Regioselective synthesis of V-shaped bistriazinyl-phenanthrolines

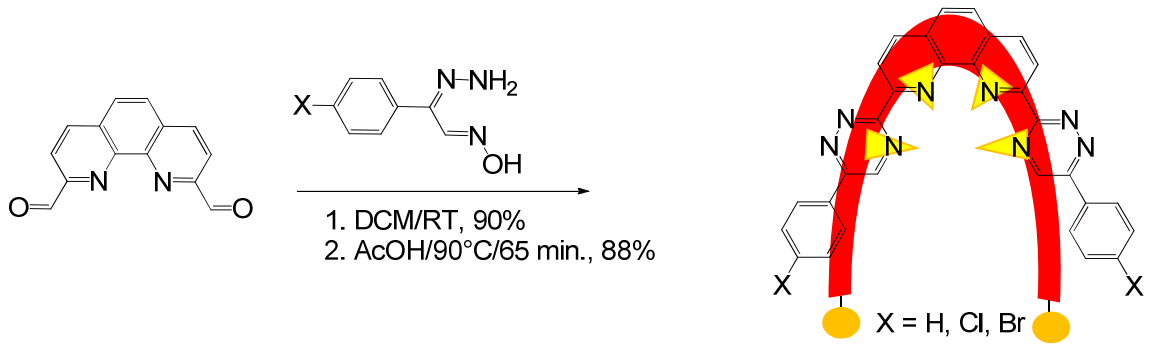
Niall T. Coogan[†], Michael A. Chimes[†], James Raftery, Pavle Mocilac[*] and Melissa A. Denecke

School of Chemistry, University of Manchester, Oxford Road, M139PL, United Kingdom

** Corresponding author: Tel. +441612754296, Fax., E-mail: pavle.mocilac@manchester.ac.uk.*

[†]Authors contributed equally.

Table of contents/abstract graphic



ABSTRACT: A new, regioselective synthesis of V-shaped 2,9-bis(6-(4-halophenyl)-1,2,4-triazin-3-yl)-1,10-phenanthrolines (4XPhBTPhen) ligands was developed, creating access to a simple and reliable synthesis of precursors for future supramolecular actinide complexing systems. Described is a reactant-directed regioselective synthetic method, which was found to be high yielding, reliable, and yields exclusively 6,6'-phenyl BTPhen derivatives (including 4-chloro and 4-bromo) in five simple steps. Molecular and crystal structures of PhBTP and PhBTPhen products are fully determined and both were found to be in space group *C2/c*. Additionally, molecular and crystal structures of *Z* and *E* isomers of 2-hydrazono-2-phenylacetaldehyde oxime, a reagent in the synthetic route, reveal existence of strong intramolecular N—H···O hydrogen bonding in the *Z* isomer explaining its lower solubility in water.

INTRODUCTION

In the last two decades bistriazinyl-bipyridines (BTBP, Figure 1a)[1] and bistriazinyl-phenantrolines (BTPhen, Figure 1b)[2] have been developed as highly selective extractands for separation of actinides (An) and lanthanides (Ln) as part of the partition and transmutation strategy (P&T) for nuclear waste management.[3-5] Tetradentate BTBP ligands (Figure 1a) were proven to be superior to previously developed tridentate bistriaziyl-piridines (BTP)[6] especially in terms of stability to hydrolysis and radiolysis.[7-9] The $CyMe_4$-BTBP[10] ligand is now considered to be a standard reference ligand for development of An/Ln nuclear separation processes. The advent of BTPhen ligands[2,11-13] improved the kinetics of complexation and $CyMe_4$-BTPhen[2,11,12,14,15] is today a promising alternative to $CyMe_4$-BTBP.

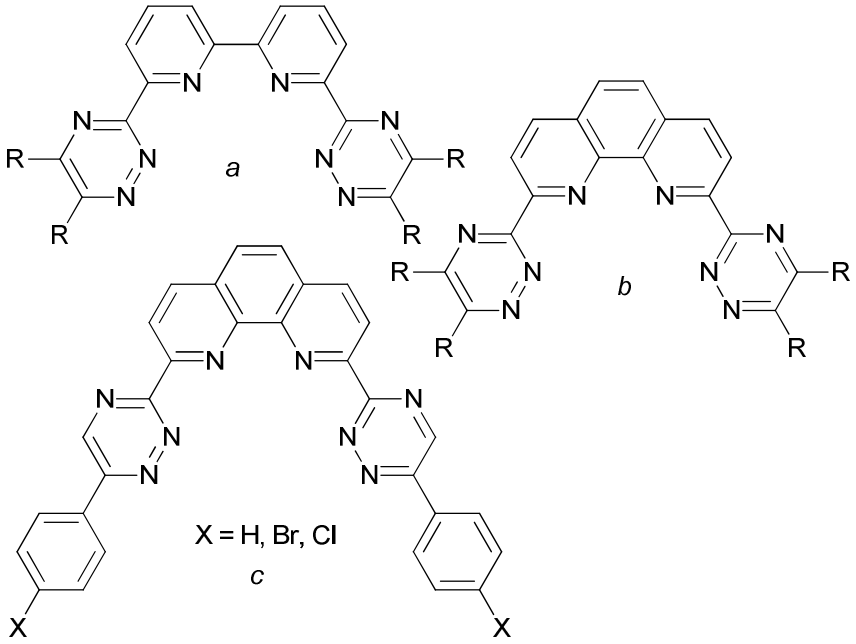


Figure 1: a) BTBP b) BTPhen c) PhBTPhen (X = H) and 4XPhBTPhen (X = Br, Cl)

BTPhen ligands complex An(III)/Ln(III) cations in a 2:1 ratio; two BTPhen molecules donate eight nitrogen atoms to bind one cation. Ideally the two ligand molecules would be

oriented relative to each other by a 90° angle.[11] In reality, however, the angle formed between the two ligands is less than 90° as a water or nitrate molecule is also found in the central metal ion primary coordination sphere, yielding a metal cation coordination number of 9 or 10.[2,11]

One can conceive a hypothetical ligand incorporating two BTPhen moieties, held in proximity to each other at a 90° orientation and at approximately the ideal distance for complexation. Such a ligand should have the ability to complex An(III)/Ln(III) cations in a 1:1 ratio and may be thermodynamically superior[16] to current ligands forming 2:1 or 3:1 complexes. Ideally such a ligand should be flexible enough that complexes can form quickly and easily and be able to sterically accommodate additional nitrate or water molecules, as well as be easily stripped in a separation process application. A straightforward candidate system comprises two mechanically interlocked macrocycles, each containing a BTPhen moiety, forming a supramolecular catenane.[17] The catenanes are well known and widely investigated molecules in the area of supramolecular and macrocyclic chemistry and have been shown to have unique complexing behaviour.[18] We are developing BTPhen based catenanes, designed to have high affinity for f-block elements. Some current trends in supramolecular chemistry are already directed towards utilisation of f-elements.[19]

The first step towards a BTPhen-based catenane is formation of appropriate precursor molecules. Phenanthroline based catenanes[18] are topologically similar to BTPhen moieties, therefore an extended V-shaped BTPhen molecule capable of undergoing macrocyclisation reaction to the desired catenane is a promising precursor. We have targeted synthesizing such a V-shaped BTPhen precursor, where additional 4-bromophenyl rings are added onto the BTPhen 1,2,4-triazine rings at their 6 and 6' positions (2,9-bis(6-(4-bromophenyl)-1,2,4-triazin-3-yl)-

1,10-phenanthroline, **4BrPhBTPhen**, Figure 1c). A chloro version (**4ClPhBTPhen** Figure 1c) with chlorine atoms instead of bromine is also interesting for macrocyclisation.

Current synthetic strategy for BTPhens is condensation of phenanthroline biscarbohydrozonamide with symmetric alkyl or phenyl diketones to yield various disubstituted BTPhens.[2,11-15,20] An analogous synthetic pathway to 4BrPhBTPhen would be reaction of phenanthroline biscarbohydrozonamide with an asymmetric dione, such as 2-(4-bromophenyl)-glyoxal. However, due to the better reactivity of aldehyde with the hydrazine moiety formation of the undesired product, 5-substituted 1,2,4-triazine ring, will be favoured. Since two triazine rings have to be formed the expected yield of the 6,6'-substituted V-shaped BTPhen would be unacceptably low. Therefore, a different synthetic strategy is needed to synthesise 4XPhBTPhen ligands (X = Br, Cl); herein we report successful development of a new regiospecific synthetic route for their synthesis.

Possible new strategies

Several strategies for regioselective synthesis of 6,6'-substituted BTPhens were considered based on literature sources[21-25] describing formation of 3,6-disubstituted 1,2,4-triazine rings. The first (route A) involves deprotonation of 1,10-phenanthroline-2,9-dicarboxamide with sodium *tert*-butoxide, condensation of the deprotonated dicarboxamide with 2-(4-bromophenyl)-glyoxal to form (N^2Z,N^9Z)-N^2,N^9-bis(2-(4-bromophenyl)-2-oxoethylidene)-1,10-phenanthroline-2,9-dicarboxamide and final formation of the triazine rings by treating the product with hydrazine.[21] The second strategy (route B) starts with conversion of 1,10-phenanthroline-2,9-dicarbaldehyde into 2,9-bis((*E*)-hydrazonomethyl)-1,10-phenanthroline and subsequent condensation of the

obtained bishydrazone with (*Z*)-2-(4-bromophenyl)-2-oxoacetaldehyde oxime into the desired 4BrPhBTPhen ligand.[22] The third strategy (route C) is a modification of route B: instead of reacting 1,10-phenanthroline-2,9-dicarbaldehyde with hydrazine, (*Z*)-2-(4-bromophenyl)-2-oxoacetaldehyde oxime is allowed to react with hydrazine to form (*1E,2Z*)-2-(4-bromophenyl)-2-hydrazonoacetaldehyde oxime; subsequent condensation with 1,10-phenanthroline-2,9-dicarbaldehyde yields the desired 4BrPhBTPhen ligand product.[23-25]

