Tetrahedron xxx (2015) 1–8

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# 2-Bromo-1-(1*H*-pyrazol-4-yl)ethanone: versatile precursors for novel mono-, bis- and poly{6-(1*H*-pyrazol-4-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines}

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ARTICLE INFO

*Article history:*
Received 30 October 2015
Received in revised form 25 November 2015
Accepted 10 December 2015
Available online xxx

*Keywords:*
Cyclocondensation
Alkylation
Triazolothiadiazine
Pyrazole

ABSTRACT

A simple synthesis of novel mono-, bis- and poly{6-(1*H*-pyrazol-4-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines} is reported. The formation of the target compounds was achieved by the reaction of 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone with the appropriate aminotriazolethiol or by the reaction of 6-pyrazolyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-3-thiol with the appropriate di- and poly(bromo) compounds. The structures of the newly synthesized compounds were established by spectroscopy and elemental analyses.



## 1. Introduction

Pyrazole derivatives are an important class of heterocyclic compound for being key substructures in a variety of compounds with important biological properties.[1] They are known to possess a wide spectrum of activities such as antimicrobial,[2,3] antiinflammatory,[4,5] antiparasitic,[6] antidepressant,[7] antiviral,[8] antifungal,[9] and antitumour activities.[10,11] Moreover, the pyrazole nucleus represent the core unit in a variety of drugs such as celecobix (Celebrex),[12] sildenafil (Viagra),[13] and rimonabant (Acomplia).[14]

Moreover, much attention has been paid over the past decade for the synthesis of 1,2,4-triazoles and their heterocyclic fused analogues, triazolothiadiazines, for their therapeutically importance. They are reported to possess a wide spread of medical applications such as antibacterial, antifungal, anticancer, antitumour, anticonvulsant, anti-inflammatory, antimicrobial activity and analgesic properties.[15–19]

In addition, compounds including bis-heterocyclic moieties were encountered in many bioactive natural products.[20] Recent reports showed that among libraries of derivatized heterocycles, the most active library compounds have a bis-heterocyclic structure.[21–24] Bis-heterocycles in which two bioactive heterocycles are tethered *via* a flexible linker were reported to be anticancer[25–28] and as antimicrobial agents.[29] Along with these activities, some bis-heterocyclic derivatives also exhibited potent antialzheimer and antiprion activity.[30]

In addition, bis-heterocyclic compounds separated by a carbon chain or other functional group have also been recently reported as corrosion inhibitors.[31]

Furthermore, over recent years there have been an increasing number of reports of so-called 'multi-armed' molecules.[32] For example, benzene cores appended by six flexible arms, each terminated by an anionic group, have recently been shown to form micelles in aqueous solution.[32a,b] Multi-armed molecules, in which a combination of an aromatic core and aromatic side chains find uses as discotic liquid crystals.[32q] Some multi-armed derivatives with arms containing donor atoms have been utilized as metal ion ligands.[33] Multi-armed compounds have also been used as building units for dendrimers.[34] Some conjugated multi-armed compounds exhibit interesting properties in materials science.[35,36]

Motivated by these findings, we report herein on the synthesis of some novel mono-, bis- and poly heterocyclic compounds incorporating a combination of pyrazole and [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine pharmacophores for the first time. The combination of two pharmacophores into a single molecular skeleton is a well-established approach for designing more potent drugs with significant increase in activity.

The strategy used for the synthesis of the target {6-(1*H*-pyrazol-4-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine} depends mainly on the initial formation of 2-bromo-1-(5-methyl-1-phenyl-1*H*-

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http://dx.doi.org/10.1016/j.tet.2015.12.024
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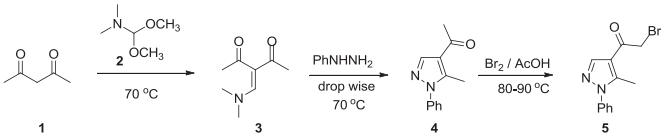
pyrazol-4-yl)ethanone (**5**) as a key intermediate and subsequent reaction with the appropriate aminotriazolethiol. The amino and mercapto groups in these compounds serve thereby as readily accessible nucleophilic centres for the preparation of *N*-bridged heterocycles.

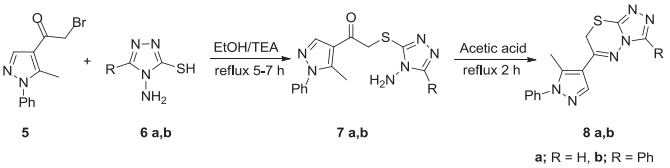
## 2. Results and discussion

The desired 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl) ethanone (**5**) was synthesized by the reaction of phenylhydrazine with ((dimethylamino)methylene)pentane-2,4-dione (**3**), obtained upon treatment of acetylacetone with dimethylformamide dimethylacetal (DMFDMA), to give 1-phenyl-5-methyl-4-acetypyrazole (**4**)[37] followed by bromination upon treatment with $Br_2$ in AcOH to give **5**[38] (Scheme 1).



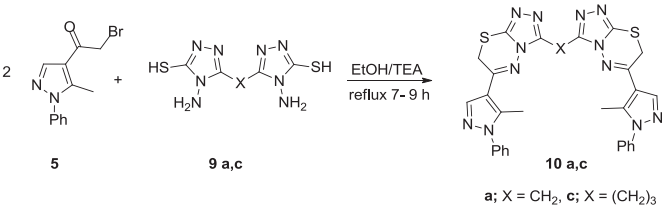

**Scheme 1.** Synthesis of 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone.

Thus, reaction of **5** with 4-amino-3-mercapto-1,2,4-triazole derivatives **6a**,**b**[39] in refluxing ethanol in the presence of a few drops of triethylamine as catalyst, afforded the novel pyrazolyl(5,6-dihydro-*s*-triazolo[3,4-*b*]thiadiazines) **8a** and **8b** in 70 and 75% yields, respectively, *via* initial formation of 2-(4-amino-5-methyl-4*H*-1,2,4-triazol-3-ylthio)-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl) ethanone, followed by cyclocondensation in refluxing acetic acid (Scheme 2).



