Synthesis of 3-(carboxyarylalkyl)imidazo[2,1-*f*][1,2,4]triazines as potential inhibitors of AMP deaminase†

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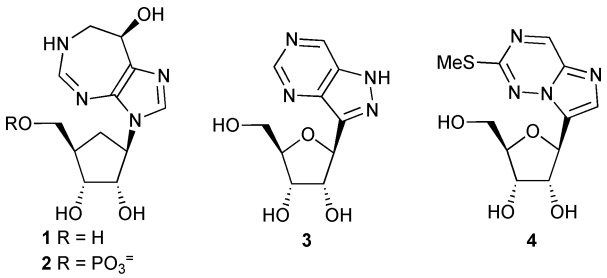
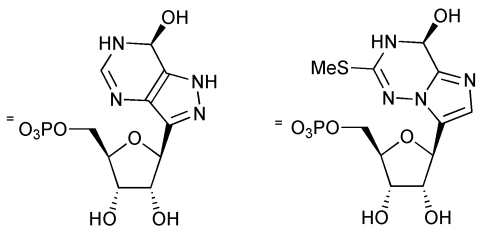
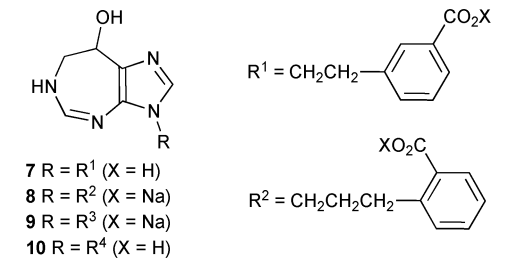
C-Ribosyl 1,2,4-triazolo[1,2,4]triazines which are able to undergo covalent hydration are of interest as potential inhibitors of AMP deaminase. In a search for compounds with improved bioavailability we have synthesized compounds in which the sugar has been replaced by carboxyarylalkyl based ribose phosphate mimics. The target carboxyarylalkyl imidazotriazines **11** and **12** were synthesized using a linear seven step sequence starting from simple benzoate derivatives. Alternatively, the hydroxyethyl imidazotriazine **39** is available in five steps and this synthon was used to prepare the imidazotriazines **34** and **48** in a short convergent manner.

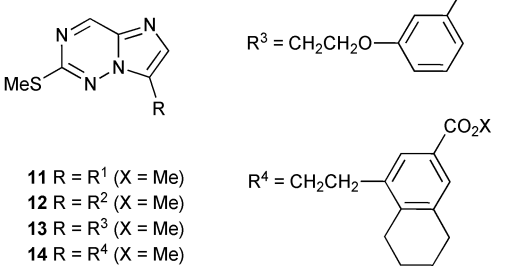
Introduction

The enzyme AMP deaminase (AMPDA, EC 3.5.4.6) is a potential target for novel herbicides[1,2] and antiischemic drugs.[3] For example, the herbicidally active natural product carbocyclic coformycin (**1**)[4] has been shown to undergo *in planta* 5′-phosphorylation to give the nucleotide **2**, which is a potent inhibitor of AMPDA (IC_{50} = 20 nM).[1] Modified C-nucleosides are also of interest as potential AMPDA inhibitors, as exemplified by the ribosides **3**[2,5] and **4**.[6] In order to inhibit AMPDA, these compounds must undergo 5′-phosphorylation and a covalent hydration of the aglycone ring to give the nucleotide derivatives **5** and **6**.[7] Kasibhatla and co-workers have described simplified inhibitors, as exemplified by structures **7–9** (K_i = 0.5–32 μM),[8] in which the entire sugar phosphate moiety of inhibitor **2** has been replaced by a benzoic acid attached to the aglycone by a 2- or 3-atom tether. Of special note is the inhibitor **10** (K_i = 15 nM),[3,8] containing a more lipophilic tetrahydronaphthoic acid side chain as the ribose phosphate mimic, which has a similar AMPDA inhibition potency to the nucleotide **2**. Inhibitors **7–10** are important because, compared to polar nucleotide based inhibitors such as compound **2**, they are expected to show improved bioavailability and hence, biological activity.[3] However, the diazepinol aglycone present in these structures is comparatively difficult to synthesize and rather unstable.[9] Therefore, it is of interest to try and replace the diazepinol with a more stable and easily accessible aglycone, such as the imidazotriazine present in structure **4**.[6] In addition, because esters have often been shown to be effective prodrugs with enhanced delivery properties,[10] we were interested in replacing the polar acids and salts in structures **7–10** with more lipophilic methyl esters.









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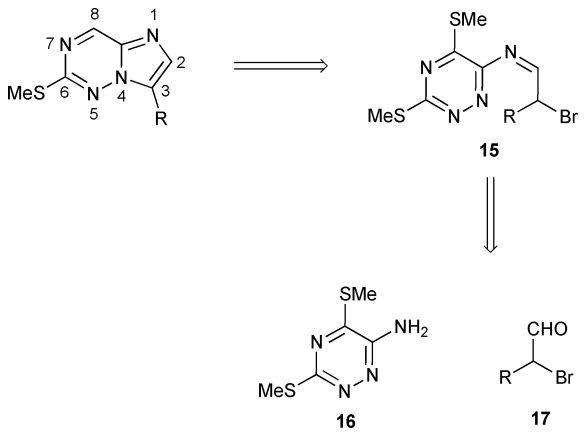
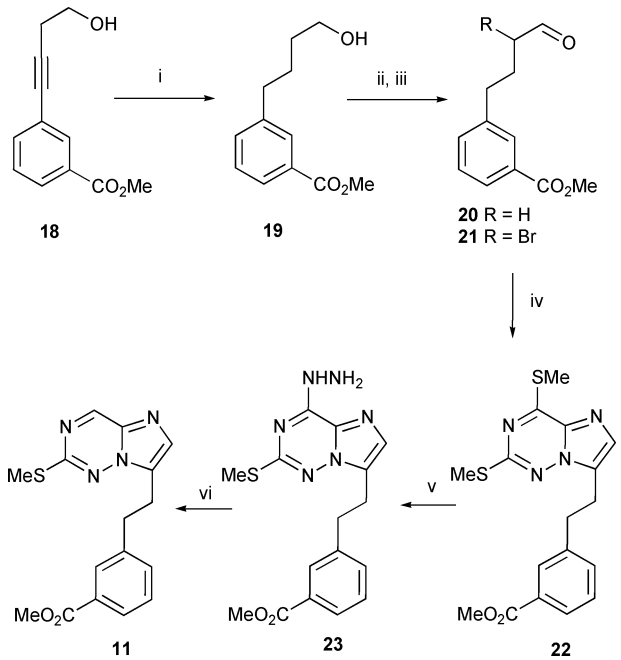
This paper describes new synthetic routes leading to the potential AMPDA hybrid-inhibitors **11–14**, in which an imidazotriazine aglycone is attached to a carboxyarylalkyl ribose phosphate mimic. Disconnection of the *C*3-*N*4 bond in **11–14**, with introduction of a second methylsulfanyl group, leads to the imines **15** which should be obtainable by condensation of the known aminotriazine **16**[6,11] and the bromoaldehydes **17** (Scheme 1).