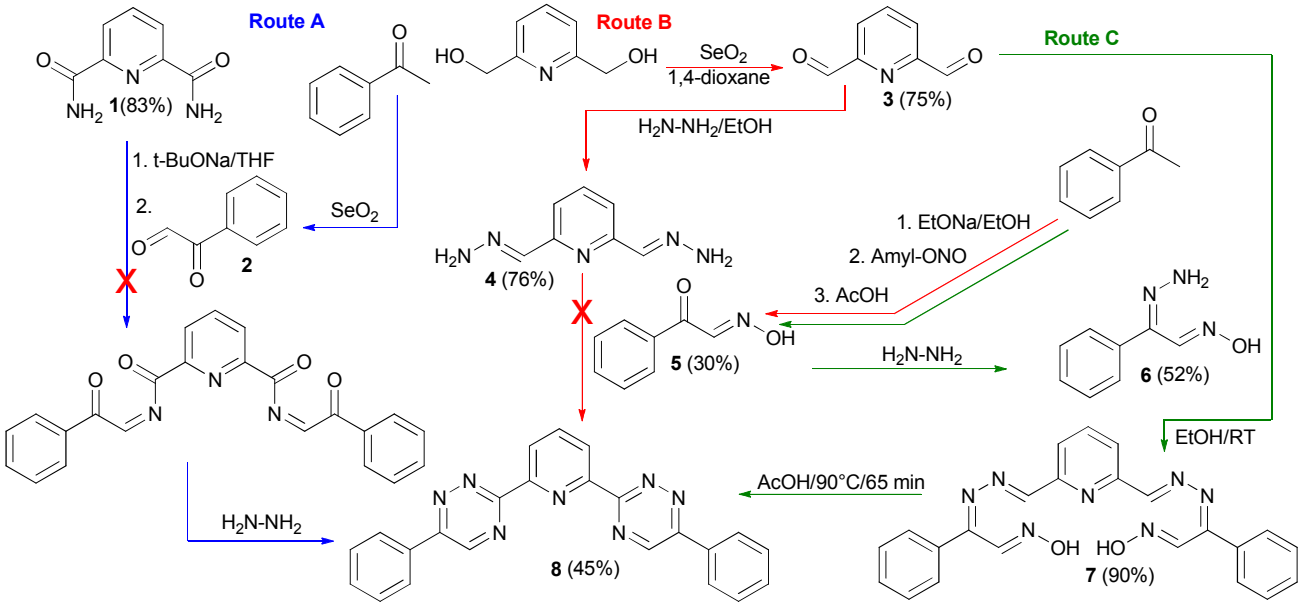
RESULTS AND DISCUSION

Investigation of new synthetic strategies: model reactions

Since the key reagent, 2,9-dimethyl-1,10-phenanthroline or neocuproine is commercially available but relatively expensive all strategies were initially tested using pyridine (Scheme 1) instead of phenanthroline derivatives, yielding the corresponding 2,6-bis(6-phenyl-1,2,4-triazin-3-yl)pyridine (6,6'-PhBTP) derivative. In addition, the non-substituted version of the precursor was first synthesised giving the phenyl derivatives.

Route A: Synthesis of the starting reagents for route A in Scheme 1, pyridine-2,6-dicarboxamide (**1**) and 2-phenylglyoxal (**2**), are described experimental section. Compound **1** was obtained from a cascade of simple reactions[26] as a pure product in excellent yield (83%). Compound **2** was synthesised[27] successfully but was found to be in the form of a hydrate, which could not be fully dried. Further challenges for this synthetic route A were the insolubility of compound **1** in most organic solvents (only sparingly soluble in THF) and failed attempts of deprotonation with sodium *tert*-butoxide. As route

A was also not expected to be regioselective (some 5,5' and 5,6 products were expected), this route A was abandoned.



Scheme 1: Possible synthetic strategies to obtain 2,6-bis(6-phenyl-1,2,4-triazin-3-yl)pyridine (compound **8**, 6,6'-PhBTP),

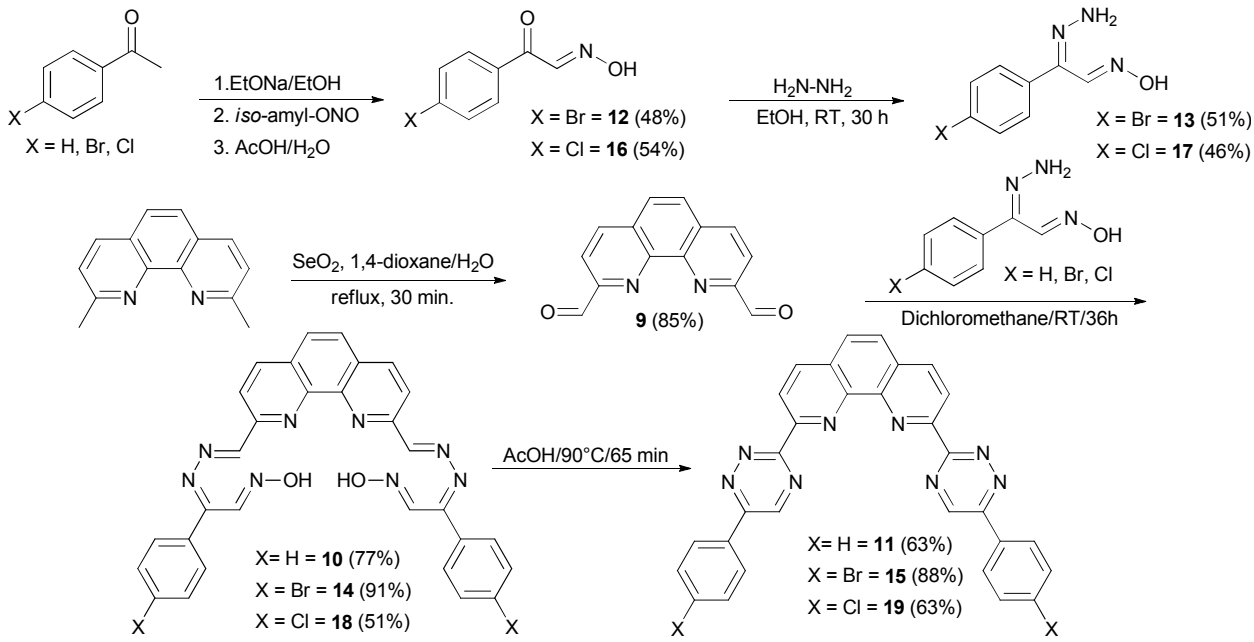
Route B Oxidation[28] of pyridine-2,6-diyldimethanol with selenium dioxide gave pyridine-2,6-dicarbaldehyde (**3**) in 75% yield. Compound **3** was reacted[29] with hydrazine monohydrate in ethanol at room temperature overnight and gave 2,6-bis((*E*)-hydrazonomethyl)pyridine (**4**) in good yield (76%). (*E*)-2-oxo-2-phenylacetaldehyde oxime or *iso*-nitrosoacetophenone (**5**) was made[23-25,30,31] by deprotonation of acetophenone with sodium ethoxide, subsequent reaction with *iso*-penthyl nitrite to yield sodium oximate and neutralisation by addition of acetic acid; **5** was obtained in a yield of only 30%. Condensation of compounds **4** and **5** in ethanol, as described in the literature[22] was not possible since compound **4** is insoluble in ethanol and other solvents, such as THF, 1,4-dioxane and acetic acid. Attempts to drive the reaction at higher temperature

under reflux did not work. Route B was hence necessarily modified to obtain the V-precursor products.

Route C Modification of route B using the synthetic procedures published by Kozhevnikov[23] et al. was chosen for the successful synthesis of 6,6'-phenyl derivatives of the triazine rings. Treating compound **5**[23,24] with hydrazine monohydrate in ethanol, addition of water and cooling of the reaction mixture prompted precipitation of (1*E*,2*Z*)-2-hydrazono-2-phenylacetaldehyde oxime or *iso*-nitrosoacetophenone hydrazine (**6**) with 52% yield. Note that the desired ***Z*-6** isomer is obtained, as it is significantly less soluble in water than its ***E*-6** isomer, (1*E*,2*E*)-2-hydrazono-2-phenylacetaldehyde oxime. Reaction of ***Z*-6** with dicarbaldehyde **3** in ethanol resulted in formation of a yellow, insoluble precipitate (90% yield), the intermediate 2,6-bis(3-phenyl-1-hydroxy-1,4,5-triazahexatriene-6-yl)pyridine (**7**), which was then successfully aromatised by heating in acetic acid at 90°C for 65 minutes to give 2,6-bis(6-phenyl-1,2,4-triazin-3-yl)pyridine or PhBTP (**8**) in acceptable yield (45%). Purification was accomplished by recrystallization from DMSO.

All characterisation data (NMR, MS and elemental analysis) confirmed the identity and demonstrated the purity of the product **8**. Mass spectroscopy (MALDI) gave a clean spectrum suggesting absence of eventual *N*-oxide by-product.

The success of route C for the BTP derivative led us to use it for synthesis of 6,6-phenyl-bistriazinyl-phenanthrolines.



Scheme 2: Syntheses of PhBTPhen (**11**), 4BrPhBTPhen (**15**) and 4ClPhBTPhen (**19**)

Synthesis of 2,9-bis(6-phenyl-1,2,4-triazin-3-yl)-1,10-phenanthroline (PhBTPhen, 11)

The synthesis of PhBTPhen (**11**, Scheme 2) was performed in an analogous manner but beginning with oxidation[12] of 2,9-dimethyl-1,10-phenanthroline (neocuproine) with selenium dioxide instead of pyridine-2,6-diyldimethanol. Pure product, 1,10-phenanthroline-2,9-dicarbaldehyde (**9**), was obtained after column chromatography in good yield (85%). Dicarbaldehyde **9** was then reacted with ***Z*-6** in dichloromethane (instead of ethanol, due to better solubility of **9**) to form the intermediate 2,6-bis(3-phenyl-1-hydroxy-1,4,5-triazahexatriene-6-yl)-1,10-phenanthroline (**10**) as yellow, insoluble precipitate in good yield (77%). Intermediate **10** was then aromatized by heating it in acetic acid, giving 2,9-bis(6-phenyl-1,2,4-triazin-3-yl)-1,10-phenanthroline (**11**) in 63% yield as a yellow powder.

Characterisation data (^{1}H-NMR, ^{13}C-NMR, IR, MS-MALDI and elemental analysis) gave sufficient proof that isolated material is compound **11**. Both ^{1}H- and ^{13}C NMR

spectra show no significant presence of impurities or by-products. A sample suitable for elemental analysis was obtained by recrystallization from DMSO, the result suggests the presence of water and DMSO; we assume water and solvent are bound in the inner, hydrogen-accepting (complexation) cleft of the compound.