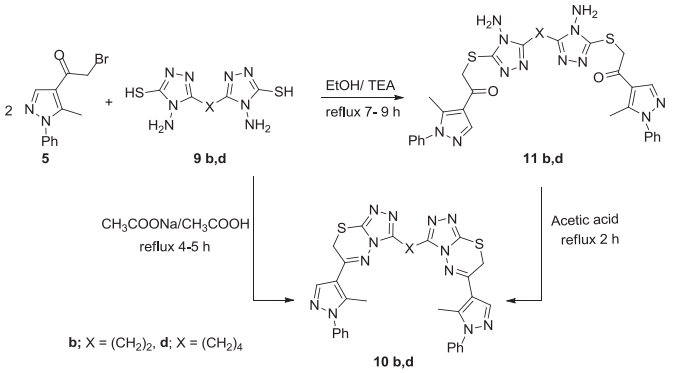

**Scheme 2.** Synthesis of pyrazolyl(5,6-dihydro-*s*-triazolo[3,4-*b*]thiadiazines).

In continuation of this work, we also describe simple and efficient routes for the synthesis of novel bis(6-pyrazolyl-*s*-triazolo [3,4-*b*][1,3,4]thiadiazines) **10a**–**d** in which the pyrazolyl-triazolothiadiazine is linked to the alkyl spacer through the triazole ring (Schemes 3 and 4).




**Scheme 3.** Synthesis of bis(6-pyrazolyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines) linked to methylene or propylene spacer.

The synthetic approach used for the synthesis of the target bis-compounds **10a**,**c** includes the initial formation of the appropriate bis(4-amino-5-mercapto-1,2,4-triazol-3-yl)alkanes **9a**,**c** as precursors, which upon treatment with two equivalents of **5** in refluxing EtOH, containing few drops of triethylamine, afforded the corresponding bis(6-pyrazolyl triazolothiadiazines) **10a** and **10c** in 73 and 70% yields, respectively.

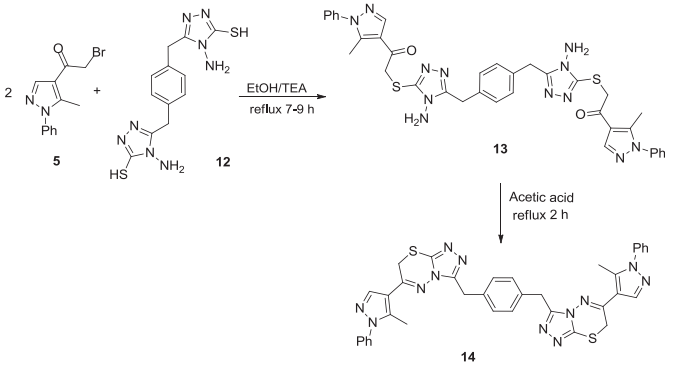



**Scheme 4.** Synthesis of bis(6-pyrazolyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines) linked to ethyl or butyl spacer.

The bis(triazoles) **9a**–**d** can be obtained by a one-step reaction between aliphatic dicarboxylic acids and two molar equivalents of thiocarbohydrazide at the melting temperature for 30 min according to the method described by Xu *et al.*[40]

The reaction pathway is assumed to involve S-alkylation to give the corresponding bis(aminotriazole) intermediates, followed by intramolecular cyclocondensation to give **10**. The proposed mechanism was confirmed by the possible isolation of the corresponding bis(triazolyl)bis(sulfanediyl)bis(1*H*-pyrazol-4-yl)ethanone **11b** and **11d** upon treatment of **9b**,**d** with two equivalents of **5** in refluxing EtOH containing a few drops of triethylamine. The latter compounds underwent cyclocondensation in refluxing acetic acid to give **10b** and **10d**, respectively (Scheme 4). Compounds **10b**,**d** can also be alternatively obtained in 79, 80% yield in a one step reaction of **9b**,**d** with **5** in refluxing acetic acid containing sodium acetate.

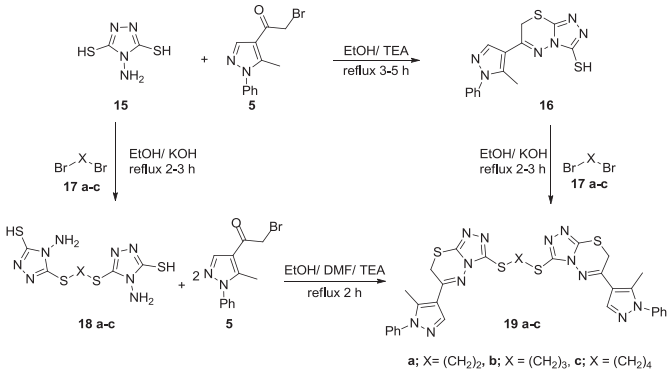
The same methodology was extended to the preparation of bis(*s*-triazolo[3,4-*b*][1,3,4]thiadiazines) **14** in which the pyrazolyl-triazolothiadiazine is linked to a benzene core *via* an alkyl linkage as depicted in Scheme 4. Thus, treatment of 5,5′-(1,4-phenylenebis(methylene))bis(4-amino-4*H*-1,2,4-triazole-3-thiol) **12** with two equivalents of **5** in refluxing EtOH containing a few drops of triethylamine afforded the corresponding bis(amino-triazoles) **13**. The latter compound underwent cyclocondensation in refluxing acetic acid to give **14** (Scheme 5). Compound **12** was obtained by the reaction of one mole of 2,2′-(1,4-phenylene)diacetic acid with two moles of thiocarbohydrazide under fusion conditions.[41]




**Scheme 5.** Synthesis of bis(6-pyrazolyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines) linked to xylyl spacer.

We also studied the synthesis of novel twofold branched pyrazolyltriazolothiadiazines **18a**–**c** which are linked to an alkyl spacer *via* a thioether group as outlined in Scheme 6.

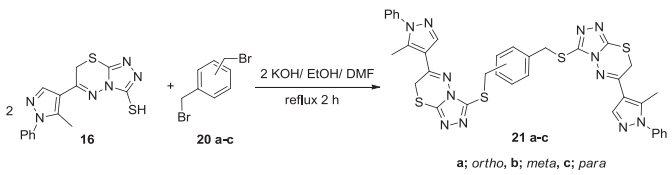
Please cite this article in press as: Salem, M. E.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.12.024




**Scheme 6.** Synthesis of bis(6-pyrazolyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines) linked to alkyl spacer *via* thioether group.

