = O), 1596 (C = C), 1494 (C = N), 1178 (C = S). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 13.09 (s, 1H, NH), 8.91-7.26 (m, 11H, Ar-H), 4.26-4.21 (q, 2H, O$\underline{C}H_2CH_3$), 1,02-0.99 (t, 3H, $OCH_2\underline{C}H_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 165.1, 160.1 (C = O), 157.8, 148.2, 143.9, 138.3, 130.1, 129.6, 128.6, 128.6, 128.2, 125.5 (C = C), 62.0 (O$\underline{C}H_2CH_3$), 13.4 ($OCH_2\underline{C}H_3$). *Anal. calcd. for* $C_{21}H_{17}N_5O_3S$ (419 g/mol): C, 60.13; H, 4.09; N, 16.70,;S, 7.64. Found: C, 59.95; H, 3.90; N, 16.50, S, 7.50.

Ethyl-3-{[(5-methyl-1,3,4-thiadiazol-2-yl)-amino]-carbonyl}-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (4g)

Compound **4g** wassynthesized from **2** (0.35 g, 1.0 mmol) and **3b** (0.12 g, 1.0 mmol) according to the general procedure. The crude product was purified by recrystallization from ethanol. Yield: 65%; m.p.: 168-169°C. IR (ATR, cm^{-1}): 3167 (N-H), 1723, 1710(C = O), 1594 (C = C), 1500 (C = N), 1166 (C = S). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 12.73 (s, 1H, NH), 7.42-7.25 (m, 10H, Ar-H), 4.24-4.19 (q, 2H, O$\underline{C}H_2CH_3$), 2,74 (s, 3H, $C_2H_2N_2S\underline{C}H_3$), 1.02-0.99(t, 3H, $OCH_2\underline{C}H_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 164.5, 160.8 (C = O), 158.4, 157.6, 147.5, 138.3, 130.1, 129.5, 128.9, 128.8, 128.6, 128.2, 125.5, 113.4 (C = C), 61.9 (O$\underline{C}H_2CH_3$), 15.3 (S$\underline{C}H_3$), 13.4 (OCH_2CH_3). *Anal. calcd. for* $C_{22}H_{19}N_5O_3S$ (433 g/mol): C, 60.96; H, 4.42; N, 16.16; S, 7.40. Found: C, 60.76; H, 4.20; N, 15.95, S, 7.20.

Ethyl-3-{[(5-ethyl-1,3,4-thiadiazol-2-yl)-amino]-carbonyl}-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (4h)

Compound **4h** wassynthesized from **2** (0.35 g, 1.0 mmol) and **3c** (0.13 g, 1.0 mmol) according to the general procedure. The crude product was purified by recrystallization from i-propanol. Yield: 72%; m.p.: 155-156°C. IR (ATR, cm^{-1}): 3246 (N-H), 1680, 1668(C = O), 1595 (C = C), 1494 (C = N), 1179 (C = S). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 12.66 (s, 1H, N-H), 7.45-7.21 (m, 10H, Ar-H), 4.28-4.16 (q, 2H, O$\underline{C}H_2CH_3$), 2,74 (s, 3H, $C_2H_2N_2S\underline{C}H_3$), 1.02-0.99 (t, 3H, $OCH_2\underline{C}H_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 164.5, 160.8 (C = O), 158.4, 157.6, 147.5, 138.3, 130.1, 129.5, 128.9, 128.8, 128.6, 128.2, 125.5, 113.4 (C = C), 61.9 (O$\underline{C}H_2CH_3$), 23.6 (S$\underline{C}H_2$), 14.2 (S$\underline{C}H_3$), 13.4. *Anal. calcd.for* $C_{23}H_{21}N_5O_3S$ (447 g/mol): C, 61.73; H, 4.73; N, 15.65; S, 7.17. Found: C, 61.50; H, 4.50; N, 15.30; S, 6.95.