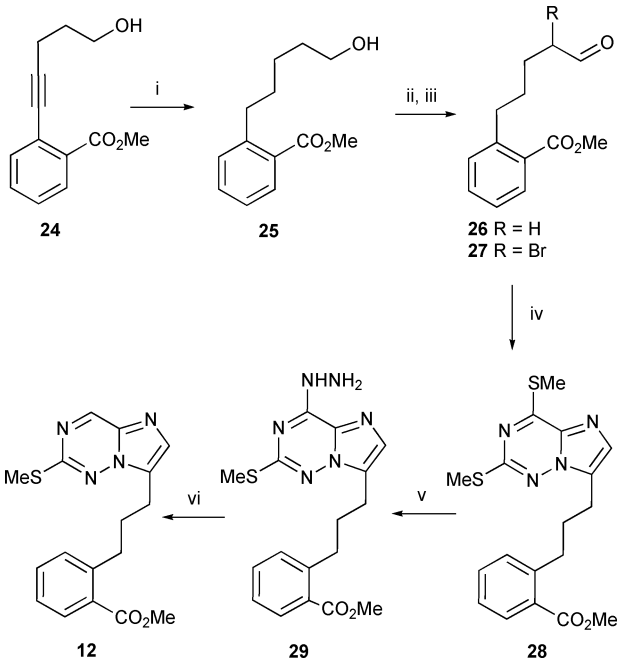
Scheme 1

Results and discussion

The first two target molecules **11** and **12** were synthesized following a common route as detailed in Schemes 2 and 3. The syntheses began with a Sonogashira[12] coupling reaction of 3-butynol and 4-pentynol with methyl 3-iodobenzoate and methyl 2-iodobenzoate



Scheme 2 *Reagents, conditions and yields*: (i) 5% Pd/C, H_2, EtOAc (65%); (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 to give **20** (80%); (iii) Amberlyst A-26 (Br_3^- form), $CHCl_3$ to give **21** (62%); (iv) **16**, $CHCl_3$, 4 Å mol. sieve, reflux (58%); (v) N_2H_4, MeOH (72%); (vi) HgO, $CHCl_3$ (33%).

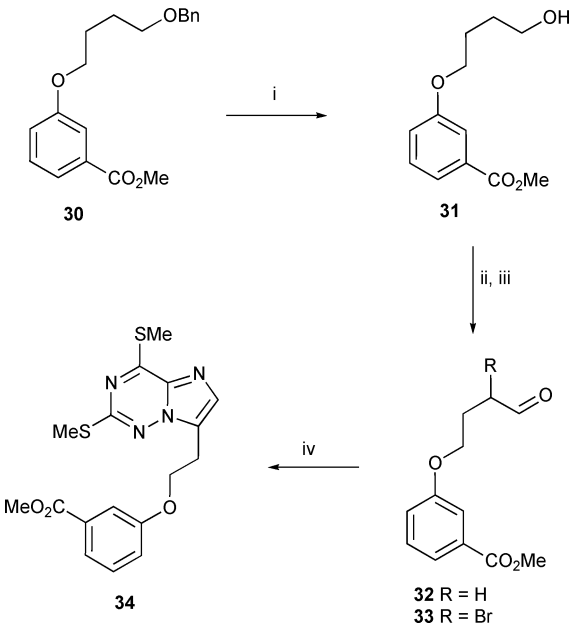


Scheme 3 *Reagents, conditions and yields*: (i) 5% Pd/C, H_2, EtOAc (91%); (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 to give **26** (79%); (iii) Amberlyst A-26 (Br_3^- form), $CHCl_3$ to give **27**; (iv) **16**, $CHCl_3$, 4 Å mol. sieve, reflux (50% over two steps); (v) N_2H_4, MeOH (54%); (vi) HgO, $CHCl_3$ (37%).

to give the alkynols **18** and **24**, respectively. Hydrogenation over palladium on charcoal yielded the homologous alcohols **19** and **25** which were oxidized to the corresponding aldehydes **20** and **26** using Swern[13] conditions. Bromination to give the bromoaldehydes **21** and **27** was achieved using polymer supported tribromide according to the method described by Bongini *et al.*[14] Subsequent condensation of 6-aminotriazine **16**[6] with the bromoaldehydes **21** and **27** in refluxing chloroform yielded the bis-sulfides **22** and **28**. Finally, the 8-methylmercapto group was removed in a two step sequence involving initial displacement with hydrazine hydrate to give the hydrazines **23** and **29**, followed by oxidation with yellow mercuric oxide to yield the target imidazotriazines **11** and **12**.

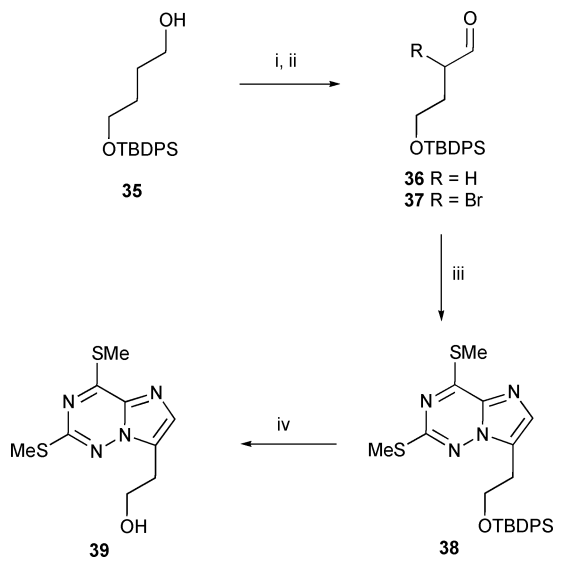
We next turned our attention to the synthesis of imidazotriazine **13** in which the benzoate is attached to the rest of the molecule *via* an ether linkage. In this case the key intermediate **30** was synthesized *via* a Mitsunobu[15] coupling reaction of 4-benzyloxy-1-butanol and methyl 3-hydroxybenzoate (Scheme 4). Hydrogenolysis to remove the benzyl protecting group, followed by oxidation and bromination as previously described, yielded the bromoaldehyde **33**. This reactive intermediate was allowed to react without purification with the 6-aminotriazine **16**[6] to give the imidazotriazine **34**. Although the synthetic routes to compounds **11**, **12** and **34** are straightforward and work well, a more convergent route would enable new analogues to be more efficiently prepared. Therefore, it was decided to refocus our synthetic efforts in this direction and the alcohol **39** was identified as an interesting intermediate from which a variety of target molecules, including **13** and **14**, should be accessible.

The synthesis of the imidazotriazine **39** was achieved in five steps and 23% overall yield, starting from 1,4-butanediol which was monoprotected to give the *t*-butyldiphenylsilyl (TBDPS) ether derivative **35** according to the method described by



Scheme 4 *Reagents, conditions and yields*: (i) 5% Pd/C, H_2, EtOAc (98%); (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 to give **32** (62%); (iii) Amberlyst A-26 (Br_3^- form), $CHCl_3$ to give **33**; (iv) **16**, $CHCl_3$, 4 Å mol. sieve, reflux (42% over two steps).