The two possible approaches, Path A and Path B for **19a**–**c**, are given in Scheme 6. In the case of Path-A, 6-pyrazolyl-7*H*-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazine-3-thiol (**16**) has been synthesized in the first step in 88% yield, upon treatment of 4-amino-4*H*-1,2,4-triazole-3,5-dithiol (**15**) with one equivalent of **5** in refluxing EtOH containing triethylamine. Twofold substitution of the appropriate dibromoalkane **17a**–**c** with two equivalents of **16** in refluxing EtOH containing KOH afforded **19a**–**c** in 70–76% yields. Alternatively, this can also be achieved via Path-B, where the desired bis(sulfanediyl)bis(4-amino-4*H*-1,2,4-triazole-3-thiols) **18a**–**c** were obtained by twofold substitution of the appropriate dibromoalkane **17a**–**c** with two equivalents of 4-amino-4*H*-1,2,4-triazole-3,5-dithiol (**15**)[42] in refluxing EtOH containing KOH.[43] Subsequent reaction of **18a**–**c** with **5** in refluxing ethanol-DMF mixture in the presence of a few drops of triethylamine as a catalyst afforded **19a**–**c** in 74–80% yields.

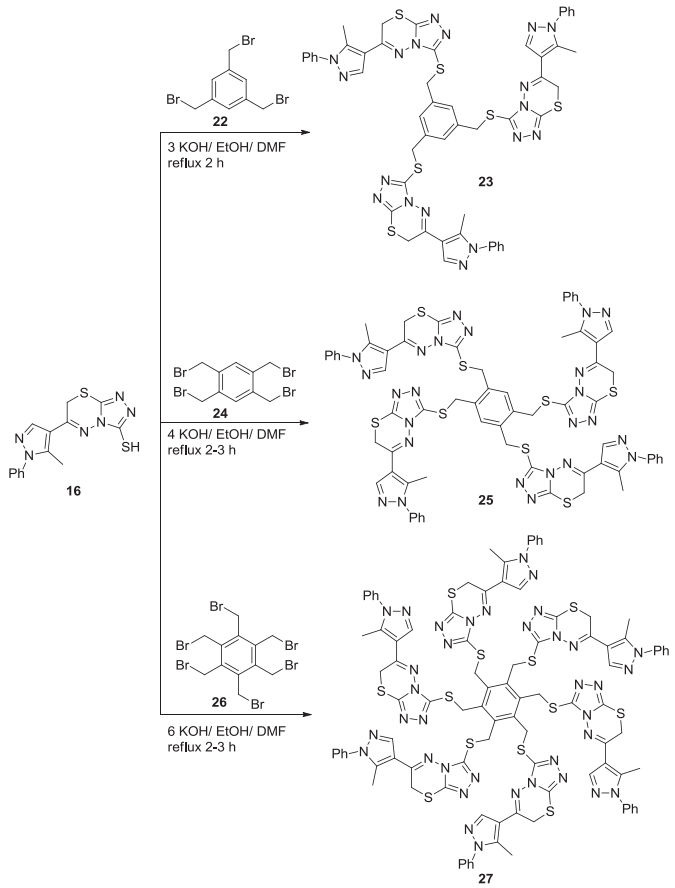
The same methodology described in Path A was extended to the preparation of bis(pyrazolyltriazolothiadiazines) **21a**–**c** in which the pyrazolyltriazolothiadiazines are linked to a benzene core *via* sulfanylmethylene spacers. Thus, twofold substitution of the appropriate bis(bromomethyl)benzene **20a**–**c** with two equivalents of **16** under similar conditions afforded **21a**, **21b** and **21c** in 65, 73 and 78% yields, respectively (Scheme 7).




**Scheme 7.** Synthesis of bis(6-pyrazolyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines) linked to xylyl spacer via thioether group.

All compounds were characterized by their elemental analysis, IR, $^1$H NMR and mass spectra. The spectral data agree with the proposed structures. Thus, the disappearance of $NH_2$ stretching bands in the IR spectra of triazolothiadiazines, together with the disappearance of the characteristic peaks belonging to primary amine in their $^1$H NMR spectra are evidences for the cyclocondensation of 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl) ethanone with the corresponding bis-aminotriazoles. In addition, the presence of $SCH_2$ protons, resonated at $\delta$ 4.42–4.61 ppm as singlet signals integrating four protons, clearly indicated that ring closure reaction occurred. All other protons were seen at the expected chemical shifts and integral values.

Encouraged by the above results, our study was extended to expand the scope of this reaction to prepare novel three-, four-, and sixfold branched pyrazolyltriazolothiadiazines, which are linked to a benzene core *via* sulfanylmethylene spacers (Scheme 8).




**Scheme 8.** Synthesis of poly(pyrazolyltriazolothiadiazines) linked to a benzene core *via* sulfanyl-methylene spacers.

The synthetic utility of **16** as building blocks for novel 1,3,5-tris- and 1,2,4,5-tetrakis(6-pyrazolyl-7*H*-[1,2,4]triazolo-[3,4-*b*][1,3,4] thiadiazines) **23** and **25** was investigated (Scheme 8). Thus, three- and fourfold substitution of tris(bromomethyl)benzene **22** and tetrakis(bromomethyl)-benzene **24** with three and four equivalents of 6-pyrazolyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-3-thiol (**16**) in refluxing EtOH/DMF mixture containing KOH afforded **23** and **25** in 66 and 63% yields, respectively. The same methodology can be extended to the preparation of 1,2,3,4,5,6-hexakis((6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*] [1,3,4]-thiadiazin-3-ylthio)methyl)benzene (**27**). Thus, sixfold substitution of hexakis(bromomethyl)benzene **26** with six equivalents of **16** under similar conditions afforded **27** in 60% yield (Scheme 8).

The structures of the new synthesized compounds were confirmed by IR, NMR, mass spectra and elemental analysis. The symmetry of compounds **23**, **25** and **27** are manifested by a single set of signals characteristic of the equivalent $SCH_2$ and 5-methyl groups in the $^1$H NMR spectra.

## 3. Conclusion

We have developed a simple method for the preparation of 2-bromo-1-(1*H*-pyrazol-4-yl)ethanone and studied its synthetic utility as building blocks for novel mono-, bis- and poly{6-(1*H*-

pyrazol-4-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine}. 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. They offer an advantage of their easy synthesis in a simple one step or two step procedure from inexpensive starting materials. Our current studies are directed to examine the inclusion behaviour of the new compounds as well as to extend the scope of this method to cover additional multi-armed heterocyclic compounds.