Ethyl-3-({[5-(methylthio)-1,3,4-thiadiazol-2-yl]-amino}-carbonyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (4i)

Compound **4i** wassynthesized from **2** (0.35 g, 1.0 mmol) and **3d** (0.15g, 1.0 mmol) according to the general procedure. The crude product was purified by recrystallization from methanol. Yield: 66%;m.p.: 160-161°C. IR (ATR, cm^{-1}): 3100 (N-H), 1682, 1659(C = O), 1595 (C = C), 1498 (C = N), 1184 (C = S). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 12.80 (s, 1H, NH), 7.42-7.25 (m, 10H, Ar-H), 4.25-4.20 (q, 2H, O$\underline{C}H_2CH_3$), 2.72 (s, 1H, S$\underline{C}H_3$), 1.03-0.99 (t, 3H, $OCH_2\underline{C}H_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 164.5, 162.2 (C = O), 158.1, 157.6, 147.6, 143.8, 138.3, 130.1, 129.6, 128.9, 128.9, 128.6, 128.2, 125.5, 113.4 (C = C), 62.0 (O$\underline{C}H_2CH_3$), 16.3 (S$\underline{C}H_3$),

13.4 ($OCH_2\underline{C}H_3$). *Anal. calcd. for* $C_{22}H_{19}N_5O_3S_2$ (465 g/mol): C, 56.76; H, 4.11; N, 15.04; S, 13.78. Found: C, 56.58; H, 3.99; N, 14.91; S, 13.58.

Ethyl-3-({[5-(ethylthio)-1,3,4-thiadiazol-2-yl]-amino}-carbonyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (4j)

Compound **4j** wassynthesized from **2** (0.35 g, 1.0 mmol) and **3e** (0.16 g, 1.0 mmol) according to the general procedure. The crude product was purified by recrystallization from i-propanol. Yield: 61%; m.p.: 140-141°C. IR (ATR, cm^{-1}): 3132 (N-H), 1680, 1666(C = O), 1594 (C = C), 1492 (C = N), 1178 (C = S). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 12.82 (s, 1H, NH), 7.44-7.25 (m, 10H, Ar-H), 4.24-4.19 (q, 2H, $O\underline{C}H_2CH_3$), 3,33-3.27 (q, 2H, $S\underline{C}H_2CH_3$), 1.49-1.45 (t, 3H, $OCH_2\underline{C}H_3$), 1.02-0.99 (t, 3H, $SCH_2\underline{C}H_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 164.5, 160.9 (C = O), 158.4, 157.6, 147.6, 143.8, 138.3, 130.1, 129.6, 128.9, 128.9, 128.6, 128.2, 125.5, 113.4 (C = C), 62.0 ($O\underline{C}H_2CH_3$), 28.7 ($S\underline{C}H_2CH_3$), 14.7 ($OCH_2\underline{C}H_3$), 13.4 ($SCH_2\underline{C}H_3$). *Anal. calcd. for* $C_{23}H_{21}N_5O_3S_2$ (479 g/mol): C, 57.60; H, 4.41; N, 14.60; S, 13.37. Found: C, 57.48; H, 4.30; N, 14.45; S, 13.10.

General procedure for the synthesis of compound 7 derivatives

A mixture of pyrazole carboxylic acid dichloride (**6**) (1.0 mmol), and the appropriate 2-amino-1,3,4-thiadiazole derivatives **3** (4.0 mmol) was heated under reflux condition in freshly distilled acetonitrile (25 mL) for 5 h. The solvent was evaporated in vacuo and residue was washed with water. The precipitated crude product was filtered and crystallized from the appropriate solvent.

1,5-Diphenyl-*N*,*N*'-di-1,3,4-thiadiazol-2-yl-1*H*-pyrazole-3,4-dicarboxamide (7a)

Compound **7a** wassynthesized from **6** (0.34 g, 1.0 mmol) and **3a** (0.10 g, 1.0 mmol) according to the general procedure. The crude product was purified by recrystallization from methanol. Yield: 63%; m.p.: 289-290 °C. IR (ATR, cm^{-1}): 3379, 3233 (N-H), 1668, 1658(C = O), 1594 (C = C), 1497 (C = N), 1186 (C = S). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 12.01 (br., 1H, N-H), 8.99-7.26 (m, 10H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 160.9, 158.6 (C = O), 158.2, 150.9, 148.8, 147.9, 139.8, 137.9, 130.3, 130.0, 129.3, 129.1, 128.5, 127.5, 125.3, 115.6 (C = C), 62.0 (OCH_2Me), 28.7 (SCH_2Me), 14.7 ($OCH_2\underline{C}H_3$), 13.4 ($SCH_2\underline{C}H_3$). *Anal. calcd. for* $C_{21}H_{14}N_8O_2S_2$ (474 g/mol): C, 53.15; H, 2.97; N, 23.61; S, 13.52. Found: C, 52.95; H, 2.90; N, 23.50; S, 13.30.

