Functionalised 1,2,4-triazino[5,6-*b*]indoles

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3-Ethoxycarbonylmethylthio-5*H*-1,2,4-triazino[5,6-*b*]indole (**2**) and 5-ethoxycarbonylmethyl-3-ethoxycarbonylmethylthio-5*H*-1,2,4-triazino[5,6-*b*]indole (**4**) have been prepared from 2,5-dihydro-3*H*-1,2,4-triazino[5,6-*b*]indole-3-thione (**1**). The reaction of **2** and **4** with hydrazine hydrate gave the respective mono- and bishydrazide derivatives **3** and **5**. Reaction of the monohydrazide **3** with acetylacetone, various carbonyl compounds and monosaccharides afforded the respective hydrazones **6** and **8–14**. Dehydrative cyclization of **6** and **9** with boiling acetic anhydride afforded the pyrazole and 1,3,4-oxadiazoline derivatives **7** and **15**, and reaction of **3** with CS_2/KOH followed by hydrazinolysis afforded **16**.

Keywords: fused indoles, fused 1,2,4-triazines, 1,2,4-triazoles, pyrazoles, acylhydrazones, monosaccharides

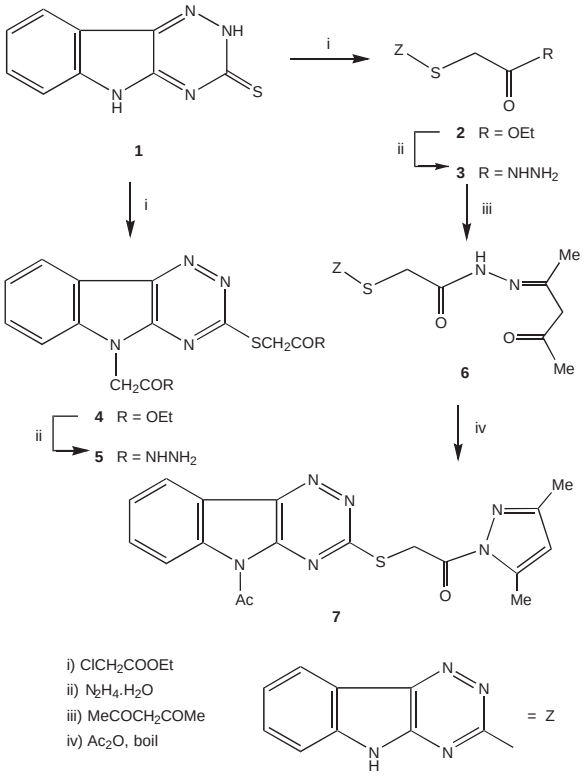
Hydrazides are a well known class of organic compound.[1-6] They are useful as pharmaceuticals and as complexing agents, and are of potential synthetic value, particularly for the synthesis of heterocyclic compounds.[1-4] 1,2,4-Triazinoindoles have been considered to be of potential medicinal interest,[5-7] and many of their derivatives have been synthesised[8-13] and tested for their antiviral activity,[14-24] and as bactericides,[14,25] fungicides,[26] and antihypertensive,[27] anesthetic and analgesic[28] agents. By compiling the biological activities of triazinoindoles, hydrazides and their cyclised derivatives such as oxadiazolines, we sought to investigate the feasibility of the 1,2,4-triazino[5,6-*b*]indole-3-thione acting as a useful carrier for various heterocyclic compounds *via* its functionalisation at the 3 and/or 5 position by a group capable of constructing heterocyclic rings.

Results and discussion

The 1,2,4-triazino[5,6-*b*]indolethione (**1**)[16,17] has more than one site for alkylation, either on the triazine ring, the indole ring, or the thione sulfur atom. Treatment of **1** with chloroacetic acid gave the *S*-carboxymethyl derivative.[26] Similarly, alkylation of **1** in *N*,*N*-dimethylformamide and ethanol in the presence of potassium carbonate with an equimolar amount of ethyl chloroacetate afforded a product which was identified as **2**, indicating that the carbethoxymethylation had occurred at the sulfur site. When the reaction was performed with two molar equivalents of ethyl chloroacetate in the presence of sodium hydride, product **4** could be isolated, with ethoxycarbonylmethyl groups on both sulfur and nitrogen. (Scheme 1)