## 4. Experimental section

### 4.1. Materials and methods

Melting points were determined in open glass capillaries with a Gallenkamp apparatus. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. The infrared spectra were recorded as potassium bromide disks on a Pye Unicam SP 3-300 and Shimaduz FTIR 8101 PC infrared spectrophotometer. NMR spectra were recorded with a Varian Mercury VXR-300 NMR spectrometer at 300 MHz ($^1$H NMR) and at 75 MHz ($^{13}$C NMR). Mass spectra (EI) were obtained at 70 eV with a type Shimadzu GCMQP 1000 EX spectrometer. Analytical thin-layer chromatography was performed using pre-coated silica gel 60,778 plates (Fluka), and the spots were visualized with UV light at 254 nm.

### 4.2. Synthesis of 2-(4-amino-5-substituted-4*H*-1,2,4-triazol-3-ylthio)-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone 7a,b

A mixture of 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl) ethanone (**5**) (2.79 g, 10 mmol) and the appropriate 5-substituted-4-amino-4*H*-1,2,4-triazole-3-thiol **6a** or **6b** (10 mmol) were dissolved in ethanol (20 mL), TEA (1 mL) was added and the reaction mixture was refluxed for 5–7 h. The reaction mixture then left to cool, the solid product was filtered off to afford the title compounds **7a**,**b**.

*4.2.1. 2-(4-Amino-4H-1,2,4-triazol-3-ylthio)-1-(5-methyl-1-phenyl-1H-pyrazol-4-yl)ethanone (**7a**).* (2.35 g, 75%) as a white powder, mp 133–135 °C; [Found: C, 53.19; H, 4.32; N, 26.62; S, 10.33. $C_{14}H_{14}N_6OS$ requires C, 53.49; H, 4.49; N, 26.73; S, 10.20%]; $\nu_{max}$ (Neat film) 3429, 3337, 1660, 1402, 935 cm$^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.51 (s, 3H, $CH_3$), 4.65 (s, 2H, $CH_2$), 6.12 (s, 2H, $NH_2$), 7.52–7.58 (m, 5H, aromatic), 8.38 (s, 1H, H-3 pyrazole), 8.44 (s, 1H, H-3 triazole).

*4.2.2. 2-(4-Amino-5-phenyl-4H-1,2,4-triazol-3-ylthio)-1-(5-methyl-1-phenyl-1H-pyrazol-4-yl)ethanone (**7b**).* (3.00 g, 77%) as a white powder, mp 190–192 °C; [Found: C, 61.19; H, 4.46; N, 21.40; S, 8.03. $C_{20}H_{18}N_6OS$ requires C, 61.52; H, 4.65; N, 21.52; S, 8.21%]; $\nu_{max}$ (Neat film) 3435, 3330, 1669, 1503, 764 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 2.54 (s, 3H, $CH_3$), 4.56 (s, 2H, $CH_2$), 5.37 (s, 2H, $NH_2$), 7.36–7.51 (m, 10H, aromatic), 8.09 (s, 1H, H-3 pyrazole).

### 4.3. Synthesis of 3-substituted-6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazine 8a,b

2-(4-Amino-5-substituted-4*H*-1,2,4-triazol-3-ylthio)-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone **7a**,**b** (5 mmol) was cyclized to thiadiazine ring when refluxed in acetic acid (10 mL) for 2 h then left to cool; few drops of water were added. The solid product was filtered off and recrystallized from ethyl acetate for **8a**, and ethanol for **8b**.

*4.3.1. 6-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)-7H-[1,2,4]triazolo-[3,4-b][1,3,4]thiadiazine (**8a**).* (1.03 g, 70%) as a creamy crystal, mp 160–162 °C; [Found: C, 56.59; H, 4.11; N, 28.20; S, 10.65. $C_{14}H_{12}N_6S$ requires C, 56.74; H, 4.08; N, 28.36; S, 10.82%]; $\nu_{max}$ (Neat film) 3135, 3079, 1632, 1584, 1450 cm$^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.59 (s, 3H, $CH_3$), 4.34 (s, 2H, H-6 thiadiazine), 7.52–7.59 (m, 5H, aromatic), 8.26 (s, 1H, H-3 pyrazole), 9.07 (s, 1H, H-3 triazole); *m*/*z* (EI, 70 eV) 296 (100, M$^+$), 196 (15.3), 183 (13.8), 118 (47.7), 104 (14.3), 77 (46.9%).

*4.3.2. 6-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)-3-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**8b**).* (1.39 g, 75%) as a colourless crystal, mp 228–230 °C; [Found: C, 64.39; H, 4.11; N, 22.20; S, 8.55. $C_{20}H_{16}N_6S$ requires C, 64.50; H, 4.33; N, 22.56; S, 8.61%]; $\nu_{max}$ (Neat film) 3055, 2924, 1628, 1551, 1457 cm$^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.58 (s, 3H, $CH_3$), 3.93 (s, 2H, H-6 thiadiazine), 7.43–7.98 (m, 10H, aromatic), 8.09 (s, 1H, H-3 pyrazole), $\delta_C$ (75 MHz, DMSO) 13.1, 23.7, 114.9, 125.4, 126.0, 127.8, 128.5, 128.7, 129.2, 130.0, 138.3, 140.2, 141.2, 142.1, 151.3, 152.1; *m*/*z* (EI, 70 eV) 372 (100, M$^+$), 196 (19.2), 183 (15.5), 128 (10.0), 118 (26.8), 103 (42.1), 77 (36.3%).

### 4.4. Synthesis of bis(6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)alkane 10a,c

A mixture of 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl) ethanone (**5**) (5.58 g, 20 mmol) and the appropriate bis(4-amino-5-mercapto-1,2,4-triazol-3-yl)alkane **9a** or **9c** (10 mmol) was dissolved in ethanol (30 mL), TEA (2 mL) was added, and the reaction mixture was refluxed for 7–9 h then left to cool. The solid product was filtered off and recrystallized from EtOH/DMF to afford the title compounds **10a**,**c**.

*4.4.1. Bis(6-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-7H-[1,2,4]-triazolo [3,4-b][1,3,4]thiadiazin-3-yl)methane (**10a**).* (4.40 g, 73%) as a brown powder, mp<300 °C; [Found: C, 57.30; H, 4.04; N, 27.71; S, 10.38. $C_{29}H_{24}N_{12}S_2$ requires C, 57.60; H, 4.00; N, 27.80; S, 10.61%]; $\nu_{max}$ (Neat film) 3099, 2966, 1664, 1555, 1464 cm$^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.50 (s, 6H, $CH_3$), 4.29 (s, 2H, $CH_2$), 4.55 (s, 4H, H-6 thiadiazine), 7.47–7.58 (m, 10H, aromatic), 8.24 (s, 2H, H-3 pyrazole); *m*/*z* (EI, 70 eV) 604 (10.4, M$^+$), 557 (10.7), 479 (11.2), 379 (12.5), 296 (13.1), 256 (15.1), 199 (18.8), 182 (39.3), 128 (46.6), 118 (32.5), 96 (47.4), 77 (95.6), 64 (100%).