***N*,*N*'-bis(5-methyl-1,3,4-thiadiazol-2-yl)-1,5-di-phenyl-1*H*-pyrazole-3,4-dicarboxamide (7b)**

Compound **7b** wassynthesized from **6** (0.34 g, 1.0 mmol) and **3b** (0.12 g, 1.0 mmol) according to the general procedure. The crude product was purified by recrystallization from methanol. Yield: 77%; m.p.: 261-262 °C. IR (ATR, cm^{-1}): 3147 (N-H), 3075(N-H), 1671, 1660(C = O), 1563 (C = C), 1489 (C = N), 1189 (C = S). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 13.80, 10.95 (br., 2H, N-H), 7.47-7.19 (m, 10H, Ar-H), 2.78, 2.68 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 161.7, 160.5 (C = O), 160.3, 158.1, 150.9, 139.9, 137.9, 130.4, 129.9, 129.3, 129.1, 128.4, 128.1, 125.4, 115.7, (C = C), 15.5, 15.3 (CH_3). *Anal. calcd. for* $C_{23}H_{18}N_8O_2S_2$ (502 g/mol): C, 54.97; H, 3.61; N, 22.30; S, 12.76. Found: C, 54.80; H, 3.50; N, 22.10; S, 12.50.

***N*,*N*'-bis(5-ethyl-1,3,4-thiadiazol-2-yl)-1,5-di-phenyl-1*H*-pyrazole-3,4-dicarboxamide (7c)**

Compound **7c** wassynthesized from **6** (0.34 g, 1.0 mmol) and **3c** (0.13 g, 1.0 mmol) according to the general procedure. The crude product was purified by recrystallization from acetic acid. Yield: 57%; m.p.: 236-237 °C. IR (ATR, cm^{-1}): 3191 (N-H), 3075 (N-H), 1671, 1647(C = O), 1612 (C = C), 1495 (C = N), 1222 (C = S). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 13.80, 11.29 (br, 2H, N-H), 7.47-7.18 (m, 10H, Ar-H), 3.13-3.01 (q, 2H, CH_2), 1.47-1.35 (t, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = δ 168.2, 167.0 (C = O), 160.6, 158.4, 158.2, 157.6, 150.6, 140.1, 137.9, 130.4, 129.8, 129.2, 129.0, 128.3, 128.1, 125.4, 115.8 (C = C), 29.6, 23.6 (CH_2), 14.1, 14.0 (CH_3). *Anal. calcd. for* $C_{25}H_{22}N_8O_2S_2$ (530 g/mol): C, 56.59; H, 4.18; N, 21.12; S, 12.09. Found: C, 56.45; H, 4.05; N, 20.95; S, 11.91.

_N,N'_-bis[5-(methylthio)-1,3,4-thiadiazol-2-yl]-1,5-di-phenyl-1_H_-pyrazole-3,4-dicarbox-amide (7d)

Compound **7d** wassynthesized from **6** (0.34 g, 1.0 mmol) and **3d** (0.15 g, 1.0 mmol) according to the general procedure. The crude product was purifiedby recrystallization from acetic acid. Yield: 47%; m.p.: 264-265 °C. IR (ATR, cm^{-1}): 3386, 3152 (N-H), 1677, 1656(C = O), 1594 (C = N)-1495 (C = C), 1186 (C = S). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.48-7.24 (m, 10H, Ar-H), 2.84, 2.74 (s, 3H, SCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = δ 161.0, 160.2 (C = O), 157.6, 157.5, 144.5, 142.3, 138.5, 137.3, 133.5, 129.7, 129.6, 129.5129.2, 128.9, 128.6, 128.4, 127.4, 125.2, 122.6 (C = C), 14.2, 14.1 (CH_3). *Anal. calcd. for* $C_{23}H_{18}N_8O_2S_4$ (566 g/mol): C, 48.75; H, 3.20; N, 19.77; S, 22.63. Found: C, 48.55; H, 2.95; N, 19.55; S, 22.50.