In order to explain these alkylation results, the HSAB principle[29] has been considered. The soft polarisable sulfur is alkylated first under soft conditions, leading to preferential alkylation at sulfur to give **2**. The structures of **2** and **4** were deduced from their spectra. Compound **2** showed an NH absorption band at 3208 cm^{-1} in the IR and an NH proton signal at δ 8.61 ppm in the NMR. The spectrum of **4** showed the absence of SH and NH protons. The ethyl groups showed as triplets and quartets with consistent integrations. Two singlets at δ 4.12 and 5.04 ppm appeared in the spectrum of **4** due to the S- and N-methylene groups respectively, whereas, **2** showed only one singlet at δ 4.14 ppm.

Reaction of **2** and **4** with hydrazine hydrate gave the corresponding hydrazides **3** and **5**, respectively. Their IR spectra showed a shift of the carbonyl band to lower wavelength than in the esters, confirming that hydrazinolysis had taken place. Moreover, the presence of amide absorptions ruled out the possibility of displacement of the substituent at the 3-position by the hydrazine.



Scheme 1

Reaction of the hydrazide **3** with acetylacetone gave the hydrazone **6**, whose ^{1}H NMR spectrum revealed the presence of two methyl, two methylene, and two NH groups, in addition to four aromatic protons. Boiling **6** in acetic anhydride for 5 hrs caused dehydrative cyclisation of the hydrazone moiety as well as acetylation of the indole N–H to give the pyrazole derivative **7**. The infrared spectrum of **7** showed no NH absorption band, that appeared in its precursor at 3209 cm^{-1}, and the appearance of an *N*-acetyl band at 1725 cm^{-1}. ^{1}H NMR spectrum of **7** showed the absence of a signal at δ 3.76 ppm in compound **6** which also confirmed the mode of cyclisation.

Reaction of the hydrazide **3** with acetaldehyde, benzaldehyde, *p*-nitrobenzaldehyde, cinnamaldehyde and acetophenone gave the corresponding hydrazones **8**–**12**. Reaction of **3** with D-galactose and D-mannose gave the hydrazones **13** and **14**, respectively. Compound **9** underwent dehydrative cyclisation and subsequent acetylation on treatment with boiling acetic anhydride to give **15** as confirmed from its elemental analysis and spectral data. Its IR spectrum showed the presence of absorption bands at 1705 and 1675 cm^{-1}, corresponding to the *N*-acetyl groups on the indolyl and oxadiazoline moieties.

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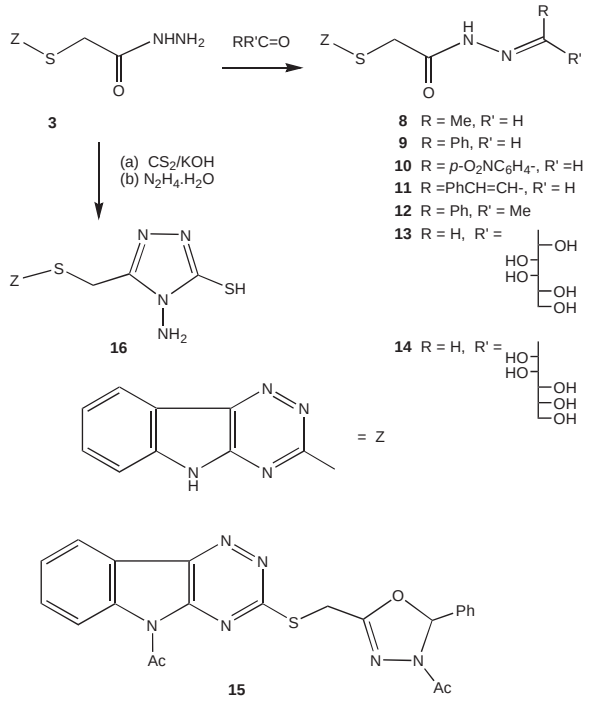
† Dedicated to my Professor El Sayed H.El Ashry on the occasion of his 60th birthday.