*4.4.2. 1,3-Bis(6-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)propane (**10c**).* (4.42 g, 70%) as a pale yellow powder, mp 118–122 °C; [Found: C, 58.53; H, 4.34; N, 26.35; S, 10.22. $C_{31}H_{28}N_{12}S_2$ requires C, 58.84; H, 4.46; N, 26.56; S, 10.13%]; $\nu_{max}$ (Neat film) 3102, 2966, 1653, 1548, 1462 cm$^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.19–2.22 (m, 2H, $CH_2$), 2.51 (s, 6H, $CH_3$), 2.97 (t, 4H, $CH_2$, $J$ = 6.9 Hz), 4.25 (s, 4H, H-6 thiadiazine), 7.5–7.59 (m, 10H, aromatic), 8.24 (s, 2H, H-3 pyrazole); $\delta_C$ (75 MHz, DMSO) 13.1, 23.3, 23.6, 23.8, 114.9, 125.3, 128.7, 129.2, 129.6, 138.3, 139.7, 140.1, 140.9, 150.9; *m*/*z* (EI, 70 eV) 632 (2.7, M$^+$), 557 (3.0), 424 (8.4), 379 (21.0), 255 (19.1), 191 (24.4), 159 (40.4), 128 (62.8), 118 (52.8), 96 (40.6), 77 (56.1), 64 (100%).

### 4.5. Synthesis of bis(6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)alkane 10b,d

*4.5.1. Procedure A.* 2,2′-(5,5′-(Ethane-1,2-diyl)bis(4-amino-4*H*-1,2,4-triazole-5,3-diyl))bis(sulfanediyl)bis(1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone) **11b** or 2,2′-(5,5′-(butane-1,4-diyl)bis(4-amino-4*H*-1,2,4-triazole-5,3-diyl))bis(sulfanediyl)bis(1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone) **11d** was cyclized to thiadiazine ring when refluxed in acetic acid (10 mL) for 2 h. The reaction mixture then left to cool; few drops of water were added. The

Please cite this article in press as: Salem, M. E.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.12.024

formed solid product was filtered off and recrystallized from EtOH/DMF to afford **10b**,**d**.

*4.5.2. Procedure B.* A mixture of 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**5**) (5.58 g, 20 mmol) and the appropriate bis(4-amino-5-mercapto-1,2,4-triazol-3-yl)alkane **9b** or **9d** (10 mmol) was dissolved in acetic acid (10 mL), sodium acetate (2 g) was added, and the reaction mixture was refluxed for 4–5 h. The reaction mixture then left to cool, the solid product was filtered off and recrystallized from EtOH/DMF to afford **10b**,**d**.

*4.5.3. 1,2-Bis(6-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-7H-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazin-3-yl)ethane (**10b**).* ((A) 4.44 g, 72%; (B) 4.88 g, 79%) as a white powder, mp 256–258 °C; [Found: C, 58.19; H, 4.15; N, 27.20; S, 10.38. $C_{30}H_{26}N_{12}S_2$ requires C, 58.23; H, 4.24; N, 27.17; S, 10.36%]; $\nu_{max}$ (Neat film) 3107, 2989, 1659, 1551, 1458 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.55 (s, 6H, $CH_3$), 3.2 (s, 4H, $CH_2$), 4.22 (s, 4H, H-6 thiadiazine), 7.4–7.57 (m, 10H, aromatic), 8.25 (s, 2H, H-3 pyrazole); *m*/*z* (EI, 70 eV) 618 (3.7, $M^+$), 473 (11.8), 424 (17.3), 379 (32.2), 317 (38.0), 239 (39.6), 198 (19.6), 183 (71.9), 155 (42.1), 128 (62.0), 118 (95.2), 96 (35.7), 77 (99.6), 64 (100%).

*4.5.4. 1,4-Bis(6-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-7H-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazin-3-yl)butane (**10d**).* ((A) 4.84 g, 75%; (B) 5.16 g, 80%) as a creamy powder, mp 186–190 °C; [Found: C, 59.19; H, 4.54; N, 25.90; S, 9.88. $C_{32}H_{30}N_{12}S_2$ requires C, 59.42; H, 4.68; N, 25.99; S, 9.92%]; $\nu_{max}$ (Neat film) 3064, 2912, 1645, 1551, 1462 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO) 1.82 (br, 4H, $CH_2$), 2.52 (s, 6H, $CH_3$), 2.87 (br, 4H, $CH_2$), 4.26 (s, 4H, H-6 thiadiazine), 7.53 (s, 10H, aromatic), 8.25 (s, 2H, H-3 pyrazole); *m*/*z* (EI, 70 eV) 646 (32.5, $M^+$), 629 (28.3), 579 (28.6), 510 (26.1), 427 (31.8), 363 (31.2), 296 (34.3), 200 (33.4), 183 (65.6), 155 (42.0), 129 (36.9), 118 (45.2), 80 (84.3), 77 (67.5), 64 (100%).

### 4.6. Synthesis of 2,2′-(5,5′-(ethane-1,2-diyl)bis(4-amino-4*H*-1,2,-4-triazole-5,3-diyl))bis(sulfanediyl)bis(1-(5-methyl-1-phenyl-1-*H*-pyrazol-4-yl)ethanone) (11b) and 2,2′-(5,5′-(butane-1,4-diyl)-bis(4-amino-4*H*-1,2,4-triazole-5,3-diyl))bis(sulfanediyl)-bis(1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone) (11d)

A mixture of 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl) ethanone (**5**) (5.58 g, 20 mmol) and the appropriate bis(4-amino-5-mercapto-1,2,4-triazol-3-yl)alkane **9b** or **9d** (10 mmol) was dissolved in ethanol (30 mL), TEA (2 mL) was added. The reaction mixture was refluxed for 7–9 h then left to cool. The solid product was filtered off to afford the title compounds **11b** and **11d**.