Brimble and co-workers.[16] Sequential oxidation, bromination and condensation with the 6-aminotriazine **16**[6] yielded the TBDPS protected imidazotriazine **38** (Scheme 5). The structure of this key intermediate was confirmed by single-crystal X-ray diffraction (Fig. 1).[17] Removal of the silyl ether using tetrabutylammonium fluoride (TBAF) yielded the deprotected alcohol **39** ready for further derivatisation.



Scheme 5 *Reagents, conditions and yields*: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 to give **36** (85%); (ii) Amberlyst A-26 (Br_3^- form), $CHCl_3$ to give **37** (90%); (iii) **16**, $CHCl_3$, 4 Å mol. sieve, reflux (62%); (iv) n-$Bu_4N^+F^-$, THF (72%). TBDPS = *t*-butyldiphenylsilyl.

Before continuing with inhibitor synthesis it was decided to first investigate the removal of the methylsulfanyl groups in the

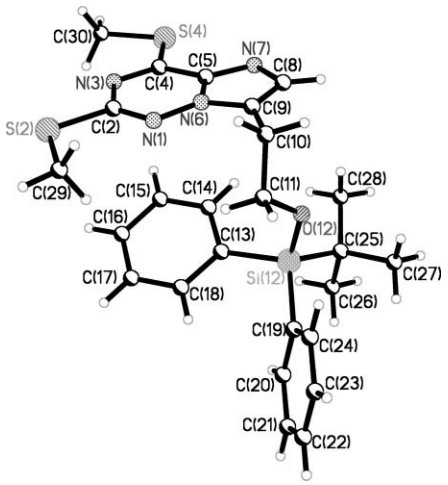
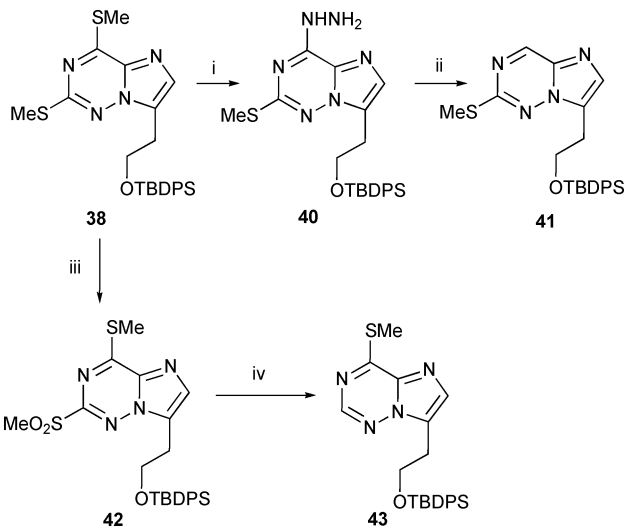


Fig. 1 X-Ray crystal structure of imidazotriazine **38**.

precursor **38**. The 8-methylmercapto group was removed as before in a two step sequence involving initial displacement with hydrazine hydrate to give the hydrazine **40**, followed by oxidation with yellow mercuric oxide to yield the target imidazotriazine **41** (Scheme 6). It was also possible to remove the 6-methylsulfanyl using a two step oxidation-reduction procedure.[6] In our previous studies, a selective oxidation of the 6-methylsulfanyl group in related systems had been achieved using either *m*-chloroperbenzoic acid (MCPBA) or acidic potassium permanganate.[6] In the case of the imidazotriazine **38**, only a modest conversion to the sulfone **42** was achieved using MCPBA and no product at all was obtained using permanganate, possibly due to the acid lability of the silicon protecting group. However, good results were obtained using ruthenium tetroxide which gave a near quantitative yield of the desired sulfone **42**. Treatment of the sulfone with sodium borohydride removed the 6-substituent to yield the 6-unsubstituted imidazotriazine **43** (Scheme 6). In addition to the bis-sulfide **38**, the monosulfides **41** and **43** are also potential precursors for use in more convergent inhibitor synthesis strategies.



Scheme 6 *Reagents, conditions and yields*: (i) N_2H_4, EtOH; (ii) HgO, EtOH (51% over two steps); (iii) $RuCl_3$, $NaIO_4$, H_2O, CH_3CN, EtOAc (96%); (iv) $NaBH_4$, MeOH, $CHCl_3$ (67%). TBDPS = *t*-butyldiphenylsilyl.

Having confirmed the feasibility of accessing 8- and 6-unsubstituted imidazotriazines, we turned our attention back to the synthesis of new inhibitors starting from the key synthon **39**. Our first target was a resynthesis of compound **34**, which was efficiently achieved in a single step using a Mitsunobu[15] coupling between the alcohol **39** and methyl 3-hydroxybenzoate (Scheme 7). In order to attach the tetrahydronaphthoate side chain required for target inhibitor **14** we envisaged using a cross-metathesis reaction.[18] To this end, the alcohol **39** was first converted to the mesylate derivative **44** and then treated with DBU to give the olefin **45** (Scheme 7). The cross-metathesis partner, styrene **47**, was obtained in a single step from the previously described bromide **46**[3] upon treatment with DBU. Although cross metathesis reactions on sulfur-containing compounds are known,[19] the presence of sulfur in a substrate can be problematic due to catalyst sequestration. Therefore, it was especially pleasing that the cross metathesis reaction between the olefins **45** and **47** proceeded smoothly in the presence of the Hoveyda-Grubbs second generation catalyst[20] to give the desired product **48**, albeit in a modest 38% yield. In the next step, however, in which we tried to hydrogenate the alkene, none of the conditions we tried (*eg.* H_2, Pd/C or Pt/C; TFA/Et_3SiH) showed any trace of the desired hydrogenation product, possibly due to interference by the methylsulfanyl groups.