Synthesis of 2,9-bis(6-(4-halophenyl)-1,2,4-triazin-3-yl)-1,10-phenanthrolines (4XPhBTPhen, X = Br, Cl)

Synthesis of 4XPhBTPhen where X = Br, Cl (**15, 19**) was performed in a similar manner as for **11**, following the synthetic route C (Scheme 2). However, the halo derivative of **5**, (*E*)-2-(4-bromophenyl)-2-oxoacetaldehyde oxime (**12**) and (*E*)-2-(4-chlorophenyl)-2-oxoacetaldehyde oxime (**16**) were used. Compounds **12** and **16** were synthesised from commercially available 4-bromoacetophenone and 4-chloroacetophenone using the same procedure as for compound **5**, but with additional purification by column chromatography to obtain pure **12** in 48% and **16** in 54% yield. Compounds **12** and **16** were then converted into (1*E*,2*Z*)-2-(4-bromophenyl)-2-hydrazonoacetaldehyde oxime (**13**) and (1*E*,2*Z*)-2-(4-chlorophenyl)-2-hydrazonoacetaldehyde oxime (**17**) in 51% and 46% yield in a manner analogous to the synthesis of compound **6**, the only difference being that separation of the ***Z*-13** and ***Z*-17** isomers by precipitation was achieved just by adding water, without additional cooling. This was because the lower solubility of halogenated derivatives, compared to non-halogenated ***Z*-6** and ***E*-6,** gives a mixture of isomers during cooled precipitation; therefore, cooling was avoided. Obtained compounds ***Z*-13** and ***Z*-17** were then reacted with 1,10-phenanthroline-2,9-dicarbaldehyde (**9**) in the same manner as described for the product **11** *via* intermediates (**14**) and (**18**) respectively, obtained in 91%

and 51% yield, to finally give 2,9-bis(6-(4-bromophenyl)-1,2,4-triazin-3-yl)-1,10-phenanthroline (**15**) and 2,9-bis(6-(4-chlorophenyl)-1,2,4-triazin-3-yl)-1,10-phenanthroline (**19**) as a light orange to yellow powder in 88% (for **15**) and 63% (for **19**) yield. Samples suitable for elemental analysis were obtained by recrystallization from pyridine.

As with the other syntheses, characterisation of the products (^{1}H-NMR, ^{13}C-NMR, IR, MS-MALDI and elemental analysis,) confirmed their identities and showed that the products **15** and **19** contain only 6,6-substituted triazine in BTPhen without significant quantities of by-products or impurities. Again, both IR and elemental analysis suggest the presence of water in the solid state that cannot be removed by drying in vacuum.

General characteristic of the compounds 8, 11, 15 and 19

All obtained ligands are light yellow to orange microcrystalline powders with melting points above 300°C, that are insoluble in water, as well as in most organic solvents including hydrocarbons, alcohols, acetone, chlorinated hydrocarbons, acetonitrile, ethyl acetate, etheric solvent such as THF, 1,4-dioxane and diglyme. Solubility in DMF, DMSO and pyridine is found to be limited at room temperature but improves considerably when heated. Compound **11** was the most soluble – dissolves (5 mg/ml) in warm DMF at 62°C. Compounds **15** (4BrPhBTPhen) and **19** (4ClPhBTPhen) were found to be soluble in hot DMF (5 mg/ml at 112°C for **15** and 98°C for **19**), DMSO (5 mg/ml at 110°C for **15** and 115°C for **19**) and in pyridine (2.5 mg/ml at 105°C for **15** and 5 mg/ml at 104°C for **19**). The compounds are fully soluble in trifluoroacetic acid. Solubility studies are summarised in Table 1 in ESI, Section 2. Elemental analysis suggests that the

compounds 11, 15 and 16 are hygroscopic, while XRD shows compound 11 with a molecule of solvent in the complexation cleft.

Molecular structures of 8 (PhBTP) and 11 (PhBTPhen)

The product **8** was found to be in *C2/c* space group with $Z = 4$ and $Z' = 0.5$. Suitable single crystals were grown by slow cooling of saturated hot solution from 120°C to room temperature over 72 hours in a NMR tube (the *hot-box* technique). All crystallographic details and data are given in ESI, Section 3.1.

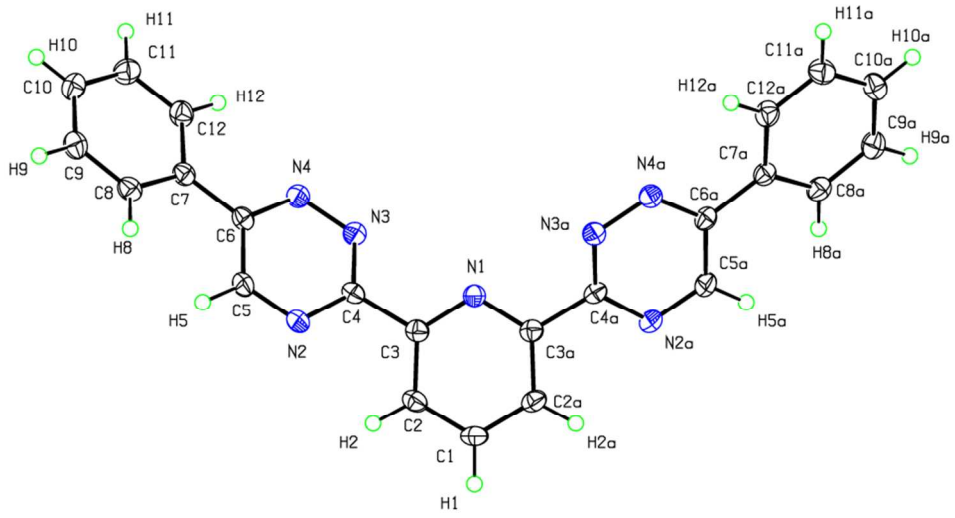


Figure 2: An ORTEP diagram of the compound **8** (PhBTP) at 50% probability presenting molecular structure.

Molecular structure of **8** (Figure 2) shows C_2 symmetry around the crystal rotation axis (symmetry code: -x, y, 1/2-z). The molecule is not planar; the triazine and phenyl rings are rotated from the pyridine ring by 33.15(5)° and 46.14(6)° respectively. Due to C_2 symmetry the triazine rings are related to each other by 49.24(5)° while the phenyl rings are related by 58.80(5)°. The angle between two branches (C10-Cg1-C10^i, i = - x, y, 1/2-

z, Cg1 = N1→C3^{i}) is 110.21°, distance between C10 and C10^{i} is 15.914 Å, while between C1 and C10 is 10.568 Å. In total, the solid state molecule of **8** resembles a V-shaped propeller. The main intermolecular interaction in crystal structure of the compound **8** is shown in Figure 3, while a detailed description of intermolecular interactions is given in ESI, Section 3.1.

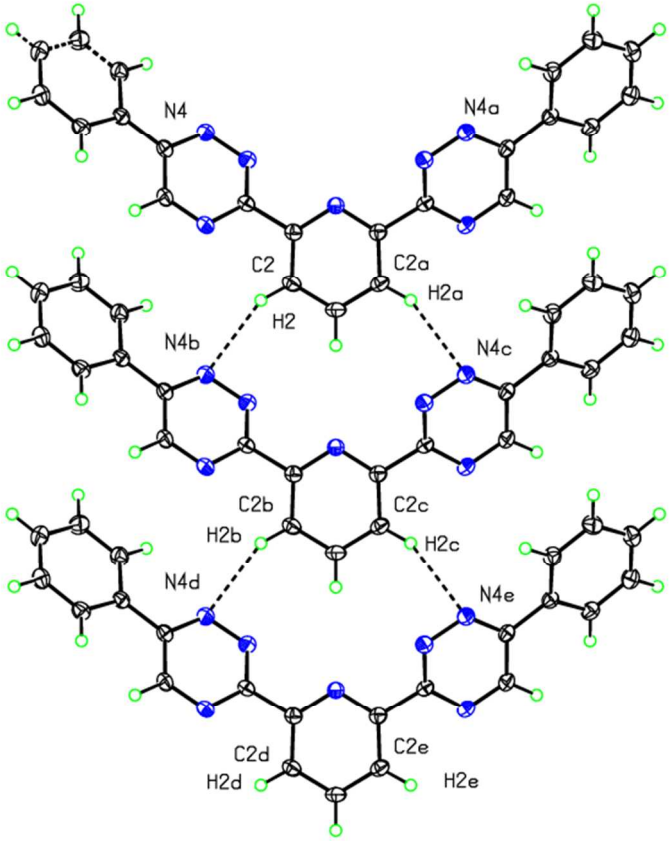


Figure 3: ORTEP diagram of the intermolecular interaction in solid compound **8** (PhBTP) at 50% probability: two strong C2—H2···N4^{ii} (C2···N4^{ii} = 3.454(2) Å, *ii* = x,-1+y,z) interactions are indicated.

Product **11** was found to be in *C2/c* space group with *Z* = 8 and *Z'* = 1, with a disordered solvate of dimethylformamide in its cleft. The single crystals were also grown in DMF using a "hot-box" technique giving yellow, long plate-like crystals. The selected single crystal was found to be twined, with major component of 0.827(3) and minor of

0.173(3). Twining was resolved by using TwinRotMat function included in the PLATON software package.[32] All crystallographic details and data are given in ESI, Section 3.2.

The molecular structure of **11** (Figure 4a) is also non-planar. In the phenanthroline core rings A (N1-C1-C9-C10-C11-C12) and B (N2-C3-C4-C5-C6-C2) are twisted by angle of 12.67(0.25)°. The triazine ring T1 (C13-N4-N5-C14-C15-N3) is related to the ring A by 24.44(13)°, while the phenyl ring P1 (C16→C21) is more co-planar with the ring A (4.97(27)°). In the opposite branch, the ring B and the triazine ring T2 (C22-N7-N8-C24-C23-N6) are relatively co-planar (9.15(0.32)°), whereas the phenyl ring P2 (C25→C30) is rotated against the ring B by 22.22(27)°. The distances C8-C18 and C7-C28 are 12.534 Å and 12.581 Å, respectively, while the distance C19-C28 is 14.665 Å. Generally the two branches of the molecule form an angle of 64.82(12)° (the angle between averaged hypothetical lines C8-C9-C12-C13-C14-C16-C19 and C7-C6-C3-C22-C24-C25-C28) and are distorted from planarity by 15.34(13)° (angle between two averaged hypothetical planes: the ring A and the phenyl ring P1 versus the ring B and the triazine ring T2). In total, the molecule has a slight helical form (Figure 4b).