*4.6.1. 2,2′-(5,5′-(Ethane-1,2-diyl)bis(4-amino-4H-1,2,4-triazole-5,3-diyl))bis(sulfanediyl)bis(1-(5-methyl-1-phenyl-1H-pyrazol-4-yl) ethanone) (**11b**).* (5.23 g, 80%) as a pale yellow powder, mp 238–240 °C; [Found: C, 54.96; H, 4.53; N, 25.43; S, 9.65. $C_{30}H_{30}N_{12}O_2S_2$ requires C, 55.03; H, 4.62; N, 25.67; S, 9.79%]; $\nu_{max}$ (Neat film) 3432, 3351, 3066, 2968, 1662, 1551, 1456 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.50 (s, 6H, $CH_3$), 3.10 (s, 4H, $CH_2$), 4.63 (s, 4H, $CH_2$), 6.03 (s, 4H, $NH_2$), 7.51–7.58 (m, 10H, aromatic), 8.38 (s, 2H, H-3 pyrazole); $\delta_C$ (75 MHz, DMSO) 11.9, 15.9, 21.0, 119.0, 125.3, 128.7, 138.0, 139.0, 141.9, 142.9, 150.9, 155.4, 188.4; *m*/*z* (EI, 70 eV) 654 (4.2, $M^+$), 473 (4.1), 429 (4.3), 384 (4.5), 300 (4.7), 197 (5.7), 149 (6.3), 121 (4.8), 111 (5.1), 80 (100%).

*4.6.2. 2,2′-(5,5′-(Butane-1,4-diyl)bis(4-amino-4H-1,2,4-triazole-5,3-diyl))bis(sulfanediyl)bis(1-(5-methyl-1-phenyl-1H-pyrazol-4-yl) ethanone) (**11d**).* (5.79 g, 85%) as a white powder, mp 148–150 °C; [Found: C, 56.12; H, 5.21; N, 24.39; S, 9.52. $C_{32}H_{34}N_{12}O_2S_2$ requires C, 56.29; H, 5.02; N, 24.62; S, 9.39%]; $\nu_{max}$ (Neat film) 3415, 3337, 3010, 2898, 1664, 1543, 1449 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO) 1.74 (br, 4H, $CH_2$), 2.50 (s, 6H, $CH_3$), 2.71 (br, 4H, $CH_2$), 4.61 (s, 4H, $CH_2$), 5.91 (s, 4H, $NH_2$), 7.51–7.58 (s, 10H, aromatic), 8.37 (s, 2H, H-3 pyrazole).

### 4.7. 2,2′-(5,5′-(1,4-phenylenebis(methylene))bis(4-amino-4*H*-1,2,4-triazole-5,3 diyl))bis(sulfanediyl)bis(1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone) (13)

A mixture of 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl) ethanone (**5**) (5.58 g, 20 mmol) and 5,5′-(1,4-phenylenebis(methylene))bis(4-amino-4*H*-1,2,4-triazole-3-thiol) (**12**) (3.34 g, 10 mmol) was dissolved in ethanol (30 mL), TEA (2 mL) was added and the reaction mixture was refluxed for 7–9 h. The reaction mixture was then left to cool and the solid product was filtered off to afford **13** (5.03 g, 69%) as a creamy solid, mp 162–164 °C; [Found: C, 59.11; H, 4.52; N, 22.89; S, 8.58. $C_{36}H_{34}N_{12}O_2S_2$ requires C, 59.16; H, 4.69; N, 23.00; S, 8.77%]; $\nu_{max}$ (Neat film) 3447, 3328, 1663, 1540, 876 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.49 (s, 6H, $CH_3$), 4.03 (s, 4H, $CH_2$), 4.61 (s, 4H, $CH_2$), 5.91 (s, 4H, $NH_2$), 7.2–7.55 (m, 14H, aromatic), 8.36 (s, 2H, H-3 pyrazole); *m*/*z* (EI, 70 eV) 730 (1.7, $M^+$), 657 (1.5), 594 (1.5), 415 (1.7), 372 (1.4), 301 (1.6), 213 (1.7), 185 (3.9), 130 (1.7), 95 (2.1), 80 (100), 79 (10.8), 64 (27.1%).

### 4.8. 1,4-Bis((6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)methyl)benzene (14)

A solution of **13** (0.730 g, 1 mmol) in acetic acid (10 mL) was heated under reflux for 2 h. The solid obtained upon cooling and dilution with few drops of water was filtered off and recrystallized from ethanol to afford **14** (0.451 g, 65%) as a creamy solid, mp 198–200 °C; [Found: C, 62.19; H, 4.11; N, 24.25; S, 9.08. $C_{36}H_{30}N_{12}S_2$ requires C, 62.23; H, 4.35; N, 24.19; S, 9.23%]; $\nu_{max}$ (Neat film) 3175, 2918, 1660, 1540, 1455 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.37 (s, 6H, $CH_3$), 4.18 (s, 4H, $CH_2$), 4.23 (s, 4H, H-6 thiadiazine), 7.18–7.57 (m, 14H, aromatic), 8.22 (s, 2H, H-3 pyrazole); *m*/*z* (EI, 70 eV) 694 (5.1, $M^+$), 570 (5.5), 444 (5.3), 379 (11.3), 296 (9.8), 239 (13.6), 183 (42.5), 159 (46.3), 128 (60.5), 118 (34.0), 77 (52.9), 64 (100%).

### 4.9. 6-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo-[3,4-*b*][1,3,4]-thiadiazine-3-thiol (16)

A mixture of 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl) ethanone (**5**) (2.79 g, 10 mmol) and 4-amino-4*H*-1,2,4-triazole-3,5-dithiol (**15**) (1.48 g, 10 mmol) was dissolved in ethanol (30 mL), TEA (1 mL) was added and the reaction mixture was refluxed for 3–5 h then left to cool. The solid product was filtered off and recrystallized from EtOH/DMF to afford **16** (2.88 g, 88%) as a pale yellow solid, mp 298–300 °C; [Found: C, 51.08; H, 3.45; N, 25.47; S, 19.45. $C_{14}H_{12}N_6S_2$ requires C, 51.20; H, 3.68; N, 25.59; S, 19.53%]; $\nu_{max}$ (Neat film) 3131, 2978, 2426, 1631, 1544, 1454 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.68 (s, 3H, $CH_3$), 4.31 (s, 2H, H-6 thiadiazine), 7.52–7.58 (m, 5H, aromatic), 8.25 (s, 1H, H-3 pyrazole) 13.8 (s, 1H, SH); $\delta_C$ (75 MHz, DMSO) 13.1, 23.3, 115.0, 125.3, 128.6, 129.2, 138.5, 139.7, 140.5, 140.8, 151.4, 164.7; *m*/*z* (EI, 70 eV) 328 (100, $M^+$), 295 (10.6), 228 (6.8), 184 (24.6), 118 (38.9), 77 (62.0%).