_N,N'_-bis[5-(ethylthio)-1,3,4-thiadiazol-2-yl]-1,5-diphenyl-1_H_-pyrazole-3,4-dicarbox-amide (7e)

Compound **7e** wassynthesized from **6** (0.34 g, 1.0 mmol) and **3e** (0.16 g, 1.0 mmol) according to the general procedure. The crude product was purified by recrystallization from acetic acid. Yield: 55%; m.p.: 220-221°C. IR (ATR, cm^{-1}): 3340, 3140 (NH), 1675, 1657(C = O), 1605 (C = C), 1491 (C = N), 1178 (C = S). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 12.26 (br, 2H, N-H), 7.48-7.25 (m, 10H, Ar-H), 3.35-3.20 (q, 2H, CH_2), 1.51-1.41 (t, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = δ 176.1, 162.5 (C = O), 160.7, 160.4, 158.7, 157.9, 150.6, 139.9, 137.9, 130.3, 129.9, 129.2, 129.0, 128.4, 128.0, 125.3, 115.6 (C = C), 28.7, 28.7 (CH_2), 14.7, 14.6 (CH_3). *Anal. calcd. for* $C_{25}H_{22}N_8O_2S_2$ (594 g/mol): C, 50.49; H, 3.73; N, 18.84; S, 21.57. Found: C, 50.35; H, 3.51; N, 18.69; S, 21.45.

X-ray Crystallography

For the crystal structure determination, single-crystals of molecule **4d** was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). Graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å)and oscillation scans technique with $\Delta w = 5°$ for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement was performed using Crystal Clear (Rigaku/MSC Inc. 2005) software.[15]The structures were solved by direct methods using SHELXS-97 and refined by a full-matrix least-squares procedure using the program SHELXL-97.[16]_ENREF_22H atoms were positioned geometrically and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance.

The crystal structure of the molecule **4d** with the atom labeling and the dimeric structure are shown in Fig. 1. The crystallographic data and structural refinement details for compound **4d** is given in Table 1. Compound **4d** crystallizes in the triclinic *P*-1 space group with two molecules per unit cell. The bond lengths of pyrazole C-N, N-N vary from 1.345(3) Å to 1.378(3) Å and shorter than the corresponding single bond distances. This fact suggests multiple bond order and confers aromaticity to the ring. The aromatic groups attached to the pyrazole ring are twisted considerably due to the steric hindrance.

Deviation of the bond angle from 120° in the 1,3,4-thiadiazole ring is a common feature in five-membered rings. Thiadiazole bond distances are as follows; S1-C24 1.728(3) Å, S1-C25 1.733(3) Å, N4-N5 1.392(3) Å, N4-C24 1300(3) Å and N4-C24 1.290(3) Å. C-N and C-S bond in thiadiazole ring involves carbon atom with sp^2 hybridization. The values found for bond angles and lengths are similar to those reported in related compounds.[17,18] The dihedral angle between the thiadiazole and the phenyl rings is found to be 38.3°. Ring planarity and π-electron delocalization lead to the conclusion that the thiadiazole ring is aromatic in the studied compound. Selected bond lengths and angles are presented in Table S 1

In the solid state, the compound **4d** is stabilized via effective *intra*-molecular N3-H···N4 bonding, which leads to the formation of dimeric structure. Along with that C13-H···O1 [$D\cdots A$ = 3.510(3) Å] and C4-H···O1 [$D\cdots A$ = 3.446(3) Å] interactions have a contribution in the formation of a stable structure.