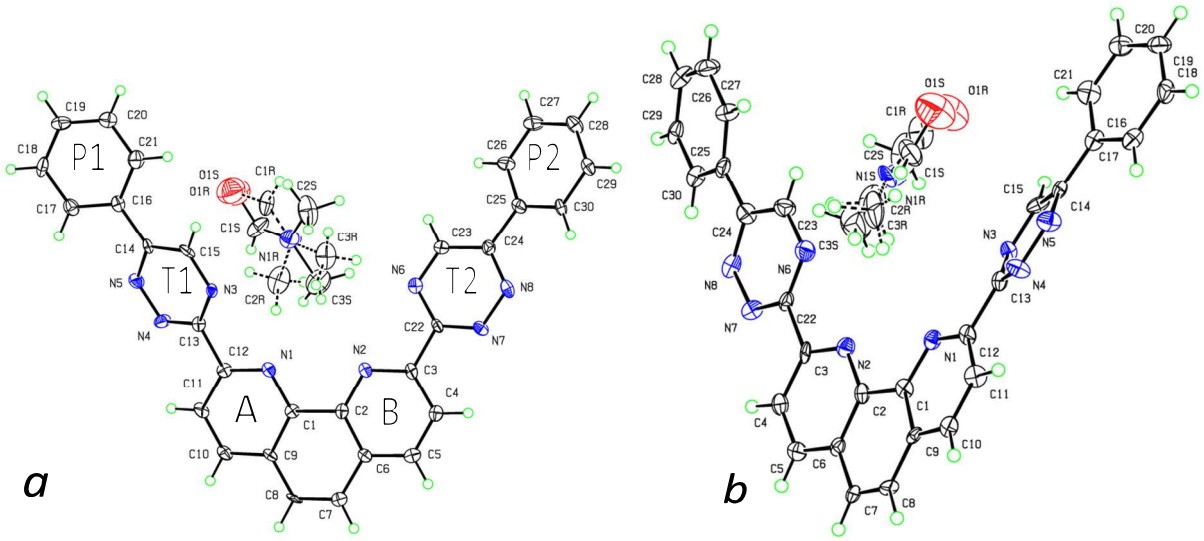


Figure 4: ORTEP diagrams of the compound **11** (PhBTPhen) at 50% probability presenting molecular structure; a) phenanthroline rings A and B, T1 (triazine ring 1), T2 (triazine ring 2), P1 (phenyl ring 1), P2 (phenyl ring 2).

The dimethylformamide molecule is found to be disordered with a major orientation "S" (0.598(12) occupancy) and a minor orientation "R" rotated 180°C about a hypothetical axis along O1S and C1S atoms (nearly parallel with the *c*-axis). The disorder presumably arises from the clash between the atom N6 of the PhBTPhen molecule and the methyl atom C3R. The solvent molecule resides in the cleft of the PhBTPhen molecule and is bound to it *via* C3S—H3SC···N1 (C3S···N1 = 3.344(17) Å) interaction. Oxygen atoms of both "S" and "R" orientations strongly interact with the neighbouring PhBTPhen molecule and play important role in crystal structure formation by linking two neighbouring PhBTPhen molecules (Figure 5). Detailed description of intermolecular interaction is given in ESI, Section 3.2.

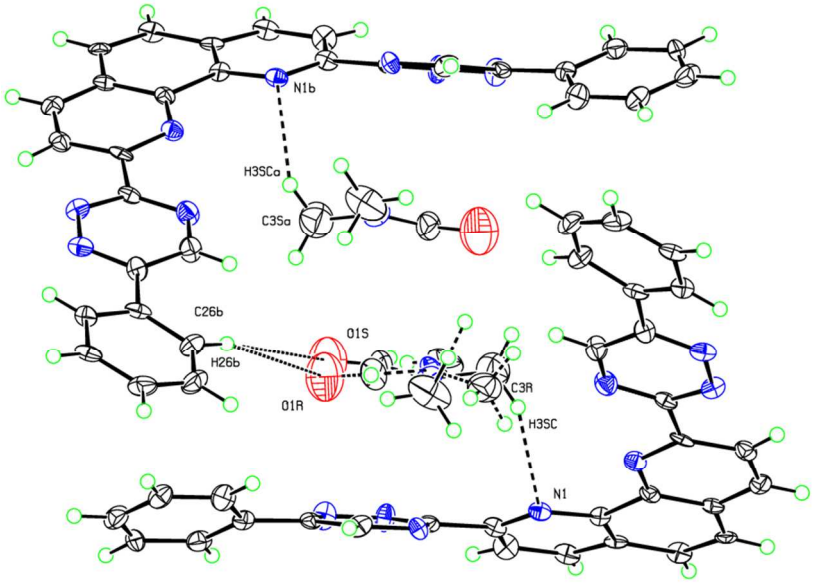


Figure 5: Solvent molecules form bridges across neighbouring PhBTPhen molecules and across the two arms of a V-shaped molecule *via* C—H···O/N interactions

Molecular and crystal structures of 2-hydrazono-2-phenylacetaldehyde oxime (*Z*-6 and *E*-6) isomers

As described, the isolated crystalline product **6** was the ***Z*-6** isomer. The ***E*-6** isomer was formed during the reaction, as evidenced by thin layer chromatography of the reaction solution. The ***E*-6** isomer was purified by column chromatography and the structures of both isomers determined using single crystal XRD. Lower solubility of the ***Z*-6** isomer in water compared to the ***E*-6** isomer is well known[23,24] but our intention was to understand the cause of this phenomenon from their structures.

The ***Z*-6** isomer aggregates in monoclinic system, space group $P2_1/n$ (No.14). Bulk polycrystalline material readily crystallises from any solvent, however a single crystal grown from $CDCl_3$ was used for structure determination. Detailed crystallographic parameters are listed in the ESI, Section 3.3.

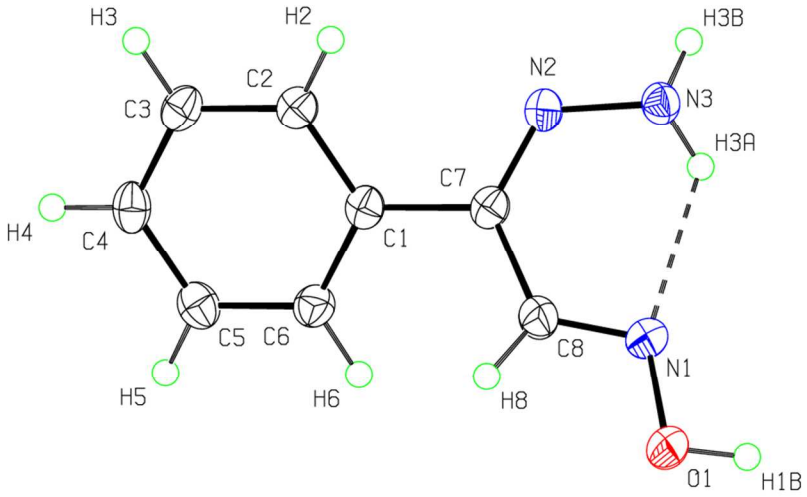


Figure 6: An ORTEP diagram of ***Z*-6** at 50% probability presenting molecular structure and the internal N3—H3A···N1 hydrogen bonding.

The most important feature of the ***Z*-6** molecular structure (Figure 6) is the N3—H3A···N1 intramolecular hydrogen bond (N3···N1) = 2.7388(14) Å. This hydrogen bond is a direct consequence of the *Z*-configuration, where H3 atoms are in proximity to the N1 atom; this creates a 6-member ring (N1—C8—C7—N2—N3···H3), forming a stable moiety. Conjugation of the C8=N1 and C7=N2 imine bonds additionally stabilises this ring. The 6-member ring is nearly planar apart from the N1 atom that deviates from the N3—N2—C7—C8 plane by approx. 15°. The phenyl ring is rotated from the N3—N2—C7—C8 plane by approx. 35°. The N3—H3A···N1 internal hydrogen bonding and consequent stable ring formation is likely the main reason why ***Z*-6** is more lipophilic then ***E*-6** and therefore less soluble in water. Molecular packing diagram in the ***Z*-6** solid is shown in Figure 7. Detailed description of all relevant intermolecular interactions in crystal structure is given in ESI, Section 3.3.

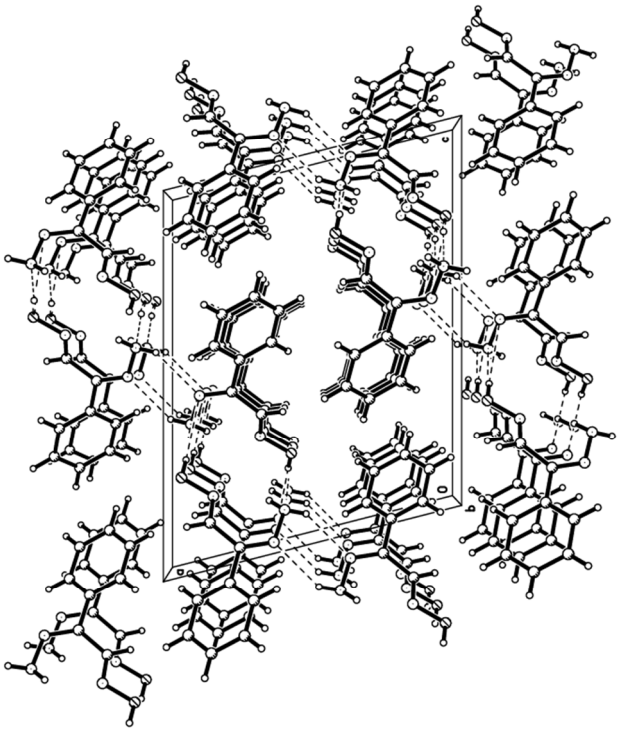


Figure 7: Molecular packing diagram in the ***Z*-6** crystal, view along the *b*-axis.