### 4.10. Synthesis of bis(6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-ylthio)alkane 19a–c

*4.10.1. Procedure A.* To a solution of KOH (0.112 g, 2 mmol) in EtOH (20 mL) was added the 6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-3-thiol (**16**) (0.65 g, 2 mmol). The resulting mixture was refluxed for 2–3 h with the appropriate di-bromo alkane **17a**–**c** (1 mmol). The reaction mixture

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then left to cool and the solid product was filtered off and recrystallized from EtOH/DMF to give **19a**–**c**.

*4.10.2. Procedure B.* To a solution of KOH (1.12 g, 20 mmol) in EtOH (20 mL), 4-amino-4*H*-1,2,4-triazole-3,5-dithiol (**15**) (2.96 g, 20 mmol) was added. The resulting mixture was refluxed for 2–3 h with the appropriate di bromo alkane **17a**–**c** (10 mmol) then left to cool. The solid product was filtered off and recrystallized from EtOH/DMF to afford the appropriate 5,5′-(alkane-1,4-diylbis(sulfanediyl))bis(4-amino-4*H*-1,2,4-triazole-3-thiol) **18a**–**c**. To a mixture of the appropriate bis(4-amino-4*H*-1,2,4-triazole-3-thiol) **18a**–**c** (10 mmol) in ethanol (30 mL), 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**5**) (5.58 g, 20 mmol) and TEA (2 mL) were added. The reaction mixture was refluxed for 2–3 h then left to cool and the solid product was filtered off and recrystallized from EtOH/DMF to afford **19a**–**c**.

*4.10.3. 1,2-Bis(6-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-ylthio)ethane (**19a**).* ((A) 0.477 g, 70%; (B) 5.04 g, 74%) as a white powder, mp 272–274 °C; [Found: C, 52.56; H, 3.64; N, 24.84; S, 18.59. $C_{30}H_{26}N_{12}S_4$ requires C, 52.77; H, 3.84; N, 24.61; S, 18.78%]; $\nu_{max}$ (Neat film) 3104, 2992, 1642, 1551, 1458 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.55 (s, 6H, $CH_3$), 3.57 (s, 4H, $CH_2$), 4.34 (s, 4H, H-6 thiadiazine), 7.51–7.53 (m, 10H, aromatic), 8.26 (s, 2H, H-3 pyrazole); *m*/*z* (EI, 70 eV) 682 (1.8, $M^+$), 589 (1.9), 447 (1.8), 356 (17.5), 328 (100), 295 (22.6), 184 (29.9), 155 (16.7), 128 (18.8), 118 (87.7), 77 (65.0%).

*4.10.4. 1,3-Bis(6-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-ylthio)propane (**19b**).* ((A) 0.528 g, 76%; (B) 5.35 g, 77%) as an orange powder, mp 235–237 °C; [Found: C, 53.65; H, 4.01; N, 24.22; S, 18.23. $C_{31}H_{28}N_{12}S_4$ requires C, 53.43; H, 4.05; N, 24.12; S, 18.40%]; $\nu_{max}$ (Neat film) 3060, 2969, 1648, 1548, 1454 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.19–2.25 (m, 2H, $CH_2$), 2.6 (s, 6H, $CH_3$), 3.30–3.35 (m, 4H, $CH_2$), 4.33 (s, 4H, H-6 thiadiazine), 7.51–7.54 (m, 10H, aromatic), 8.26 (s, 2H, H-3 pyrazole); *m*/*z* (EI, 70 eV) 696 (0.6, $M^+$), 369 (3.9), 328 (98.6), 296 (22.9), 184 (30.0), 118 (73.1), 77 (100%).

*4.10.5. 1,4-Bis(6-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-ylthio)butane (**19c**).* ((A) 0.532 g, 75%; (B) 5.68 g, 80%) as a yellow powder, mp 238–240 °C; [Found: C, 54.01; H, 4.33; N, 23.91; S, 17.93. $C_{32}H_{30}N_{12}S_4$ requires C, 54.06; H, 4.25; N, 23.64; S, 18.04%]; $\nu_{max}$ (Neat film) 3083, 2992, 1631, 1549, 1455 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO) 1.86 (br, 4H, $CH_2$), 2.58 (s, 6H, $CH_3$), 3.25 (br, 4H, $CH_2$), 4.33 (s, 4H, H-6 thiadiazine), 7.51–7.55 (m, 10H, aromatic), 8.26 (s, 2H, H-3 pyrazole); $\delta_C$ (75 MHz, DMSO) 13.0, 24.2, 28.0, 30.1, 114.7, 125.3, 128.6, 129.2, 138.3, 140.3, 141.0, 141.3, 149.4, 151.2; *m*/*z* (EI, 70 eV) 710 (1.5, $M^+$), 351 (2.0), 328 (100), 295 (12.9), 196 (19.8), 184 (31.6), 118 (50.0), 77 (62.2%).

### 4.11. Synthesis of bis((6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-ylthio)methyl)-benzene 21a–c

To a solution of KOH (0.112 g, 2 mmol) in EtOH (20 mL) was added the 6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazine-3-thiol (**16**) (0.65 g, 2 mmol). The resulting mixture was refluxed for 2–3 h with the appropriate bis(bromomethyl)benzene **20a**–**c** (1 mmol). The reaction mixture then left to cool, the solid product was filtered off and recrystallized from DMF to afford **21a**–**c**.

*4.11.1. 1,2-Bis((6-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-ylthio)methyl)benzene (**21a**).* (0.492 g, 65%) as an orange crystal, mp 173–175 °C; [Found: C, 56.72; H, 4.21; N, 22.36; S, 16.73. $C_{36}H_{30}N_{12}S_4$ requires C, 56.97; H, 3.98; N, 22.15; S, 16.90%]; $\nu_{max}$ (Neat film) 3102, 2967, 1639, 1548, 1453 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.56 (s, 6H, $CH_3$), 4.29 (s, 4H, H-6 thiadiazine), 4.61 (s, 4H, $CH_2$), 7.22–7.57 (m, 14H, aromatic), 8.23 (s, 2H, H-3 pyrazole); *m*/*z* (EI, 70 eV) 758 (0.7, $M^+$), 369 (3.9), 328 (100), 270 (8.0), 196 (14.3), 184 (20.1), 118 (60.5), 77 (38.1%).