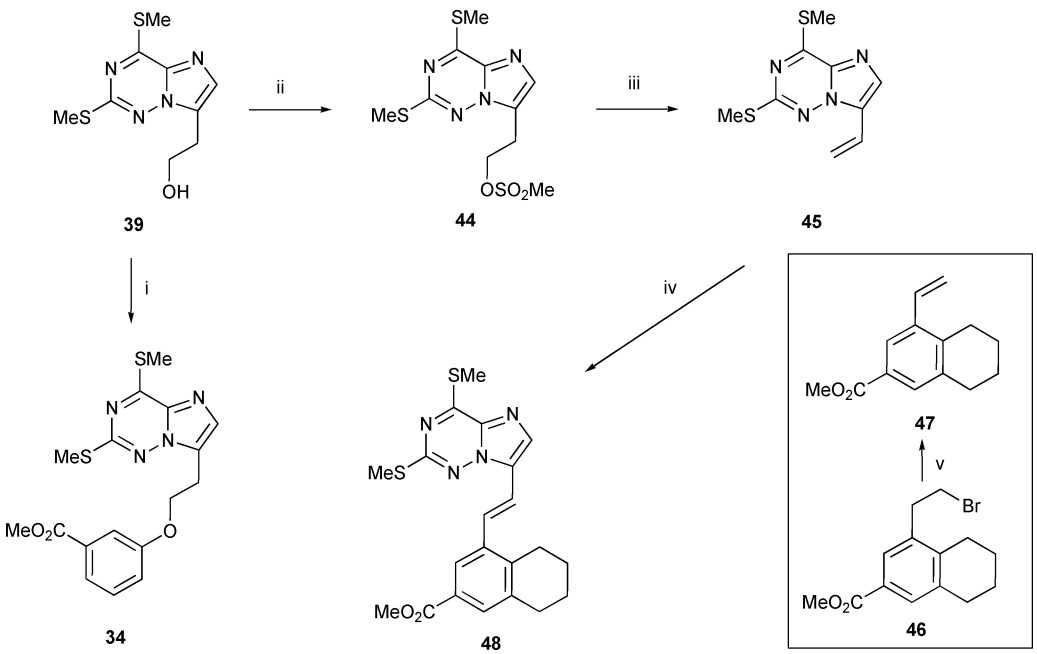
Biological testing results showed that compounds **11** and **12** did not exhibit any significant herbicidal activity. This may be because inhibitors bearing simple benzoic acid side chains are insufficiently potent to achieve an *in vivo* effect[8] and for this reason the desulfurisation of the sulfide **34** to give the target compound **13** has not been pursued. However, significantly better inhibition is expected for compounds bearing the tetrahydronaphthoate side chain[3,8] and we hope that the methodology developed for the synthesis of imidazotriazines **11**, **12** and **41** can be applied to the synthesis of target inhibitor **14** in the future.

In summary, the synthesis of the first examples of potential AMPDA inhibitors combining an imidazotriazine ring with a carboxyalkylaryl ribose mimic, compounds **11** and **12**, have been successfully synthesized. In addition, the imidazotriazinyl alcohol **39** has been prepared and shown to be an interesting synthon which can be used in more convergent synthetic strategies towards other new inhibitors.

Experimental

Commercially available reagents were used without further purification and solvents were dried using standard procedures as required. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF254. Plates were visualized under UV light (254, 360 nm) or stained with $KMnO_4$ solution. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrix silica 60. IR spectra were recorded using a Nicolet Magna FT-550 spectrometer. ^1H and ^{13}C NMR spectra were recorded using Bruker 300, 400 or 500 MHz instruments (^1H frequencies; the corresponding ^{13}C frequencies were 75, 100 or 125 MHz) and *J* values are quoted in Hz. In the ^{13}C NMR spectra, signals corresponding to CH, CH_2, or CH_3 groups are assigned from DEPT. Mass spectra were recorded on a Micromass GCT time of flight high resolution mass spectrometer, on a Finnigan MAT 95 SQ spectrometer or on a Bruker-Daltonics esquire 2000 under electron impact (EI), chemical ionisation (CI) or electrospray (ES) conditions. Elemental analysis was carried out on a Perkin Elmer 2400 CHN analyser. Melting points were determined on a Reichert-Köfler hot stage apparatus and are uncorrected.

Experimental details for compounds **18–21**, **24–26**, **30–32**, and **35–37** are given in the Electronic supplementary information (ESI).



Scheme 7 *Reagents, conditions and yields*: (i) methyl 3-hydroxybenzoate, $(NCO_2i\text{-}Pr)_2$, PPh_3, THF (54%); (ii) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (iii) DBU, THF (58% over two steps); (iv) **47**, Hoveyda-Grubbs second generation catalyst, $PhCH_3$, 80 °C (38%); (v) DBU, THF (53%).

6,8-Bis(methylsulfanyl)-3-[2-(3-methoxycarbonylphenyl)ethyl]-imidazo[2,1-*f*][1,2,4]triazine 22

A solution of 6-amino-3,5-di(methylsulfanyl)[1,2,4]triazine **16** (0.30 g, 1,60 mmol) and 3-(3-bromo-4-oxobutyl)benzoic acid methyl ester **21** (0.45 g, 1.58 mmol) in $CHCl_3$ containing activated 4 Å molecular sieves (0.9 g) was heated at reflux for 48 h. The molecular sieves were filtered off over a short pad of Celite, and the reaction mixture washed with water and brine, dried over $MgSO_4$ and evaporated *in vacuo.* Purification by column chromatography (30–50% ethyl acetate in heptane) yielded the title compound **22** as a colourless solid (0.34 g, 0.91 mmol, 58%); mp 122–124 °C (ethyl acetate); (Found: C, 54.5; H, 4.9; N, 15.0. $C_{17}H_{18}N_4O_2S_2$ requires C, 54.5; H, 4.9; N, 14.8%); (Found: MH^+, 375.0955. $C_{17}H_{19}N_4O_2S_2$ requires 375.0949); ν_{max} ($CHCl_3$)/cm^{-1} 3689, 3600, 3054, 2956, 2932, 1720, 1575, 1508, 1441, 1356, 1280, 1204, 1150, 1107; δ_H (300 MHz; $CDCl_3$) 7.84 (1 H, s), 7.82 (1 H, m), 7.29 (3 H, m), 3.85 (3 H, s), 3.19 (2 H, t, $J = 7.5$), 3.04 (2 H, t, $J = 7.5$), 2.60 (3 H, s), 2.54 (3 H, s); δ_C (75 MHz; $CDCl_3$) 167.44 (C), 163.36 (C), 161.38 (C), 141.33 (C), 133.40 (CH), 133.02 (C), 131.46 (CH), 130.79 (C), 129.87 (CH), 129.52 (C), 128.99 (CH), 128.07 (CH), 52.56 (CH_3), 33.73 (CH_2), 25.49 (CH_2), 14.63 (CH_3), 12.17 (CH_3); *m/z* (CI) 375 (MH^+, 100%), 329 (10), 225 (12), 127 (17), 101 (15), 75 (11).

8-Hydrazino-6-methylsulfanyl-3-[2-(3-methoxycarbonylphenyl)-ethyl]imidazo[2,1-*f*][1,2,4]-triazine 23

Hydrazine monohydrate (0.18 mL, 3.7 mmol) was added to a solution of the 6,8-bis(methylsulfanyl)-3-[2-(3-methoxycarbonylphenyl)ethyl]imidazo[2,1-*f*][1,2,4]triazine **22** (138 mg, 0.37 mmol) in MeOH (3 mL) and the reaction was stirred at ambient temperature for 20 h. After this time the precipitated product was removed by filtration and recrystallized from $CHCl_3$ to give the title compound **23** as a colourless solid (95 mg, 0.27 mmol, 72%); mp 172–174 °C ($CHCl_3$); (Found: MH^+, 359.1283. $C_{16}H_{19}N_6O_2S$ requires 359.1290); ν_{max} ($CHCl_3$)/cm^{-1} 3427, 3335, 3060, 2972, 2954, 2932, 1719, 1630, 1600, 1556, 1523, 1443, 1406, 1341, 1289, 1264, 1178, 1109, 1084; δ_H (300 MHz; $CDCl_3$) 8.53 (1 H, s), 7.85–7.81 (2 H, m), 7.29 (2 H, m), 7.17 (1 H, s), 4.14 (2 H, s), 3.85 (3 H, s), 3.15 (2 H, m), 3.04 (2 H, m), 2.53 (3 H, s); δ_C (75 MHz; $CDCl_3$) 167.52 (C), 162.47 (C), 152.01 (C), 141.60 (C), 133.44 (CH), 130.78 (C), 129.93 (CH), 129.69 (C), 129.21 (CH), 128.96 (CH), 128.47 (C), 128.01 (CH), 52.57 (CH_3), 33.98 (CH_2), 30.13 (CH_2), 14.50 (CH_3); *m/z* (CI) 359 (MH^+, 13%), 358 (M^+, 7), 205 (17), 204 (100).