A single crystal of the ***E*-6** isomer was grown using the slow diffusion method (diffusion of diethyl ether into solution of ***E*-6** in dichloromethane). It crystallises in a triclinic system, space group $P\bar{1}$ (No.2) having two molecules (A and B) in the asymmetric unit (Z'=2). Detailed crystallographic parameters are listed in the ESI, Section 3.4.

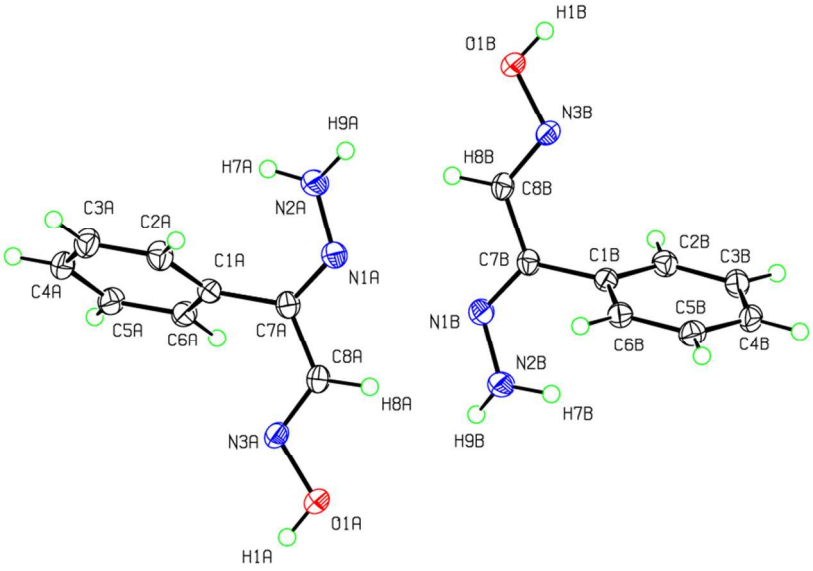


Figure 8: ORTEP diagrams of the molecules A and B of the ***E*-6** crystal structure (50% probability displacement ellipsoids).

Two molecules, A and B (Figure 8) have generally similar geometry, their main difference being the degree of rotation of the phenyl ring relative to the near planar backbones formed by N2—N1—C7—C8—N3—O1 atoms (the RMS deviation of fitted atoms for hypothetical mean planes are 0.0378 for the molecule A and 0.0317 for the molecule B). The C8—C7 bonds are 1.4592(17) Å and 1.4556(17) Å, which indicates presence of N1=C7—C8=N3 conjugation. Two mean planes of the A and B backbones are nearly parallel; they form an angle of 4.36(10)°. In the molecule A the phenyl ring

(C1A→C6A) is rotated against the mean plane N2A—N1A—C7A—C8A—N3A—O1A by average of 57.02(7)°, while the similar relation in the molecule B is 70.78(4)°. Therefore, conjugation with adjacent N1=C7—C8=N3 is highly unlikely. Detailed description of all relevant intermolecular interactions in ***E*-6** crystal structure is given in ESI, Section 3.4.

Crystallographic investigation of ***Z*-6** and ***E*-6** isomers showed that crystal packing of both isomers (see ESI, Sections 3.3 and 3.4) is based on similar hydrogen bonding and is even stronger in *E* isomer than in *Z* isomer. The similar melting points observed for ***Z*-6** (102-104°C) and ***E*-6** (106-108°C) also suggest that lattice energies of both isomers are similar. We conclude that intermolecular hydrogen bonding in ***Z*-6** is the cause for higher hydrophobicity of the molecule (less strong dipole) and consequent lower water solubility.

CONCLUSIONS

The extended V-shaped BTPhen based ligands, PhBTPhen and 4XPhBTPhen (X = Br, Cl), were successfully synthesised and a new reactant-driven regioselective method for its synthesis has been developed. The five-step synthetic method proved to be simple, robust, reproducible and reliable, giving only 6,6'-phenyl substituted BTPhens in good yield. The first two steps, preparation of reactants (1*E*,2*Z*)-2-(phenyl)-2-hydrazonoacetaldehyde oximes or hydrazones of *iso*-nitrosoacetophenones, are found to be lower yielding (approx. 50% per step, total yield of 25%). Their advantage is they start with inexpensive, commercially readily available acetophenones and reagents. The final two steps, formation of 1,2,4-triazine rings, were found to be very high yielding (up to 91 and 88%,

respectively) and avoid chromatographic purifications, nevertheless delivering a product with high purity.

Although this method for regioselective formation of substituted 1,2,4-triazine rings has been used[23-25] for preparation of 6,6-phenyl BTP based derivatives, this is the first time it was successfully applied to give phenanthroline (BTPhen) based compounds. The mechanism of the 1,2,4-triazine ring cyclisation was explained in original work of Kozhevnikov[24] et al. and considered an E1cb elimination of water.

The V-shaped BTPhen derivatives prepared present an important entry point into of the design of supramolecular ligands and systems based on BTPhen moiety as complexation centre for the selective binding of minor actinides. Such ligands can be used for sequestration of actinides for integration into selective sensors, for example.

Molecular and crystal analyses of PhBTP and PhBTPhen have confirmed the structure and gave insight into the molecular geometry of these molecules and their intermolecular interactions in solid state.

In addition, our investigation reveals molecular and crystal structures of *Z* and *E* isomers of hydrazones of *iso*-nitrosoacetophenones and helps to explain their simple separation by change of solvent polarity utilized in the synthetic route to the V-shaped BTPhen derivatives. The existence of the N3—H3A···N1 internal hydrogen bond in the *Z* isomer makes it more lipophilic and therefore less soluble in water.

EXPERIMENTAL SECTION

General Information

Thin layer chromatography (TLC) was performed on Silica Gel 60 F_{254} precoated plates. Spots were visualized by UV light at 254 nm. Column chromatography was carried out using silica gel (60 Å 230-400 mesh particle size, 40-63 mm). Infra-red (IR) spectra were recorded on a FTIR instrument on the neat compounds using an attenuated total reflection (ATR) accessory with a diamond crystal. All wavenumbers ($\tilde{\nu}$) are quoted in cm^{-1}. ^{1}H and ^{13}C NMR spectra were referenced to external tetramethylsilane *via* the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). All chemical shifts are reported in parts per million (ppm) while coupling constants are reported in Hz. Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), br (broad), m (multiplet). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Assignments were made using 2D COSY and HSQC experiments. High-resolution mass spectra were recorded using electrospray ionization (ESI) on Agilent Technologies 1200 system with Micromass Q-TOF Micro™ detector and atmospheric-pressure chemical ionization (APCI) on Agilent Technologies 1260 system with Micromass Q-TOF Micro™ detector.

All spectra (^{1}H-NMR, ^{13}C-NMR, COSY, HSQC, IR and MS) are given in the Electronic supporting information (ESI) file.

Pyridine-2,6-dicarboxamide (1)

Pyridine-2,6-dicaboxylic acid (6.0000 g, 35.92 mmol) and 35 ml (57.4000 g, 482.47 mmol, 13.5 equiv.) of thionyl chloride were refluxed in an oil bath at 85°C overnight. Excess of thionyl chloride was distilled off to leave a dry, off white solid which was then dissolved in dry toluene. The solution was then stirred in an ice bath while ethanol (12 ml) was added over 15 minutes. The reaction mixture was then refluxed in an oil bath at 90 °C

overnight. Thin layer chromatography confirmed that the reaction had gone to completion (R_f [chloroform/ethyl acetate - 2:1] = 0.51). Product was purified by separation with sodium carbonate solution (12 g in 100 ml) and the aqueous layers were washed with diethyl ether (2×50 mL). The toluene and diethyl ether layers were combined and dried under vacuum to yield a light pink powder. To this, concentrated aqueous ammonia (60 ml) was added and the mixture stirred for 2 days. The product was filtered and dried to yield an off-white powder (4.9067 g, yield: 83%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.72 (2H, s), 8.12-8.20 (3H, m), 8.89 (2H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 124.2, 139.2, 149.1, 165.4; IR (ATR): $\tilde{\nu}$ 3395 (N-H), 3227 (N-H), 1661 (C=O), 1585 (C=C), 1568 (C=C); MS (ESI+): m/z 166.2 $[M+H]^+$ (calcd for $C_7H_7N_3O_2$, 165.15); Expected for $C_7H_7N_3O_2$: % C, 50.91; H, 4.27; N, 25.44, found: % C, 51.17; H, 4.50; N, 25.10.

2-Phenylglyoxal (2)

Acetophenone (1.10 ml, 1.1330 g, 9.43 mmol) was added to a stirred solution of selenium dioxide (1.1465 g, 10.33 mmol, 1.1 equiv.) in 1,4-dioxane/water (6.24 mL:0.84 mL) mixture, and was refluxed in an oil bath at 80°C for 48 hours. The precipitate was filtered off over Celite and the filtrate evaporated down to dryness to leave yellow oil. This was purified by column chromatography using acetate/*n*-hexane (1:3 then 1:1) as eluent. Fractions were combined and evaporated to give yellow oil; after 48 hours white crystals were formed (0.3881 g, yield: 27.05 %). ^{1}H NMR (400 MHz, $CDCl^3$): mixture of two products, δ 4.96 (3H, d, J = 10), 6.30 (3H, d, J = 10), 7.39-7.47 (14H, m), 7.55 (4H, t, J = 7.5), 7.61 (3H, t, J = 7.5), 8.05 (8H, d, J = 7.5), 8.13 (4H, d, J = 7.5), 9.60 (1H, s); MS (ESI+) m/z 135.1 $[M+H]^+$ (calcd for $C_8H_6O_2$, 134.13). Expected for $C_8H_6O_2$: % C, 63.15; H, 5.30; N, found: % C, 65.42; H, 5.16,

analysis suggests that sample is a mixture of 2-phenylglyoxal hydrate and 2-phenylglyoxal in ration 1:0.37: calcd. % C, 65.23; H, 15.12.