Scheme 2

3-[(4-Amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)methylthio]1,2,4-triazino[5,6-*b*]indole (**16**) was obtained from the reaction of compound **3** with CS_2/KOH followed by treating the expected intermediate dithiocarbazate salt with hydrazine hydrate. Its ^{1}H NMR spectrum indicated the predominance of the thiol tautomer in DMSO-d_6, since it showed a D_2O exchangeable signal at δ 13.0 ppm due to SH, this beside the signals characteristic for S–CH_2, NH_2 / NH and Ar–H at the expected chemical shifts. Compound **16** contains the functionalised 1,2,4-triazole ring which has itself proved to be of potential value as a key precursor for the synthesis of heterocyclic compounds.[30, 31]

Experimental

Melting points were determined on a Meltemp apparatus. IR spectra were recorded with a Unicam SP 1025 spectrometer, and ^{1}H NMR spectra with a Varian EM 200 spectrometer. The chemical shifts are expressed in the δ scale using tetramethylsilane as reference. TLC was performed on Baker flex silica gel 1B-F plates. Microanalyses were performed in the Unit of Microanalysis at Cairo University.

3-Ethoxycarbonylmethylthio-5H-1,2,4-triazino[5,6-b]indole (**2**): To a solution of compound **1**[16,17] (4.0 g, 20 mmol) in a 1 : 1 mixture of ethanol : *N*,*N*-dimethylformamide (DMF) (100 ml) was added potassium carbonate (5.52 g , 20 mmol). The mixture was heated under reflux for 30 min. and then treated with ethyl chloroacetate (2.7 g, 22 mmol). The reflux was continued for 30 min. The solid mass which separated out upon cooling was filtered off, dried and recrystallised from DMF in pale yellow crystals (4.5 g, 79% yield), m.p. 235–237 °C. IR (KBr): 3208 (NH), 1739 (OCO) and 1605 cm^{-1} (C=N). ^{1}H NMR ($CDCl_3$): δ_H = 1.26 (t, 3H, CH_3); 4.14 (s, 2H, S–CH_2); 4.28 (q, 2H, OCH_2); 7.49, 7.66 and 8.38 (2 m, d, 4H, aromatic protons) and 8.61 (bs, 1H, NH). Analysis for $C_{13}H_{12}N_4O_2S$ (288.33), calcd: C, 54.2; H, 4.2; N, 19.4; found: C, 54.3; H, 4.4; N, 19.2 %.

5-Ethoxycarbonylmethyl-3-ethoxycarbonylmethylthio-1,2,4-triazino[5,6-b]indole (**4**): Compound **1** (4.0 g, 20 mmol), ethyl chloroacetate (5.4 g, 44 mmol) and sodium hydride (0.192 g, 80 mmol) in a 1 : 1 mixture of ethanol : DMF (100 ml) was heated under reflux for 6 h. The mixture was processed as above to give a product that was recrystallised from ethanol in colourless crystals (5.7 g, 77% yield), m.p. 160–162 °C. IR (KBr): 1740, 1728 (OCO) and 1600 cm^{-1} (C=N). ^{1}H NMR ($CDCl_3$): δ_H = 1.26 (t, 6H, 2 CH_3), 4.12 and 5.04 (2 s, 4H, 2 CH_2), 4.26 (q, 4 H, 2 OCH_2) and 7.49, 7.66 and 8.43 (2m, d, 4 H, aromatic protons). Analysis for $C_{17}H_{18}N_4O_4S$ (374.41), calcd: C, 54.5; H, 4.9; N, 15.0; found: C, 54.3; H, 5.1; N, 14.6 %.

3-Hydrazinocarbonylmethylthio-5H-1,2,4-triazino[5,6-b]indole (**3**): To a solution of compound **2** (2.0 g, 7.0 mmol) in DMF (50 ml) was added hydrazine hydrate (8 ml). The mixture was heated under reflux for 3 h. The solid mass which separated out upon cooling was filtered, dried and recrystallised from DMF in colourless crystals (1.2 g, 63% yield), m.p. 262–263 °C. IR (KBr): 3325, 3290, 3199 (NH and NH_2), 1638 (OCN) and 1597 cm^{-1} (C=N). Analysis for $C_{11}H_{10}N_6OS$ (274.24), calcd: C, 48.2; H, 3.7; N, 30.7; found: C, 48.1; H, 3.5; N, 30.4 %.