6-Methylsulfanyl-3-[2-(3-methoxycarbonylphenyl)-ethyl]imidazo[2,1-*f*][1,2,4]triazine 11

Yellow mercuric oxide (4 eq.) was added to a solution of the 8-hydrazino-6-methylsulfanyl-3-[2-(3-methoxycarbonylphenyl)-ethyl]imidazo[2,1-*f*][1,2,4]triazine **23** (79 mg, 0.22 mmol) in $CHCl_3$ (1 mL) at ambient temperature. The mixture was stirred at ambient temperature for 18 h and then filtered through a short pad of Celite to remove residual mercury. Purification by column chromatography (50% ethyl acetate in heptane) yielded the title compound **11** as a pale yellow oil (24 mg, 0.073 mmol, 33%); (Found: M^+, 328.0999. $C_{16}H_{16}N_4O_2S$ requires 328.0994); ν_{max} ($CHCl_3$)/cm^{-1} 2973, 2955, 2929, 2856, 1720, 1592, 1522, 1468, 1436, 1422, 1344, 1309, 1290, 1269, 1114, 1086, 1070; δ_H (300 MHz; $CDCl_3$) 8.87 (1 H, s), 7.84–7.81 (2 H, m), 7.50 (1 H, s), 7.29–7.27 (2 H, m), 3.85 (3 H, s), 3.26 (2 H, m), 3.07 (2 H, m), 2.55 (3 H, s); δ_C (75 MHz; $CDCl_3$) 167.11 (C), 163.13 (C), 148.95 (CH), 140.81 (C), 134.22 (CH), 134.22 (C), 133.05 (CH), 130.57 (C), 129.64 (C), 129.54 (CH), 128.76 (CH), 127.88 (CH), 52.30 (CH_3), 33.14 (CH_2), 25.04 (CH_2), 14.38 (CH_3); *m/z* (EI) 328 (M^+, 72%), 297 (5), 180 (10), 179 (100).

6,8-Bis(methylsulfanyl)-3-[3-(2-methoxycarbonylphenyl)-propyl]imidazo[2,1-*f*][1,2,4]triazine 28

3-(5-Oxopentyl)benzoic acid methyl ester **26** (600 mg, 2.73 mmol) was converted to 3-(3-bromo-5-oxopentyl)benzoic acid methyl ester **27** as described above for compound **21**. The crude bromide **27** was then converted, as described above for compound **22**, to the title compound **28** which was isolated after purification as a colourless solid (536 mg, 1.38 mmol, 50%); mp 99–102 °C (MeOH); (Found: M^+, 388.1008. $C_{18}H_{20}N_4O_2S_2$ requires 388.1028); ν_{max} (CH_2Cl_2)/cm^{-1} 3408, 3145, 3064, 3049, 2987, 2955, 2938, 2866, 1749, 1716, 1602, 1575, 1510, 1488, 1432, 1363, 1320, 1212, 1186, 1149, 1136, 1089, 1026; δ_H (300 MHz; $CDCl_3$) 7.82 (1 H, m), 7.38 (1 H, m), 7.21–7.15 (3 H, m), 3.87 (3 H, s), 3.02–2.90 (4 H, m) 2.59 (3 H, s), 2.50 (3 H, s), 2.00 (2 H, quint, $J = 7.4$); δ_C (75 MHz; $CDCl_3$) 168.25 (C), 163.16 (C), 161.14 (C), 144.01 (C), 132.45 (CH), 131.41 (CH), 131.36 (CH), 131.26 (CH), 130.65 (C), 129.70 (C), 126.52 (CH), 115.40 (C), 52.35 (CH_3), 34.48 (CH_2), 29.46 (CH_2), 23.61 (CH_2), 14.58 (CH_3), 12.15 (CH_3); *m/z* (EI) 388 (M^+, 100%), 193 (50), 180 (29), 133 (10), 69 (15).

8-Hydrazino-6-methylsulfanyl-3-[3-(2-methoxycarbonylphenyl)-propyl]imidazo[2,1-*f*][1,2,4]-triazine 29

The reaction and purification were performed as described above for compound **23**. Starting from 6,8-bis(methylsulfanyl)-3-[3-(2-methoxycarbonylphenyl)propyl]imidazo[2,1-*f*][1,2,4]triazine **28** (122 mg, 0.31 mmol), the title product **29** was isolated as a colourless solid (65 mg, 0.17 mmol, 54%); mp 82–85 °C (CH_2Cl_2); (Found: MH^+, 373.1429. $C_{17}H_{21}N_6O_2S$ requires 373.1447); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3426, 3364, 2953, 2931, 1718, 1601, 1558, 1525, 1471, 1436, 1406, 1378, 1332, 1316, 1293, 1267, 1191, 1135, 1110, 1084; δ_H (300 MHz; $CDCl_3$) 9.04 (1 H, s), 7.89 (1 H, d, $J = 5.7$), 7.45–7.38 (2 H, m), 7.28–7.23 (2 H, m), 4.22 (2 H, s) 3.86 (3 H, s), 3.07 (2 H, m), 2.97 (2 H, m), 2.58 (3 H, s), 2.08 (2 H, m); δ_C (75 MHz; $CDCl_3$) 167.61 (C), 162.31 (C), 151.92 (C), 142.35 (C), 133.52 (CH), 130.61 (C), 130.26 (CH), 129.95 (C), 129.11 (C), 128.84 (CH), 127.67 (CH), 126.34 (CH), 52.54 (CH_3), 35.54 (CH_2), 29.40 (CH_2), 23.16 (CH_2), 14.43 (CH_3); *m/z* (CI) 373 (MH^+, 43%), 356 (100), 342 (6), 326 (4).