Pyridine-2,6-dicarbaldehyde (3)

Pyridine-2,6-dimethanol (1.9000 g, 13.70 mmol) and selenium dioxide (1.5150 g, 13.70 mmol, 1.0 equiv.) were dissolved in 1,4-dioxane (30 ml) and refluxed for 5 h. The mixture was left to cool and was filtered through a Celite pad before the solvent was evaporated. Thin layer chromatography confirmed that the reaction was completed [R*f* (hexane/ethylacetate - 3:1) = 0.286; R*f*($CHCl_3$) = 0.259]. The crude product was purified using a dry loaded silica column chromatography (eluent: hexane/ethyl acetate =3:1) to yield a pale orange, crystalline powder (1.7800 g, yield: 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (1H, t, J = 7.6), 8.17 (2H, d, J = 7.6), δ 10.16 (2H, *s*); ^{13}C-NMR (100MHz, $CDCl_3$): δ 125.5, 138.5, 153.1, 192.5; IR (ATR): $\tilde{\nu}$/cm^{-1} 3084 (C-H), 3017 (C-H), 2860 (C-H), 1715 (C=O), 1693 (C=N), 1580; MS (EI+) m/z 135.0 $[M]^+$ (calcd for $C_7H_5NO_2$, 135.05); Expected for $C_7H_5NO_2$: % C, 62.22; H, 3.73; N, 10.34, found: % C, 62.25; H, 3.55; N, 10.15.

2,6-Bis((*E*)-hydrazonomethyl)pyridine (4)

Compound **3** (1.000 g, 7.40 mmol) was dissolved in warm, anhydrous ethanol (20 mL) and the solution was added *via* a double ended needle to a solution of hydrazine monohydrate (0.75 ml, 15.54 mmol, 2.1 equiv.) in anhydrous ethanol (5 ml). The solution was left to stir for 3 h and then cooled on ice for 15 minutes. The resulting product was filtered and washed with anhydrous ethanol (7 ml) and diethyl ether (10 ml) yielding a white powder (0.9160 g, 76%). Thin layer chromatography confirmed the product was formed (eluent: chloroform/methanol/NH_4OH = 9 :

1 : 0.105). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 (4H, s), 7.49 (2H, d, J = 8.0), 7.61 (1H, t, J = 8.00), 7.67 (2H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 116.0, 136.2, 138.1, 154.7; IR (ATR): $\tilde{\nu}$ 3294 (N-H), 3127 (C-H Ar), 1637 (C=N), 1574 (C-C Ar); MS (ESI+): m/z 164.10 $[M+H]^+$ (calcd for $C_7H_9N_5$: 164.09); HRMS m/z for $[M+Na]^+$ calcd 186.0756, found 186.0752; Expected for $C_7H_9N_5$: % C, 51.52; H, 5.56; 42.92, found: % C, 51.50; H, 5.71; 42.98.

(*E*)-2-Oxo-2-phenylacetaldehyde oxime (5)

Acetophenone (2.33 ml, 2.4030 g, 20.00 mmol) was added drop wise to a solution of sodium (0.4600 g, 20.00 mmol, 1.0 equiv.) in dry ethanol (20 ml) and the mixture was left to stir for 35 minutes. The mixture was cooled to 0°C and *iso*-pentyl nitrite (3.76 ml, 3.2800 g, 0.28 mmol) was added drop wise. The mixture was stirred for 1 hour and left in the refrigerator for 72 h. Then, diethyl ether (25 ml) was added and the precipitated solid was collected by filtration and washed twice with diethyl ether (8 ml) and then dissolved in water (50 ml). Acetic acid was added until pH 3 and the precipitated oxime was collected by filtration and dried to yield a pale yellow to white crystalline product (0.8900 g, 30.0%). ^{1}H NMR (400 Hz, DMSO-d_6): δ 7.54 (2H, t, J =7.8), 7.67 (1H, t, J = 7.8), 7.98 (2H, d, J =7.8), 8.05 (1H, s), 12.70 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 128.4, 129.6, 133.2, 136.1, 147.7, 189.1; IR (ATR): $\tilde{\nu}$ 3244 (O-H), 3071 (C-H), 3009 (C-H), 2889 (C-H), 1674 (C=O), 1599(N=C), 1578(C=C); MS (ESI-): m/z 149.932 $[M-H]^-$ (calcd for $C_8H_6NO_2$, 148.04); HRMS m/z for $[M+H]^+$ calcd 150.0555, found 150.0561; Expected for $C_8H_7NO_2$ % C, 64.42; H, 4.73; N, 9.39, found: % C, 64.51; H, 4.68; N, 9.35.

(*1E,2Z*)-2-Hydrazono-2-phenylacetaldehyde oxime (*Z*-6)

Compound **5** (0.8161 g, 5.47 mmol) was dissolved in dry ethanol (15 ml) and hydrazine monohydrate (1.10 ml, 1.1352 g, 22.68 mmol, 4.00 equiv.) was added and left to stir for 28 h. The completion of the reaction and disappearance of the starting material was monitored using thin layer chromatography (ethyl acetate/hexane - 1:2). Water (35 mL) was then added and the reaction mixture placed into an ice/acetone/NaCl bath (< -10 °C) for two hours during which precipitate was formed and then filtered and dried (0.4660 g, yield: 52%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.24(1H, t, J = 7.3), 7.33 (2H, t, J = 7.3), 7.54 (2H, d, J = 7.3), 8.29 (1H, s), 8.94 (2H, s), 11.58 (1H, s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23(1H, t, J = 7.3 Hz), 7.29 (2H, t, J = 7.3 Hz), 7.45 (2H, d, J = 7.3 Hz), 7.94 (2H, br s) 8.16 (1H, s), 8.19 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 125.7, 127.7, 128.6, 133.0, 137.9, 146.8; IR (ATR): $\tilde{\nu}$ 3331 (N-H), 3230 (O-H), 3026, 2843, 273, 1447; MS (ESI+): m/z 163.2 $[M]^+$ (calcd for $C_8H_9N_3O$, 163.18); HRMS (ESI+): m/z for $[M+Na]^+$ calcd 186.0643, found 186.0650; Expected for $C_8H_9N_3O$: % C, 58.88; H, 5.56; N, 25.75, found: % C, 58.47; H, 5.56; N, 25.65.

(*1E,2E*)-2-Hydrazono-2-phenylacetaldehyde oxime (*E*-6)

The filtrate from the previous procedure was evaporated and obtained light yellow resin was purified by column chromatography on silica using firstly ethyl acetate/hexane (1:3) and then (1:2) to separate the ***Z*-6** (first fraction) and ***E*-6** isomer (second fraction). Obtained yellow compound ***E*-6** was dried and characterised. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70 (2H, br s), 7.12 (2H, dt, ^{3}J = 7, ^{4}J = 2), 7.35 (1H, tt, ^{3}J = 7, ^{4}J = 2), 7.42 (2H, tt, ^{3}J = 7, ^{4}J = 2), 7.82 (1H, s), 8.19 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.5, 129.3, 129.5, 129.8, 144.4, 151.6; IR (ATR): $\tilde{\nu}$ 3385, 3285, 3213, 3175, 3054, 2985, 2909, 1570, 1465; MS (ESI+) m/z 186.039 $[M+Na]^+$

(calcd for $C_8H_9N_3ONa$, 186.06); HRMS (ESI+) m/z for $[M+Na]^+$ calcd 186.0643, found 186.0643; Expected for $C_8H_9N_3O$: % C, 58.88; H, 5.56; N, 25.75, found: % C, 59.33; H, 5.70; N, 25.55.

2,6-Bis(6-phenyl-1,2,4-triazin-3-yl)pyridine, PhBTP (8)

Compound **3** (0.070 g, 0.52 mmol) and compound ***Z*-6** (0.1800 g, 1.10 mmol, 2.1 equiv.) were dissolved in ethanol (6 ml) and left to stir for 24 h. The formed yellow precipitate (compound **7**) was filtered, dried and weighed (0.2000 g, 90%). This was dissolved in acetic acid and left to reflux for 1 hour, then the yellow crude was collected on a fritted funnel No.4 and washed twice with water (5 ml). The crude was then recrystallized from DMSO to yield green-yellow powder (0.092 g, 45%). ^{1}H NMR (500 MHz, TFA-*d*): δ 7.73 (4H, t, *J* =6), 7.80 (2H, d, *J* = 8), 8.29 (4H, d, J = 6), 8.78 (1H, t, *J* = 6), 9.26 (2H, d, *J* = 6), 10.04 (2H, s); ^{13}C NMR (500 MHz, TFA-*d*): δ 127.7, 128.0, 129.4, 130.0, 134.7, 143.9, 145.3, 155.0, 156.6, 158.6; IR (ATR): $\tilde{\nu}$ 3079 (C-H), 3054 (C-H) 1463, 1290; MS (MALDI): m/z 390.775 $[M+H]^+$ (calcd for $C_{23}H_{16}N_7$, 390.15); HRMS (APCI+): m/z for $[M+H]^+$ calcd 390.1467, found 390.1456. Expected for $C_{23}H_{15}N_7$: % C, 70.94; H, 3.88; N, 25.18; found: % C, 69.00; H, 3.65; N, 24.36; analysis suggests $C_{23}H_{15}N_7\times(H_2O)_{0.48}$: calcd. % C, 69.39; H, 4.05; N, 24.63.

1,10-Phenanthroline-2,9-dicarbaldehyde (9)

Selenium dioxide (1.1620 g, 10.47 mmol, 2.1 equiv.) was dissolved in 1,4-dioxane (25 ml) and water (0.70 ml) and was heated to reflux. To this a solution of 2,9-dimethyl-1,10-phenanthroline (1.0350 g, 4.97 mmol) in 1,4-dioxane (20 ml) was added. The solution was heated under reflux

for 30 minutes and the filtered when hot. The formed crystals were washed with 1,4-dioxane and chloroform before the obtained suspension was evaporated giving raw yield of 1.3000 g and purified on silica (90 g) with dry loaded product (5 g silica) (eluent: DCM/MeOH = 9:1). Collected fractions were evaporated yielding a pale yellow powder (0.9981 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (2H, s), 8.38 (2H, d, *J* = 8.5), 8.50 (2H, d, *J* = 8.5), 10.55 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.6, 129.1, 131.7, 138.1, 146.0, 152.8, 193.5; IR (ATR): $\tilde{\nu}$ 3333 (HO), 3051 (C-H), 2851 (C-H), 2826 (C-H), 1700 (C=O); MS (APCI+): m/z 237.1 $[M+H]^+$ (calcd for $C_{14}H_8N_2O_2$, 236.06); Expected for $C_{14}H_8N_2O_2$: % C, 71.18; H, 3.41; N, 11.86, found: % C, 66.40; H, 3.80; N, 10.51; analysis suggests $C_{14}H_8N_2O_2\times(CH_3OH)_{0.38}\times(H_2O)_{0.68}$: calcd. % C, 66.53; H, 4.19; N, 10.79.