*4.11.2. 1,3-Bis((6-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-ylthio)methyl)benzene (**21b**).* (0.553 g, 73%) as a white crystal, mp 240–242 °C; [Found: C, 56.72; H, 3.81; N, 22.06; S, 16.68. $C_{36}H_{30}N_{12}S_4$ requires C, 56.97; H, 3.98; N, 22.15; S, 16.90%]; $\nu_{max}$ (Neat film) 3059, 2973, 1644, 1548, 1453 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.57 (s, 6H, $CH_3$), 4.31 (s, 4H, H-6 thiadiazine), 4.42 (s, 4H, $CH_2$), 7.25–7.55 (m, 14H, aromatic), 8.26 (s, 2H, H-3 pyrazole); *m*/*z* (EI, 70 eV) 758 (1.4, $M^+$), 454 (2.2), 328 (100), 296 (15.7), 239 (17.5), 184 (39.2), 118 (61.1), 77 (97.6%).

*4.11.3. 1,4-Bis((6-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-ylthio)methyl)benzene (**21c**).* (0.591 g, 78%) as a white crystal, mp 258–260 °C; [Found: C, 57.12; H, 4.07; N, 22.06; S, 17.02. $C_{36}H_{30}N_{12}S_4$ requires C, 56.97; H, 3.98; N, 22.15; S, 16.90]; $\nu_{max}$ (Neat film) 3080, 2961, 1633, 1549, 1454 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.56 (s, 6H, $CH_3$), 4.31 (s, 4H, H-6 thiadiazine), 4.42 (s, 4H, $CH_2$), 7.35–7.55 (m, 14H, aromatic), 8.25 (s, 2H, H-3 pyrazole); $\delta_C$ (75 MHz, DMSO) 13.0, 24.2, 34.3, 114.6, 125.3, 128.7, 129.0, 129.3, 136.4, 138.3, 140.4, 141.0, 148.9, 151.3; *m*/*z* (EI, 70 eV) 758 (8.9, $M^+$), 737 (10.3), 623 (10.7), 547 (10.3), 443 (10.5), 358 (17.0), 328 (91.1), 296 (24.5), 183 (48.1), 118 (93.4), 77 (100%).

### 4.12. Synthesis of 1,3,5-tris((6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-ylthio) methyl)benzene (23)

To a solution of KOH (0.168 g, 3 mmol) in EtOH (25 mL) was added the 6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazine-3-thiol (**16**) (0.984 g, 3 mmol). The resulting mixture was refluxed for 2–3 h with 1,3,5-tris(-bromomethyl)benzene (**22**) (0.356 g, 1 mmol). The reaction mixture was then left to cool and the solid product was filtered off and recrystallized from DMF to afford **23** (0.724 g, 66%) as a creamy powder, mp 210–212 °C; [Found: C, 55.63; H, 3.67; N, 22.84; S, 17.42. $C_{51}H_{42}N_{18}S_6$ requires C, 55.72; H, 3.85; N, 22.93; S, 17.50%]; $\nu_{max}$ (Neat film) 3100, 2971, 1664, 1548, 1453 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.55 (s, 9H, $CH_3$), 4.3 (s, 6H, H-6 thiadiazine), 4.39 (s, 6H, $CH_2$), 7.37–7.54 (m, 18H, aromatic), 8.25 (s, 3H, H-3 pyrazole); $\delta_C$ (75 MHz, DMSO) 13.1, 24.3, 34.4, 114.6, 125.3, 128.6, 129.2, 137.6, 138.3, 140.4, 141.0, 141.6, 148.8, 151.3.

### 4.13. 1,2,4,5-Tetrakis((6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-ylthio)methyl)-benzene (25)

To a solution of KOH (0.224 g, 4 mmol) in EtOH (25 mL) was added the 6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazine-3-thiol (**16**) (1.312 g, 4 mmol). The resulting mixture was refluxed for 2–3 h with 1,2,4,5-tetrakis(-bromomethyl)benzene (**24**) (0.449 g, 1 mmol). The reaction mixture was then left to cool and the solid product was filtered off and recrystallized from DMF to afford **25** (0.905 g, 63%) as an orange powder, mp 262–264 °C; [Found: C, 55.13; H, 3.72; N, 23.29; S, 17.77. $C_{66}H_{54}N_{24}S_8$: C, 55.06; H, 3.78; N, 23.35; S, 17.82%]; $\nu_{max}$ (Neat film) 3057, 2967, 1662, 1547, 1451 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.5 (s, 12H, $CH_3$), 4.28 (s, 8H, H-6 thiadiazine), 4.54 (s, 8H, $CH_2$), 7.47–7.49 (m, 22H, aromatic), 8.22 (s, 4H, H-3 pyrazole); $\delta_C$ NMR (75 MHz,

Please cite this article in press as: Salem, M. E.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.12.024

DMSO) 13.1, 24.3, 31.9, 114.6, 125.2, 128.6, 129.2, 135.1, 138.2, 140.3, 141.0, 141.7, 148.6, 151.3.

### 4.14. 1,2,3,4,5,6-Hexakis((6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-ylthio)methyl) benzene (27)

To a solution of KOH (0.336 g, 6 mmol) in EtOH (25 mL) was added the 6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazine-3-thiol (**16**) (1.968 g, 6 mmol). The resulting mixture was refluxed for 2–3 h with 1,2,3,4,5,6-hexakis(bromomethyl)benzene (**26**) (0.635 g, 1 mmol). The reaction mixture was then left to cool and the solid product was filtered off and recrystallized from DMF to afford the title compound **27** (1.27 g, 60%) as an orange powder, mp 288–290 °C; [Found: C, 54.13; H, 3.57; N, 23.53; S, 18.32. $C_{96}H_{78}N_{36}S_{12}$ requires C, 54.37; H, 3.71; N, 23.78; S, 18.14%]; $\nu_{max}$ (Neat film) 2962, 2920, 1631, 1549, 1452 $cm^{-1}$; $\delta_H$ (300 MHz, DMSO) 2.49 (s, 18H, $CH_3$), 4.26 (s, 12H, H-6 thiadiazine), 4.77 (s, 12H, $CH_2$), 7.41–7.56 (m, 30H, aromatic), 8.18 (s, 6H, H-3 pyrazole).

## Acknowledgements

Professor A.H.M.E. and Dr. A.F.D. gratefully acknowledge the Alexander von Humboldt Foundation for a research fellowship.

## Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.12.024.

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