Crystallographic data that were deposited in CSD under CCDC-1473635 registration number contain the supplementary crystallographic data for this letter. These data can be obtained free of

charge from the Cambridge Crystallographic Data Centre (CCDC) via www.ccdc.cam.ac.uk/data_request/cif and are available free of charge upon request to CCDC, 12 Union Road, Cambridge, UK (fax: +441223 336033, e-mail: deposit@ccdc.cam.ac.uk).

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Table 1: Crystal Structure and Data Refinement Parameters

Compound	**4d**
Empirical Formula	$C_{26}H_{19}N_5O_2S_2$
Formula Weight	497.6
Crystal System / Space Group	Triclinic / P-1
a / Å	8.3579(7)
b / Å	9.3663(8)
c / Å	16.0222(13)
α / °	89.334(3)
β / °	87.245(3)
γ / °	76.627(3)
V / $Å^3$	1218.84(9)
Z	2
D_{calc} (g/cm^3)	1.36
μ (mm^{-1})	0.252
Crystal size (mm)	0.10 × 0.11 × 0.13
Color / Shape	-
Temp (K)	293(2)
Theta range for collection	3.2-28.3
Reflections collected	57430
Independent reflections	6062
Data/restraints/parameters	4377/0/317
Goodness of fit on F^2	1.515

Final R indices [I > 2σ(I)]	0.0429
R indices (all data)	0.124
Largest difference peak/hole	0.327 / -0.326