6-Methylsulfanyl-3-[3-(2-methoxycarbonylphenyl)propyl]-imidazo[2,1-*f*][1,2,4]triazine 12

The reaction and purification were performed as described above for compound **11**. Starting from 8-hydrazino-6-methylsulfanyl-3-[3-(2-methoxycarbonylphenyl)propyl]imidazo[2,1-*f*][1,2,4]triazine **29** (35 mg, 0.094 mmol), the title compound **12** was isolated as a colourless solid (12 mg, 0.035 mmol, 37%); mp 126–129 °C ($CHCl_3$); (Found: M^+, 342.1146. $C_{17}H_{18}N_4O_2S$ requires 342.1150); ν_{max} ($CHCl_3$)/cm^{-1} 3442, 2954, 2929, 2856, 1718, 1592, 1520, 1488, 1436, 1423, 1346, 1291, 1205, 1187, 1164, 1135, 1112, 1087; δ_H

(300 MHz; $CDCl_3$) 8.93 (1 H, s), 7.90 (1 H, dd, $J = 1.3, 8.2$), 7.69 (1 H, s), 7.43 (1 H, dt, $J = 1.3, 8.2$), 7.29–7.23 (2 H, m), 3.86 (3 H, s) 3.11–3.04 (4 H, m), 2.58 (3 H, s), 2.13 (2 H, quint, $J = 7.5$); δ_C (75 MHz; $CDCl_3$) 168.50 (C), 162.67 (C), 149.03 (CH), 143.93 (C), 139.23 (C), 138.93 (C), 134.51 (CH), 132.51 (CH), 131.41 (CH), 131.33 (CH), 129.62 (C), 126.61 (CH), 52.35 (CH_3), 34.50 (CH_2), 29.16 (CH_2), 23.49 (CH_2), 14.62 (CH_3); *m/z* (EI) 342 (M^+, 27%), 295 (16), 283 (100), 179 (10), 76 (34).

6-Bis(methylsulfanyl)-3-[2-(3-methoxycarbonylphenoxy)ethyl]-imidazo[2,1-*f*][1,2,4]triazine 34

Method A. 3-(4-Oxobutoxy) benzoic acid methyl ester **32** (132 mg, 0.59 mmol) was converted to methyl 3-(3-bromo-4-oxobutoxy)benzoate **33** (Found: M^+, 300.0003. $C_{12}H_{13}{}^{79}BrO_4$ requires 299.9997) as described above for compound **21**. The crude bromide **33** was then converted, as described above for compound **22**, to the title compound **34** which was isolated after purification as a colourless solid (96 mg, 0.25 mmol, 42%); mp 93–96 °C (MeOH); (Found: MH^+, 391.0895. $C_{17}H_{19}N_4O_3S_2$ requires 391.0893); ν_{max} ($CHCl_3$)/cm^{-1} 2954, 2848, 2257, 1721, 1588, 1489, 1448, 1290, 1233, 1192, 1104, 1081, 1053; δ_H (300 MHz; $CDCl_3$) 7.60 (1 H, d, $J = 8.2$), 7.51 (1 H, m), 7.30 (2 H, m), 7.06 (1 H, m), 4.36 (2 H, t, $J = 6.3$), 3.90 (3 H, s), 3.44 (2 H, t, $J = 6.3$), 2.66 (3 H, s), 2.58 (3 H, s); δ_C (75 MHz; $CDCl_3$) 202.08 (CH), 167.29 (C), 165.77 (C), 162.85 (C), 161.14 (C), 159.03 (C), 157.26 (C), 131.82 (C), 129.84 (CH), 122.52 (CH), 120.20 (CH), 114.99 (CH), 67.26 (CH_2), 52.59 (CH_3), 40.96 (CH_2), 14.52 (CH_3), 12.33 (CH_3); *m/z* (CI) 391 (MH^+, 7%), 390 (M^+, 42), 374 (20), 240 (16), 239 (47), 238 (15), 226 (13), 225 (100), 192 (11), 120 (37), 106 (16), 91 (22), 86 (33), 84 (48), 49 (47), 47 (28).

Method B. The Mitsunobu reaction and purification were performed as described for compound **30**. Starting from 3-(2-hydroxyethyl)-6,8-bis(methylsulfanyl)imidazo[2,1-*f*][1,2,4]triazine **39** (24 mg, 0.094 mmol), the the title compound **34** was obtained as a colourless solid (20 mg, 0.051 mmol, 54%); physical data identical to those given above.

3-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6,8-bis(methylsulfanyl)imidazo[2,1-*f*][1,2,4]triazine 38

The reaction and purification were performed as described above for compound **22**. Starting from 4-*tert* Butyldiphenylsilyloxy-2-bromobutanal **37**, the title compound **38** (3.55 g, 8.76 mmol) was obtained as a colourless solid (2.69 g, 5.44 mmol, 62%); (Found: C, 61.0; H, 6.2; N, 11.3. $C_{25}H_{30}ON_4SiS_2$ requires C, 60.7; H, 6.1; N, 11.3%); (Found: MH^+, 495.1703. $C_{25}H_{31}ON_4SiS_2$ requires 495.1703); ν_{max} (liquid film)/cm^{-1} 3072, 3049, 2960, 2932, 2859, 1963, 1830, 1576, 1513, 1472, 1439, 1356, 1317, 1150, 1112; δ_H (300 MHz; $CDCl_3$) 7.53–7.49 (5 H, m), 7.40–7.28 (6 H, m), 4.01 (2 H, t, $J = 6.0$), 3.15 (2 H, t, $J = 6.0$) 2.67 (3 H, s), 2.43 (3 H, s), 1.00 (9 H, s); δ_C (75 MHz; $CDCl_3$) 163.08 (C), 161.61 (C), 135.82 (CH), 133.67 (C), 132.87 (C), 132.69 (CH), 130.01 (CH), 127.94 (CH), 127.80 (C), 61.15 (CH_2), 27.34 (CH_2), 27.23 (CH_3), 19.49 (C), 14.49 (CH_3), 12.14 (CH_3); *m/z* (CI) 495 (MH^+, 100%), 449 (11), 437 (8), 274 (20), 196 (16), 114 (13), 112 (22), 111 (30), 98 (33), 83 (36), 72 (55).

3-(2-Hydroxyethyl)-6,8-bis(methylsulfanyl)imidazo[2,1-*f*][1,2,4]triazine 39

A solution of tetra-*n*-butylammonium fluoride (TBAF) in THF (1 M; 0.4 mL, 0.4 mmol) was added to a solution of the methylsulfanyl imidazotriazine **38** (99 mg, 0.2 mmol) in THF (6 mL) at ambient temperature. The mixture was heated at reflux for 20 min and then concentrated under reduced pressure. The crude product was purified by column chromatography (30–50% ethyl acetate in heptane) to yield the title compound **39** as a pale yellow oil (37 mg, 0.14 mmol, 72%); (Found: M^+, 256.0449. $C_9H_{12}N_4OS_2$ requires 256.0453); ν_{max} ($CHCl_3$)/cm^{-1} 3623, 3392, 3019, 3006, 2961, 2932, 2857, 1717, 1575, 1511, 1441, 1357, 1317, 1259, 1152, 1113, 1044; δ_H (300 MHz; $CDCl_3$) 7.49 (1 H, s), 4.01 (2 H, t, *J* 6.1), 3.23 (2 H, t, *J* 6.1), 2.67 (3 H, s), 2.60 (3 H, s); δ_C (75 MHz; $CDCl_3$) 163.29 (C), 161.57 (C), 132.28 (C), 132.28 (CH), 128.07 (C), 60.66 (CH_2), 21.48 (CH_2), 14.60 (CH_3), 12.24 (CH_3); *m/z* (EI) 256 (M^+, 100%), 225 (47), 209 (10), 179 (53), 69 (20).