2,9-Bis(6-phenyl-1,2,4-triazin-3-yl)-1,10-phenanthroline (11)

Compound **9** (0.1230 g, 0.52 mmol) was dissolved in 8.0 ml of methanol/chloroform blend (5: 3) and added to compound ***Z*-6** (0.1800 mg, 1.10 mmol, 2.1 equiv.) dissolved in ethanol (2 ml). The mixture was then left to stir for 24 hours at room temperature and the formed yellow precipitate (compound **10**) was filtered and dried (0.2100 mg, yield: 76%). The yellow precipitate (0.1343 g, 0.23 mmol) was then dissolved in acetic acid (10 mL) and the solution stirred under reflux at 90 °C for 1 hour. The formed product was filtered on a fritted funnel, washed with water twice and dried to yield a yellow powder (0.0793 g, yield: 63 %). A sample for elemental analysis was prepared by recrystallization from DMSO. ^{1}H NMR (500 MHz, TFA-*d*): δ 7.79 (4H, t, *J* = 7.4), 7.84 (2H, d, *J* = 7.4), 8.32 (4H, d, *J* = 6), 8.58 (2H, s), 9.38 (2H, d, *J* =7.4), 9.52 (2H, d, *J* =7.4), 10.00 (2H, s); ^{13}C NMR (100 MHz, TFA-*d*): δ 125.5, 127.9, 128.6, 129.7, 130.0, 133.2, 134.4,

137.5, 145.0, 145.9, 154.6, 155.4, 158.6; IR (ATR): $\tilde{\nu}$ 3410 (O-H), 3039 (C-H), 1491, 1442, 1390; MS (MALDI): m/z 490.922 $[M+H]^+$ (calcd for $C_{30}H_{19}N_8$, 491.17), 512.962 $[M+Na]^+$ (calcd for $C_{30}H_{18}N_8Na$, 513.16): HRMS (APCI+): m/z for $[M+H]^+$ calcd 491.1733, found 491.1738. Expected for $C_{30}H_{18}N_8$: % C, 73.46; H, 3.70; N, 22.84, found: % C, 68.09; H, 3.92; N, 20.81; analysis suggests $C_{30}H_{18}N_8\times(C_2H_6OS)_{0.5}\times(H_2O)_{0.9}$: calcd. % C, 68.21; H, 4.22; N: 20.53.

(*E*)-2-(4-Bromophenyl)-2-oxoacetaldehyde oxime (12)

4-Bromoacetophenone (4.5800 g, 20.00 mmol) was dissolved in dry ethanol (8 ml) and added dropwise to a solution of sodium (0.4600 g, 20.00 mmol) in dry ethanol (12 mL). The mixture was left to stir at room temperature for 35 minutes then 3.76 ml (3.2800 g, 56.00 mmol, 1.4 equiv.) of *iso*-pentyl nitrate was added and left to stir for 1h then left in the fridge for 72 hours. After this diethyl ether (30 ml) was added to the deep red suspension and it was left for 30 minutes. The mixture was filtered and the precipitated solid was twice washed with diethyl ether (30 ml), dried, and then dissolved in water (70-80 ml). Undissolved red impurities were filtered off and acetic acid was added till pH 3. The formed suspension was filtered, then obtained yellow paste was re-dissolved in diethyl ether (100 ml), excess of water was removed with a Pasteur pipette and the solution was dried by the addition of anhydrous $MgSO_4$ and filtered. The diethyl ether was then removed by rota-evaporation and the product was then left to dry for 24 hours in a vacuum chamber yielding a yellow powder (2.9700 g, 58%). Since thin layer chromatography was found raw product not to be pure it was purified by column chromatography on silica (100 g) (eluent: *n*-hexane/ethyl acetate = 3:1 then 2:1). The final yield of the pure product was 2.4500 g (48%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (2H, dt, ^3J = 9,

^{4}J = 2), 7.91 (2H, dt, ^{3}J = 9, ^{4}J = 2), 8.00 (1H, s), 12.76 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 127.8, 131.9, 132.1, 135.5, 148.2, 188.6; IR (ATR): $\tilde{\nu}$ 3213 (O-H), 3093 (C-H), 1672 (C=O), 1583, 1417, 985 (N-O); MS (ESI-): m/z 225.884 $[M]^-$ (calcd for $C_8H_5NO_2Br$, 225.95); HRMS (ESI+) m/z for $[M+Na]^+$ calcd 249.9480, found 249.9477. Expected for $C_8H_6NO_2Br$: % C, 42.14; H, 2.65; N, 6.14; Br, 35.04, found: % C, 42.39; H, 2.73; N, 6.08; Br, 35.10.

(*1E,2Z*)-2-(4-Bromophenyl)-2-hydrazonoacetaldehyde oxime (13)

Compound **12** (2.2585 g, 9.90 mmol) was dissolved in dry ethanol (50 ml) in a 250 ml round-bottom flask and 2.4 ml (2.4900 g, 49.50 mmol, 5.0 equiv.) of hydrazine monohydrate was added. The reaction was then left to stir for 24 hours and completion of the reaction was monitored using thin layer chromatography (*n*-hexane/ethyl acetate = 2:1). Water (115 ml) was then added to crystallise out the product, which was then filtered and dried. This yielded a white crystalline solid (1.2218 g, yield: 51 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (2H, dt, ^{3}J = 4, ^{4}J = 2), 7.48 (2H, dt, ^{3}J = 4, ^{4}J = 2), 7.75 (1H, s), 8.08 (2H, s), 8.22 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.6, 127.1, 131.2, 131.6, 136.9, 146.3; IR (ATR): $\tilde{\nu}$ 3275 (O-H), 3128 (N-H), 2854, 1589, 1468; MS (ESI+) m/z 241.959 $[M+H]^+$ (calcd for $C_8H_9N_3OBr$, 241.99); HRMS (ESI+) m/z for $[M+H]^+$ calcd 241.9929, found 241.9939; Expected for $C_8H_8N_3OBr$: % C, 39.69; H, 3.33; N, 17.36; Br, 33.01, found: % C, 39.69; H, 3.12; N, 17.14; Br, 33.88.

2,9-Bis(6-(4-bromophenyl)-1,2,4-triazin-3-yl)-1,10-phenanthroline (15)

Compound **9** (0.6310 g, 2.67 mmol) was dissolved in dichloromethane (31 ml) in a 100 ml round-bottom flask. Compound **12** (1.3570 g, 5.60 mmol, 2.1 equiv.) was dissolved in dichloromethane (55 ml) and the solution was added into the flask with compound **9** v*ia* double-ended needle. The mixture was left to stir at room temperature for 27 hours. After this time the formed yellow precipitate (compound **14**) was filtered and dried (1.6400 g, yield: 90%) before it was crushed into powder and suspended in acetic acid (50 ml). The suspension was placed onto an oil bath at 65°C where the temperature was then raised to 90°C. It was left to stir at 90°C for 65 minutes, and then it was cooled, filtered on a fritted funnel No.5, rinsed once with acetic acid (5 mL), and several times water (10 ml) until pH of the filtrate was neutral, dried under vacuum for 24 hours giving pale orange powder (1.3800 g, yield: 88%). A sample for elemental analysis was obtained by recrystallization from pyridine. ^{1}H NMR (500 MHz, TFA-*d*) δ 7.97 (4H, d, *J* = 7), 8.23 (4H, d, *J* = 7), 8.61 (2H, s), 9.41 (2H, d, *J* = 8), 9.54 (2H, d, *J* =8), 9.98 (2H, s); ^{13}C NMR (100 MHz, TFA-*d*) δ 125.6, 127.8, 129.0, 129.8, 130.2, 133.2, 133.5, 137.6, 145.0, 146.0, 153.9, 155.5, 157.9. IR (ATR): $\tilde{\nu}$ 3418 (O-H_{water}), 3093 (C-H), 3051 (C-H), 1589, 1391, 613 (C-Br); MS (MALDI) m/z 670.959 $[M+Na]^+$ (calcd for $C_{30}H_{16}Br_2N_8Na$, 670.97), HRMS (APCI+) m/z for $[M+H]^+$ calcd 648.9920, found 648.9994; Expected for $C_{30}H_{16}Br_2N_8$: % C, 55.58; H, 2.49; ; N, 17.28, found: % C, 54.79; H, 2.34; ; N, 16.81; analysis suggests $C_{30}H_{16}Br_2N_8\times(H_2O)_{0.5}$: calcd. % C, 54.81; H, 2.61; N, 17.05.

(*E*)-2-(4-Chlorophenyl)-2-oxoacetaldehyde oxime (16)

4-Chloroacetophenone (2.6 ml, 3.0920 g, 20.00 mmol) was added drop-wise to a stirred solution of sodium (0.4600 g, 20.00 mmol) in dry ethanol (20 ml) under nitrogen and the reaction mixture was stirred for 35 minutes at room temperature. *Iso*-pentyl nitrite (3.8 ml, 3.3140 g, 28.28 mmol,

1.4 equiv.) was added drop-wise and the solution stirred for a further 1 hour before leaving in a refrigerator for 72 hours to precipitate. The precipitate was separated by centrifugation with washes of diethyl ether (3×30 ml), dissolved in water (75 mL) and any insoluble impurities filtered off. Acetic acid was then added until pH 3-4 was achieved to yield a yellow suspension. This was filtered and dried to yield a yellow powder (1.9789 g, yield: 54%). A sample suitable for elemental analysis was obtained by column chromatography as described for the compound 12. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (2H, dt, ^{3}J = 8.6, ^{4}J = 2.2), 7.99 (2H, dt, ^{3}J = 10, ^{4}J = 2.2), 8.02 (1H, s), 12.77 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.8, 128.9, 131.4, 131.6, 134.0, 148.7, 187.2; IR (ATR): $\tilde{\nu}$ 3212 (O-H), 3098 (C-H), 2983 (C-H), 1665 (C=O), 1584, 1423, 1247, 989; MS (ESI-) m/z 181.973 $[M-H]^-$ (calcd for $C_8H_6NO_2Cl$, 182.00); HRMS m/z for $[M-H]^-$ calcd 182.0009, found 182.0009; Expected for $C_8H_6NO_2Cl$: % C, 52.34; H, 3.29; N, 7.63; Cl, 19.31, found: % C, 52.31; H, 3.14; N, 7.51; Cl, 19.37.