5-Hydrazinocarbonylmethyl-3-hydrazinocarbonylmethylthio-1,2,4-triazino[5,6-b]indole (**5**): To a solution of compound **4** (1.0 g, 2.67 mmol) in DMF (20 ml) was added hydrazine hydrate (8 ml). The mixture was heated under reflux for 3 h. The product was recrystallised from DMF in colourless crystals (0.6 g, 65% yield), m.p. 280–283 °C. IR (KBr): 3315 (NH and NH_2); 1658 (OCN) and 1608 cm^{-1} (C=N). Analysis for $C_{13}H_{14}N_8O_2S$ (346.37), calcd. C, 45.1; H, 4.1; N, 32.4; found: C, 44.9; H, 4.0; N, 32.3 %.

3-(Acetylmethylethylidenehydrazinocarbonylmethylthio)-5H-1,2,4-triazino[5,6-b]indole (**6**): A solution of **3** (1.0 g, 3.64 mmol) in absolute ethanol (50 ml) and DMF (10 ml), was treated with acetylacetone (1.0 ml) and few drops of glacial acetic acid. The reaction mixture was heated under reflux for 1 h. The product that separated on cooling was filtered, dried and crystallised from ethanol-chloroform in pale yellow crystals (0.8 g, 62% yield), m.p. 234–236 °C. IR (KBr): 3209 (NH); 1739 ($COCH_3$); 1659 (OCN) and 1605 cm^{-1} (C=N). ^{1}H NMR (DMSO-d_6): δ_H = 2.21, 2.54 (2 s, 6H, 2CH_3); 3.76 (s, 2H, CH_2) 4.23 (s, 2H, S–CH_2); 7.49, 7.67 and 8.42 (2m, d, 4H, Ar–H), 11.70 (bs, 2H, 2 NH). Analysis for $C_{16}H_{16}N_6O_2S$ (356.41): Calcd. C, 53.9; H, 4.5; N, 23.6; found: C, 53.6; H, 4.4; N, 23.4 %.

3-[(3,5-Dimethylpyrazol-1-yl)carbonylmethylthio]-1,2,4-triazino[5,6-b]indole (**7**): A solution of **6** (1.0 g, 2.81 mmol) in acetic anhydride (5 ml) was heated under reflux for 5 h. The reaction mixture was poured onto crushed ice. The product that separated out was filtered off, it was crystallised from DMF - ethanol in pale yellow crystals (0.7 g, 65% yield), m.p. 144–146 °C. IR (KBr): 1725 (*N*-Ac) and 1662 cm^{-1} (OCN). ^{1}H NMR (DMSO-d_6): δ_H = 3.05 (s, 3H, CH_3CO); 3.79, 4.14 (2 s, 6H, 2 CH_3); 4.26 (s, 2H, S–CH_2), 7.25 (s, 1H, pyrazole proton); 7.57, 7.70, 8.36 and 8.67 (2 m, 2 d, 4H, Ar–H). Analysis for $C_{18}H_{16}N_6O_2S$ (380.43): calcd. C, 56.8; H, 4.2; N, 22.1; found: C, 56.5; H, 4.1; N, 22.0 %.

Reaction of 3-hydrazinocarbonylmethylthio-5H-1,2,4-triazino[5,6-b]indole with carbonyl compounds; hydrazones **8–12**, *general procedure*: To a solution of compound **3** (1.0 g, 3.64 mmol) in ethanol (50 ml) and DMF (10 ml) the respective carbonyl compound (3.64 mmol) and acetic acid (0.1 ml) were added. The reaction mixture was heated under reflux for 2 h, the solid mass which separated out upon cooling was filtered off and dried. Yields and physical properties are summarised in Table 1.

Table 1 Physical and infrared spectral data and elemental analysis of compounds **8–12**

Compound no.	Yield /%	M.P. /°C	Mol. formula (MW)	Anal., calcd/found C	H	N	IR (cm^{-1}) NH	OCN	C=N
8	82	219-221	$C_{13}H_{12}N_6OS$ (300.35)	52.0 51.9	4.0 3.8	28.0 27.8	3211	1663	1599
9	83	264-266	$C_{18}H_{14}N_6OS$ (362.41)	59.7 59.5	3.9 3.7	23.2 23.0	3180	1671	1602
10	74	248-250	$C_{18}H_{13}N_7O_3S$ (407.40)	53.1 53.0	3.2 3.0	24.1 24.3	3202	1672	1596
11	79	238-240	$C_{20}H_{16}N_6OS$ (388.45)	61.8 61.6	4.2 4.1	21.6 21.4	3230	1673	1593
12	73	240-242	$C_{19}H_{16}N_6OS$ (376.44)	60.6 60.2	4.3 4.5	22.3 21.9	3177	1672	1608