3-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-8-hydrazino-6-methylsulfanylimidazo[2,1-*f*][1,2,4]-triazine 40

The reaction and purification were performed as described above for compound **23**. Starting from 3-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-6,8-bis(methylsulfanyl)imidazo-[2,1-*f*][1,2,4]triazine **38** (2.65 g, 5.4 mmol), the title product **40** was isolated as a colourless solid (1.0 g, 2.1 mmol, 39%); mp 59–62 °C ($CHCl_3$); (Found: M^+, 478.1968. $C_{24}H_{30}N_6OSiS$ requires 478.1971); ν_{max} ($CHCl_3$)/cm^{-1} 3668, 3364, 3070, 2995, 2961, 2932, 2860, 1959, 1900, 1827, 1601, 1560, 1527, 1473, 1440, 1381, 1333, 1189, 1110, 1029; δ_H (300 MHz, $CDCl_3$) 9.58 (1 H, s), 7.56 (4 H, m), 7.49 (1 H, s), 7.43–7.26 (6 H, m) 4.22 (2 H, s), 4.01 (2 H, t, $J = 7.4$), 3.47 (2 H, t, $J = 7.4$), 2.43 (3 H, s), 1.01 (9 H, s); δ_C (75 MHz, $CDCl_3$) 162.61 (C), 156.84 (C), 151.18 (C), 135.27 (CH), 133.20 (C), 129.93 (CH), 129.51 (CH), 127.76 (C), 127.43 (CH), 60.94 (CH_2), 26.79 (CH_2), 26.65 (CH_3), 18.73 (C), 14.06 (CH_3); *m/z* (CI) 478 (M^+, 100%), 447 (36), 421 (27), 344 (31), 324 (40), 297 (76), 223 (21), 208 (12).

3-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-6-methylsulfanylimidazo[2,1-*f*][1,2,4]triazine 41

Hydrazine hydrate (25 μL, 0.52 mmol) was added under argon to a stirring solution of 3-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-6,8-bis(methylsulfanyl)imidazo-[2,1-*f*][1,2,4]triazine **38** (26 mg, 0.052 mmol) in absolute ethanol (2 ml) and the solution was heated at reflux for 1 h to give the hydrazine **40** as judged by t.l.c. The reaction mixture was cooled to rt and yellow mercury(II) oxide (113 mg, 0.52 mmol) was added, causing the reaction mixture to turn black. The mixture was heated at 80 °C for 1 h and then a second portion of mercury(II) oxide (56 mg, 0.26 mmol) was added. After heating at 80 °C for a further 1 h, a third portion of mercury(II) oxide (56 mg, 0.26 mmol) was added. The reaction mixture was heated for 1 h, cooled to rt and filtered through a column of Celite. Concentration under reduced pressure gave the title compound **41** as a pale yellow solid (12 mg, 0.027 mmol, 51%); (Found: MH^+, 449.1845. $C_{24}H_{29}N_4OSiS$ requires 449.1831); δ_H (300 MHz; $CDCl_3$) 8.87 (1 H, s), 7.73 (1 H, s), 7.51 (4 H, m), 7.41–7.29 (6 H, m), 4.03 (2 H, t, $J = 5$), 3.21 (2H, t, $J = 5$), 2.43 (3 H, s), 0.99 (9 H, s); δ_C (100 MHz, $CDCl_3$) 162.65 (C), 148.62 (CH), 135.38 (CH), 134.79 (C), 134.08 (CH), 133.17 (C), 129.63

(CH), 127.97 (C), 127.60 (CH), 60.50 (CH_2), 26.77 (CH_3), 26.54 (C) 19.06 (CH_2), 14.09 (CH_3).

3-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-methylsulfonyl-8-methylsulfanylimidazo[2,1-*f*][1,2,4]-triazine 42

Method A. A mixture of 3-[2-(*tert*-butyldiphenylsilyloxy)-ethyl]-6,8-bis(methylsulfanyl)imidazo-[2,1-*f*][1,2,4]triazine **38** (192 mg, 0.39 mmol) in CH_2Cl_2 (1 mL) and 3-chloroperoxybenzoic acid (202 mg, 1.17 mmol) was stirred at ambient temperature for 24 h. The reaction was diluted with ethyl acetate, washed with water, dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by column chromatography (30–100% ethyl acetate in heptane) to afford the title compound **42** as a colourless solid (47 mg, 0.089 mmol, 23%); mp 131–134 °C (diethyl ether); (Found: MH^+, 527.1600. $C_{25}H_{31}N_4O_3S_2Si$ requires 527.1601); ν_{max} ($CHCl_3$)/cm^{-1} 3110, 3061, 3034, 2934, 2892, 1621, 1501, 1462, 1421, 1396, 1375, 1124, 1076, 1042; δ_H (300 MHz; $CDCl_3$) 7.77 (1 H, s), 7.51–7.46 (4 H, m), 7.42–7.27 (6 H, m), 4.04 (2 H, t, $J = 5.8$), 3.26 (3 H, s) 3.22 (2 H, t, $J = 5.8$), 2.81 (3 H, s), 1.00 (9 H, s); δ_C (75 MHz; $CDCl_3$) 166.88 (C), 156.02 (C), 135.94 (C), 135.77 (CH), 133.40 (C), 130.09 (CH), 129.98 (C), 128.17 (CH), 128.01 (CH), 60.86 (CH_2), 40.22 (CH_3), 29.66 (CH_2), 27.24 (CH_3), 19.47 (C), 12.87 (CH_3); *m/z* (CI) 527 (MH^+, 100%), 454 (36), 451 (42), 434 (53), 423 (72), 419 (76), 406 (52), 399 (58), 391 (66).

Method B. A solution of 3-[2-(*tert*-butyldiphenylsilyloxy)-ethyl]-6,8-bis(methylsulfanyl)imidazo-[2,1-*f*][1,2,4]triazine **38** (46 mg, 0.093 mmol) in MeCN/EtOAc (1.2 mL/1.2 mL) was added to a vigorously stirred solution of sodium periodate (44 mg, 0.21 mmol) dissolved in water (400 μL). Ruthenium trichloride (2 mg, 0.013 mmol) was then added and vigorous stirring was continued for 1 h. After this time EtOAc (50 mL) was added, followed by brine (50 mL) and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phases was dried and evaporated *in vacuo* to give the title sulfone **42** (47 mg, 0.13 mmol, 96% theory); physical data identical to those described above.