(*1E,2Z*)-2-(4-Chlorophenyl)-2-hydrazonoacetaldehyde oxime (17)

Compound **16** (1.8500 g, 10.08 mmol) was dissolved in dry ethanol (40 ml) and hydrazine monohydrate (2.45 ml, 2.5300 g, 50.51 mmol, 5 equiv.) was added. The completion of the reaction was monitored using thin layer chromatography (ethyl acetate/*n*-hexane = 1:3). Water (95 ml) was then added to crystallise out the product, which was then filtered and dried. This yielded a white crystalline solid (0.9145 g, yield: 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 8.3), 7.39 (2H, d, J = 8.3), 7.53 (1H, s), 8.02 (2H, br s), 8.16 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.9, 128.6, 132.2, 133.4, 136.6, 145.7; IR (ATR): $\tilde{\nu}$ 3272 (N-H), 3123 (O-H), 2849.95 (C-H), 1596, 1472; MS (ESI+) m/z 197.987 $[M+H]^+$ (calcd for $C_8H_9N_3OCl$, 198.04);

HRMS (ESI-) m/z for $[M-H]^-$ calcd 196.0278, found 196.0280. Expected for $C_8H_8N_3OCl$: % C, 48.62; H, 4.08; N, 21.26; Cl, 17.94, found: % C, 48.72; H, 3.87; N, 21.16; Cl, 17.71.

2,9-Bis(6-(4-chlorophenyl)-1,2,4-triazin-3-yl)-1,10-phenanthroline (19)

The compound **9** (0.1221 g, 0.52 mmol) was dissolved in dichloromethane (10 ml) with a couple of drops of methanol to aid dissolution and the compound **17** (0.2182 g, 1.10 mmol, 2.1 equiv.) was also separately dissolved in dichloromethane (10 ml) with a couple of drops of methanol to aid dissolution. The dissolved compound **17** was then added to the solution of the compound **9** *via* double-ended needle and the mixture left to stir for 24 hours. The yielded yellow precipitate (compound **18**, 0.1541 g, yield: 50 %) which was filtered off and dried. This material (0.1343 g, 0.23 mmol) was then dissolved in acetic acid (10 ml) and the solution stirred under reflux at 90°C for 1 hour. The precipitate formed was filtered off, rinsed with acetic acid and several times with water (until pH of the filtrate was neutral) and dried to yield a yellow powder (0.0793 g, yield: 63%). ^{1}H NMR (500 MHz, TFA-*d*); δ 7.78 (4H, d, J = 8), 8.30 (2H, d, J = 8), 8.60 (1H, s), 9.39 (1H, d, J = 8), 9.53 (1H, d, J = 8), 9.97 (1H, s); ^{13}C NMR (100 MHz, TFA-*d*): δ 125.6, 127.3, 129.00, 129.7, 130.4, 133.2, 137.6, 142.0, 145.00, 146.00, 153.9, 155.5, 157.7; IR (ATR): $\tilde{\nu}$ 3429 ($O\text{-}H_{water}$), 3094 (C-H), 3044 (C-H), 1595, 1392, 1088, 611; MS (MALDI): m/z 581.271 $[M+Na]^+$ (calcd for $C_{30}H_{16}N_8Cl_2Na$, 581.08); HRMS (APCI+) m/z for $[M+H]^+$ calcd 559.0953, found 559.0970; Expected for $C_{30}H_{16}N_8Cl_2$: % C, 64.41; H, 2.88; N, 20.03; Cl, 12.68, found: % C, 57.56; H, 3.44; N, 17.76; Cl, 10.99; analysis suggests $C_{30}H_{16}Cl_2N_8\times(H_2O)_{3.8}$: calcd. % C, 57.38; H, 3.80; N, 17.85; Cl, 11.29,

ACKNOWLEDGEMENTS

The authors wish to thank Dalton Nuclear Institute for funding this project.

ASSOCIATED CONTENT

Electronic Supporting Information (ESI) file. ^{1}H-NMR, ^{13}C-NMR, COSY, HSQC, IR, and MS spectra, solubility studies data as well as detailed crystallographic analyses and data. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 1403733-1403736 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

AUTHOR INFORMATION

Corresponding Author: Pavle Mocilac, E-mail: pavle.mocilac@manchester.ac.uk.

REFERENCES

(1) Drew, M. G. B.; Foreman, M. R. S. J.; Hill, C.; Hudson, M. J.; Madic, C. *Inorg. Chem. Commun.* **2005**, *8*, 239.

(2) Lewis, F. W.; Harwood, L. M.; Hudson, M. J.; Drew, M. G. B.; Desreux, J. F.; Vidick, G.; Bouslimani, N.; Modolo, G.; Wilden, A.; Sypula, M.; Vu, T. H.; Simonin, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 13093.

(3) Gorden, A. E. V.; DeVore Ii, M. A.; Maynard, B. A. *Inorg. Chem.* **2013**, *52*, 3445.

(4) Kolarik, Z. *Chem. Rev.* **2008**, *108*, 4208.

(5) Panak, P. J.; Geist, A. *Chem. Rev.* **2013**, *113*, 1199.

(6) Kolarik, Z.; Müllich, U.; Gassner, F. *Solvent Extr. Ion Exc.* **1999**, *17*, 23.

(7) Foreman, M. R. S. J.; Hudson, M. J.; Geist, A.; Madic, C.; Weigl, M. *Solvent Extr. Ion Exc.* **2005**, *23*, 645.

(8) Nilsson, M.; Andersson, S.; Drouet, F.; Ekberg, C.; Foreman, M.; Hudson, M.; Liljenzin, J. O.; Magnusson, D.; Skarnemark, G. *Solvent Extr. Ion Exc.* **2006**, *24*, 299.

(9) Nilsson, M.; Ekberg, C.; Foreman, M.; Hudson, M.; Liljenzin, J. O.; Modolo, G.; Skarnemark, G. *Solvent Extr. Ion Exc.* **2006**, *24*, 823.

(10) Geist, A.; Hill, C.; Modolo, G.; Foreman, M. R. S. J.; Weigl, M.; Gompper, K.; Hudson, M. J.; Madic, C. *Solvent Extr. Ion Exc.* **2006**, *24*, 463.

(11) Whittaker, D. M.; Griffiths, T. L.; Helliwell, M.; Swinburne, A. N.; Natrajan, L. S.; Lewis, F. W.; Harwood, L. M.; Parry, S. A.; Sharrad, C. A. *Inorg. Chem.* **2013**, *52*, 3429.

(12) Laventine, D. M.; Afsar, A.; Hudson, M. J.; Harwood, L. M. *Heterocycles* **2012**, *86*, 1419.

(13) Afsar, A.; Laventine, D. M.; Harwood, L. M.; Hudson, M. J.; Geist, A. *Chem. Commun.* **2013**, *49*, 8534.

(14) Afsar, A.; Harwood, L. M.; Hudson, M. J.; Distler, P.; John, J. *Chem. Commun.* **2014**, *50*, 15082.

(15) Bremer, A.; Whittaker, D. M.; Sharrad, C. A.; Geist, A.; Panak, P. J. *Dalton Trans.* **2014**, *43*, 2684.

(16) Lindoy, L. F. In *The Chemistry of Macrocyclic Ligand Complexes*; Cambridge University Press: Cambridge, UK, 1990.

(17) Dietrich-Buchecker, C. O.; Sauvage, J. P.; Kintzinger, J. P. *Tetrahedron Lett.* **1983**, *24*, 5095.

(18) Beves, J. E.; Blight, B. A.; Campbell, C. J.; Leigh, D. A.; McBurney, R. T. *Angew. Chem. Int. Edit.* **2011**, *50*, 9260.

(19) Ayme, J. F.; Gil-Ramírez, G.; Leigh, D. A.; Lemonnier, J. F.; Markevicius, A.; Muryn, C. A.; Zhang, G. *J. Am. Chem. Soc.* **2014**, *136*, 13142.

(20) Afsar, A.; Harwood, L. M.; Hudson, M. J.; Westwood, J.; Geist, A. *Chem. Commun.* **2015**, *51*, 5860.

(21) Phucho, T.; Nongpiur, A.; Tumtin, S.; Nongrum, R.; Myrboh, B.; Nongkhlaw, R. L. *Arkivoc* **2008**, *2008*, 79.

(22) Alici, O.; Karatas, I. *J. Heterocyc. Chem.* **2012**, *49*, 576.

(23) Kozhevnikov, V. N.; Kozhevnikov, D. N.; Shabunina, O. V.; Rusinov, V. L.; Chupakhin, O. N. *Tetrahedron Lett.* **2005**, *46*, 1521.

(24) Kozhevnikov, V. N.; Shabunina, O. V.; Kopchuk, D. S.; Ustinova, M. M.; König, B.; Kozhevnikov, D. N. *Tetrahedron* **2008**, *64*, 8963.

(25) Kozhevnikov, V. N.; Kozhevnikov, D. N.; Nikitina, T. V.; Rusinov, V. L.; Chupakhin, O. N.; Zabel, M.; König, B. *J. Org. Chem.* **2003**, *68*, 2882.

(26) Marlin, D. S.; Olmstead, M. M.; Mascharak, P. K. *J. Mol. Struct.* **2000**, *554*, 211.

(27) Reid, C. M.; Ebikeme, C.; Barrett, M. P.; Patzewitz, E. M.; Müller, S.; Robins, D. J.; Sutherland, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2455.

(28) Alcock, N. W.; Kingston, R. G.; Moore, P.; Pierpoint, C. *Chem. Soc., Dalton Trans.* **1984**, 1937.

(29) Stoufer, R. C.; Busch, D. H. *J. Am. Chem. Soc.* **1956**, *78*, 6016.

(30) Bosiak, M. J.; Pakulski, M. M. *Synthesis-Stuttgart* **2011**, 316.

(31) Kozhevnikov, V. N.; Kozhevnikov, D. N.; Shabunina, O. V.; Rusinov, V. L.; Chupakhin, O. N. *Tetrahedron Lett.* **2005**, *46*, 1791.

(32) Spek, A. L. *J. Appl. Crystallogr.* **2003**, *36*, 7.