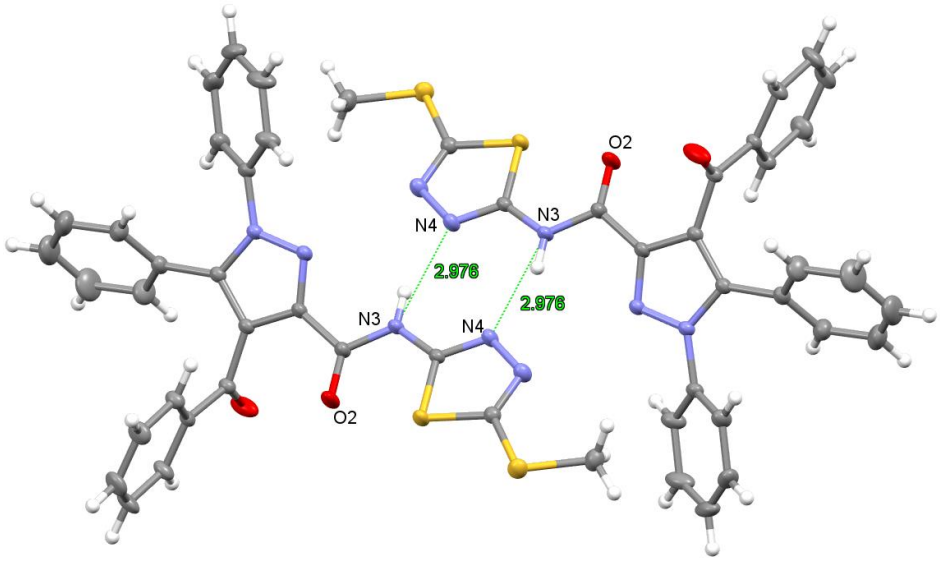
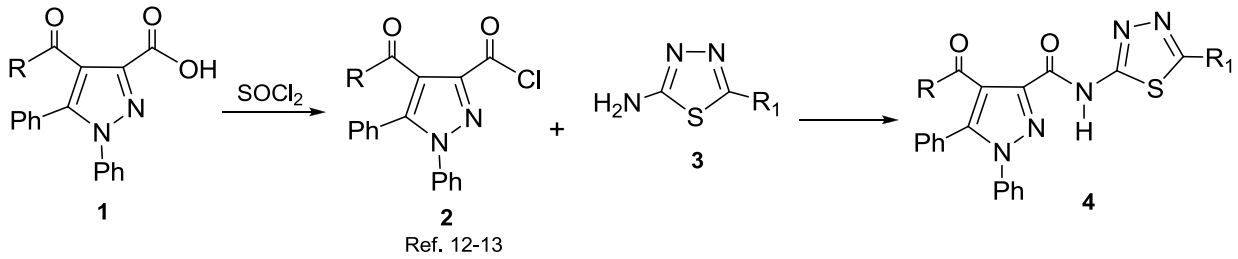
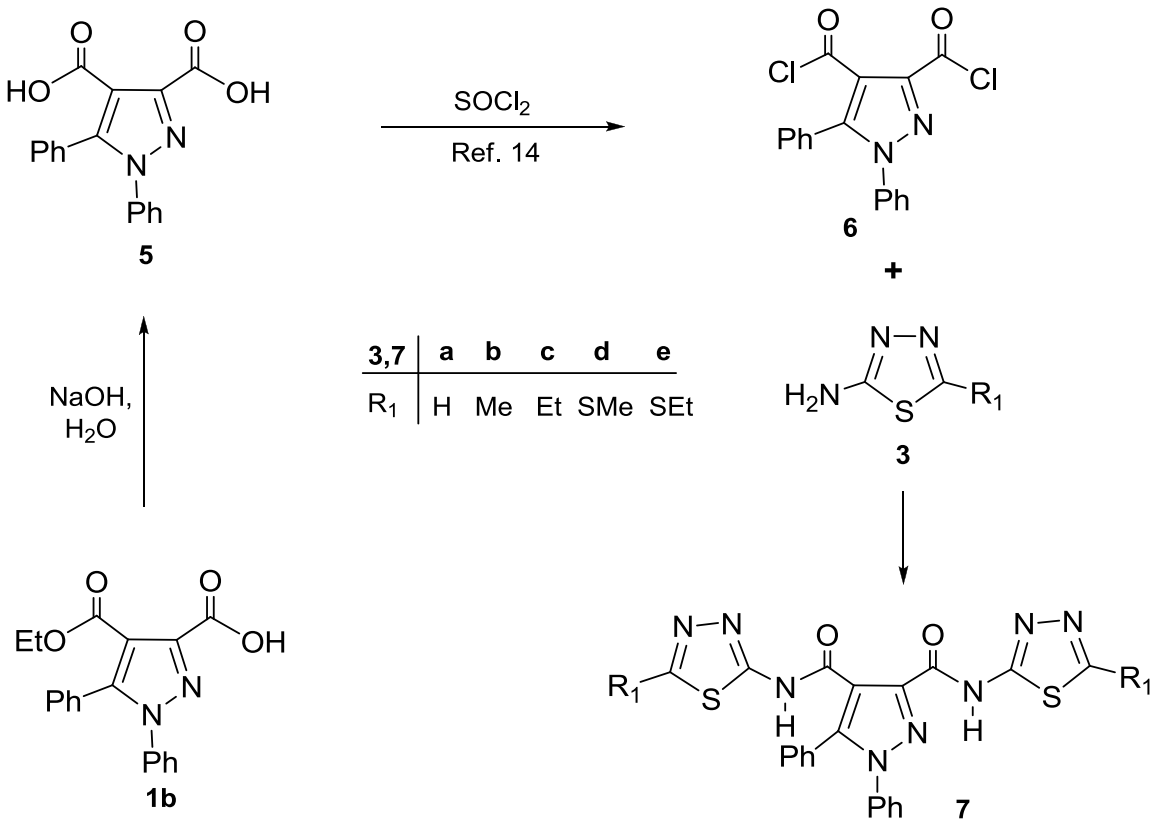


Figure 1. *Up*: Crystalstructureof the molecule **4d.** Thermal ellipsoids are drawn at the 40% probability level. *Down*: Dimeric structure with *intra*-molecular *H-bonding* geometry. Hydrogen bonds are drawn as dashed lines. Selected bond lengths [Å]: N1-N2 1.345(2), N4-N5 1.392(2), S1-C24 1.728(2), S2-C25 2.743(2),O2-C23 1.218(2), N3-H…N4 2.976(2).



4	a	b	c	d	e	f	g	h	i	j
R	Ph	Ph	Ph	Ph	Ph	OEt	OEt	OEt	OEt	OEt
R_1	H	Me	Et	SMe	SEt	H	Me	Et	SMe	SEt

Scheme 1. The synthetic route of mono thiadiazoles



Scheme 2. Synthetic pathways for the preparation of dithiadiazole derivatives