3-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-8-methylsulfanylimidazo[2,1-*f*][1,2,4]triazine 43

Sodium borohydride (5.5 mg, 0.14 mmol) was added to a solution of 3-[2-(*tert*- butyldiphenylsilyloxy)ethyl]-6-methylsulfonyl-8-methylsulfanylimidazo[2,1-*f*][1,2,4]triazine **42** (37 mg, 0.070 mmol) in methanol (0.2 mL) and $CHCl_3$ (0.2 mL) and the mixture was stirred at ambient temperature for 5 min. The mixture was quenched with water, extracted with $CHCl_3$ and washed with water. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (50% ethyl acetate in heptane) to afford the title compound **43** as a pale orange oil (21 mg, 0.047 mmol, 67%); (Found: MH^+, 449.1833. $C_{24}H_{29}N_4OSiS$ requires 449.1831); ν_{max} ($CHCl_3$)/cm^{-1} 3924, 3606, 3149, 3084, 2950, 2902, 2854, 1648, 1595, 1523, 1409, 1356, 1204, 1126, 1014; δ_H (300 MHz; $CDCl_3$) 8.24 (1 H, s), 7.54 (1 H, s), 7.44 (4 H, m), 7.32–7.19 (6 H, m), 3.94 (2 H, t, $J = 6.2$) 3.12 (2 H, t, $J = 6.2$), 2.63 (3 H, s), 0.93 (9 H, s); δ_C (75 MHz; $CDCl_3$) 166.88 (C), 146.73 (CH), 135.83 (CH), 133.66 (C), 133.40 (CH), 133.19 (C), 130.08 (C), 129.98 (CH), 127.95 (CH), 61.30 (CH_2), 40.22 (CH_2), 27.22 (CH_3), 19.47 (C), 12.13 (CH_3); *m/z* (CI) 449 (MH^+, 100%), 392 (31), 371 (40), 345 (78), 314 (54), 193 (16).

4-[(E)-2-(2,4-Bis-methylsulfanyl-imidazo[2,1-*f*][1,2,4]triazin-7-yl)-vinyl]-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid methyl ester 48

(a) Methanesulfonyl chloride (64 μL, 0.84 mmol) followed by diisopropylethylamine (DIEA) (289 μL, 1.68 mmol) were added to a solution of 3-(2-hydroxyethyl)-6,8-bis(methylsulfanyl)imidazo-[2,1-*f*]-1,2,4-triazine **39** (144 mg, 0.56 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 90 minutes at room temperature, then hydrochloric acid (1 M; 10 ml) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 ml). The combined organic phases were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated under vacuum to afford the mesylate **44** (Rf = 0.5, 100% EtOAc) which was immediately redissolved in THF (5 ml). 1,3-Diazabicyclo[5.4.0]undecane (DBU) (416 μL, 3.36 mmol) was added in one portion to the stirring mixture under argon. After stirring for 3 h at room temperature, EtOAc was added to the reaction mixture and the organic phase was washed with hydrochloric acid (1 M; 10 ml), dried and concentrated *in vacuo.* The residue was purified by column chromatography (10–50% ethyl acetate in heptane) to afford 2,4-bis-methylsulfanyl-7-vinyl-imidazo[2,1-*f*][1,2,4]triazine **45** as a yellow solid (78 mg, 0.33 mmol, 58%); (Rf = 0.67, 50% EtOAc); δ_H (400 MHz; $CDCl_3$) 7.70 (1 H, s), 7.92 (1 H, m), 6.24 (1 H, m), 5.52 (1 H, m), 2.68 (3 H, s), 2.60 (3 H, s); δ_C (100 MHz; $CDCl_3$) 164.48 (C), 161.01 (C), 133.22 (C), 131.82 (CH), 128.42 (C), 121.65 (CH), 117.56 (CH_2), 14.46 (CH_3), 12.03 (CH_3). This material was used without further purification directly in the next step.

(b) 1,3-Diazabicyclo[5.4.0]undecane (DBU) (44 mL, 294 mmol) was added to a solution of the bromide **46** (44.6 g, 150 mmol, prepared according to reference 3) in THF (300 mL) and the mixture was heated to reflux for one hour and then stirred at room temperature for 2 h. Hydrochloric acid (1 M; 150 ml) was added to the reaction mixture and the aqueous phase was extracted with *t*-BuOMe (3 × 150 ml). The combined organic extracts were dried ($MgSO_4$), concentrated and purified by column chromatography (1–8% ethyl acetate in heptane) to afford 4-vinyl-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid methyl ester **47** as a pale yellow oil (17.3 g, 80 mmol, 53%); δ_H (400 MHz; $CDCl_3$) 7.92 (1 H, s), 7.68 (1 H, s) 6.95–6.88 (1 H, m) 5.67 (1 H, m), 5.33 (1 H, m), 3.90 (3 H, s), 2.87–2.73 (4 H, m), 1.89–1.73 (4 H, m); δ_C (100 MHz; $CDCl_3$) 167.62 (C), 140.00 (C), 137.78 (C), 137.66 (C), 134.36 (CH), 129.89 (CH), 127.43 (C), 124.41 (CH), 116.77 (CH_2), 52.18 (CH_3), 30.24 (CH_2), 27.19 (CH_2), 23.21 (CH_2), 22.69 (CH_2). This material was used without further purification directly in the next step.

(c) A solution of 2,4-bis-methylsulfanyl-7-vinyl-imidazo[2,1-*f*][1,2,4]triazine **45** (67 mg, 0.28 mmol) and 4-vinyl-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid methyl ester **47** (70 mg, 0.32 mmol) in toluene (2.8 ml) was heated to 80 °C under an atmosphere of argon. When the temperature had stabilized after *ca.* 20 min., Hoveyda-Grubbs 2nd Generation catalyst {[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro[[2-(1-methylethoxy)phenyl]methylene]-ruthenium} (8 mg, 0.014 mmol) was added. After 24 h at 80 °C a second portion of catalyst (8 mg)

was added and the reaction mixture was heated for a further 24 h. The resulting dark brown reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (10–50% ethyl acetate in heptane) to afford the title compound **48** as a yellow oil (45 mg, 0.11 mmol, 38%); (Found: MH^+, 427.1255. $C_{21}H_{23}N_4O_2S_2$ requires 427.1262); ν_{max} (dry film)/cm^{-1} 2938, 2862, 1725, 1662, 1580, 1430, 1354, 1310, 1215, 1160; δ_H (400 MHz; $CDCl_3$) 8.11 (1 H, s), 7.95 (1 H, d, $J = 16.0$), 7.79 (1 H, s), 7.71 (1 H, s), 7.22 (1 H, d, $J = 16.0$), 3.89 (3 H, s), 2.92–2.82 (4H, m) 2.72 (3 H, s), 2.68 (3 H, s), 2.94–2.78 (4 H, m); δ_C (100 MHz; $CDCl_3$) 167.32 (C), 163.20 (C), 161.87 (C), 140.23 (C), 138.11 (C), 136.51 (C), 133.5 (C), 132.76 (CH), 130.16 (CH), 128.52 (CH), 128.22 (C), 127.53 (C), 123.88 (CH), 115.35 (CH), 52.14 (CH_3), 30.10 (CH_2), 27.36 (CH_2), 23.02 (CH_2), 22.46 (CH_2), 14.44(CH_3), 11.91 (CH_3); *m/z* (ES) 427 (MH^+, 100%).

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