D-Galactose acylhydrazone **13:** A solution of compound **3** (1.0 g, 3.64 mmol) in ethanol (50 ml) and DMF (10 ml) was added to a solution of D-galactose (0.66 g, 3.65 mmol) in water (5 ml) and acetic acid (0.1 ml). The reaction mixture was heated under reflux for 2 h. The solid mass which separated out upon cooling was filtered and dried. It was recrystallised from DMF in pale yellow crystals (1.0g, 63% yield), m.p. 198–200 °C. IR (KBr): 3325 (OH), 3247 (NH), 1639 (OCN) and 1600 cm^{-1} (C=N). Analysis for $C_{17}H_{20}N_6O_6S$ (436.45), calcd: C, 46.8; H, 4.6; N, 19.3; found: C, 46.5; H, 5.0; N, 19.1 %.

D-Mannose acylhydrazone **14:** The synthesis of compound **14** was carried out with D-mannose (0.66 g, 3.65 mmol) in place of the galactose. The product was recrystallised from ethanol and DMF as pale yellow crystals (0.9g, 57% yield), m.p. 205–207 °C. IR (KBr): 3459 (OH), 3230 (NH), 1641 (OCN) and 1601 cm^{-1} (C=N). Analysis for $C_{17}H_{20}N_6O_6S$ (436.45), calcd. C, 46.8; H, 4.6; N, 19.3; found: C, 46.5; H, 5.0; N, 18.9 %.

3-[(3-Acetyl-2,3-dihydro-2-phenyl-1,3,4-oxadiazol-5-yl)]methylthio]-1,2,4-triazino[5,6-b]indole (**15**): A solution of compound **9** (0.5 g, 1.4 mmol) in acetic anhydride (8 ml) was heated under reflux for 2 h, cooled, then poured onto ice-water. The solid mass which separated was filtered off and washed with water. The product was crystallised from ethanol as colourless crystals (0.3 g, 54% yield), m.p. 244–246 °C. IR (KBr): 1705 and 1675 cm^{-1} (*N*-Ac). Analysis for $C_{22}H_{18}N_6O_3S$ (446.47): calcd. C, 59.2; H, 4.1; N, 18.8; found: C, 59.0; H, 3.9; N, 18.6 %.

3-[(4-Amino-5-mercapto-4H-1,2,4-triazol-3-yl)methylthio]-1,2,4-triazino[5,6-b]indole (**16**): To an ice-cold solution of compound **3** (0.72 g, 2.63 mmol) and KOH (0.21 g , 4.57 mmol) in absolute EtOH (15 ml), CS_2 (2 ml) was added. The reaction mixture was stirred at R.T. for 12 hrs. Anhydrous diethyl ether (25 ml) was then added. The precipitate of potassium dithiocarbazate was collected by filtration, washed with ether and dried. The potassium salt was obtained in quantitative yield. To a solution of the potassium dithiocarbazate (0.78 g, 2.0 mmol) in H_2O (10 ml), hydrazine hydrate (0.3 ml, 6.0 mmol) was added. The reaction mixture was heated under reflux for 1 h, diluted with ice-cold water and acidified with conc. HCl. The obtained white precipitate was filtered, washed with water and recrystallised from EtOH. (0.45 g, 68 % yield) m.p. 241–243 °C. IR (KBr): 3276 (NH); 2632 (SH); 1606 cm^{-1} (C=N). ^1H NMR (DMSO-d_6): δ_H = 4.52 (s, 2 H, S–CH_2); 5.65 (bs, 2 H, NH_2 D_2O-exchangeable), 7.39–7.65, 8.25 (m, d, 4 H, Ar–H); 8.61 (bs, 1 H, NH, D_2O-exchangeable) and 13.00 (bs, 1 H, SH, D_2O exchangeable). Analysis for $C_{12}H_{10}N_8S_2$ (330.48): Calcd. C, 43.6; H, 3.1; N, 33.9; found: C, 43.0; H, 2.9; N, 33.7 %.

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