

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
ALICIA LLOREDA RICAURTE.
E-mail-notificacionespatentes@lloredacamacho.com

ASUNTO	Radicación	10-131479
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	
	Folios	013

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☐	Cap. I	☐
		Cap. II	☐

No. Solicitud Internacional PCT/US2009/041432
Fecha de Presentación Internacional 22 de abril de 2009.

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 45 a 187	22/octubre/2010
Reivindicaciones:	Folios 188 a 197	22/octubre/2010
	Folios 215 a 224	17/enero/2011
Prioridad:	US 61047263	23/abril/2008
	US 61139449	19/diciembre/2008

2. Análisis de la Prioridad

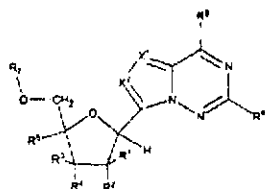
Se acepta la reivindicación de las prioridades porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "nucleósidos de imidazol[1,5-F][1,2,4]triazinil, imidazol[1,2-F][1,2,4]triazinil y [1,2,4]triazolo[4,3-F][1,2,4]triazinil para el tratamiento antiviral" (modificado en el folio 202).

El problema planteado en esta solicitud consiste en proporcionar compuestos que útiles para el tratamiento de infecciones por virus de la familia *flaviviridae*.

Para resolver este problema técnico la solicitud en estudio proporciona un compuesto de la fórmula (I) y composiciones que lo contienen.



Compuesto I

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07D 487/04; C07H 19/23; A61K 31/395, 31/7052, 31/41 31/4188 y A61P 31/12.

4. Excepción a la Patentabilidad (Art 20 D 486 literal (d))

El objeto de las reivindicaciones 21-26 no es patentable de acuerdo con el Art citado.

5. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

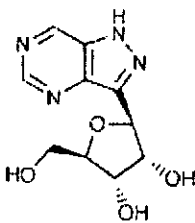
El uso de la reivindicación 27 no es patentable, de acuerdo con el Art 14.

6. Determinación del Estado de la Técnica

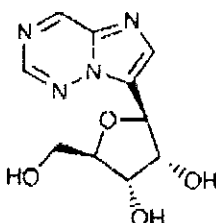
El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad más antigua: abril 23 de 2008 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación*
D1	J. Chem. Soc., Perkin Trans. 1, 1999, 2929–2936	Synthesis of C-ribosyl imidazo[2,1-f][1,2,4]triazines as inhibitors of adenosine and AMP deaminases	01/enero/1999
D2	US 20040067901	Nucleoside derivatives as inhibitors of RNA-dependent RNA viral polymerase	02/diciembre/2004

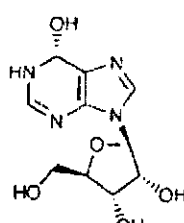
D1: divulga(Pág. 1, Abs.) que el 3-β-D-ribofuranósido de la nueva imidazo[2,1-f][1,2,4]triazina es isómero e isoelectrónico con el nucleósido deaminoformicina que es un buen inhibidor de la adenosina desaminasa (ADA)



Compuesto 1



Compuesto 3

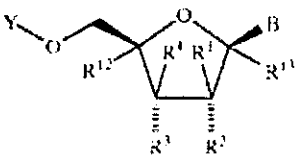


Compuesto 4

De igual forma, da a conocer que los inhibidores de la enzima desaminasa relacionada con adenosina ADA son de interés como potenciales fungicidas, y en l quimioterapia viral y del cáncer. Indicando que el isomérico ADA inhibidor (compuesto 3) es un ribóxido de purina , el cual se une a la enzima como hidrato covalente y por último refiere que un simple cambio de C-4 y N-8 del anillos pirazolo-pirimiidina (compuesto 1) da como resultado una molécula diana nueva la furanosil imidazo[2,1-f][1,2,4]triazina (compuesto 3)

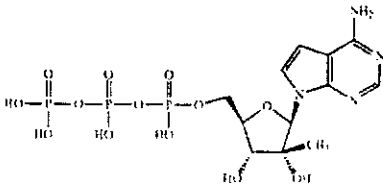
D2:http://worldwide.espacenet.com/publicationDetails/originalDocument?FT=D&date=20040408&DB=EPODOC&locale=en_EP&CC=US&NR=2004067901A1&KC=A1&ND=2 divulga(Pág. 1, Abs.) una serie de compuestos derivados nucleósidos de fórmula

l útiles como inhibidores de la replicación del ARN viral dependiente de ARN, útiles para el tratamiento de la infección por el ARN viral dependiente de ARN. Particularmente útiles como inhibidores de la polimerasa NS5B del virus de hepatitis C (VHC), como inhibidores de la replicación del VHC y para el tratamiento de la infección por hepatitis C.

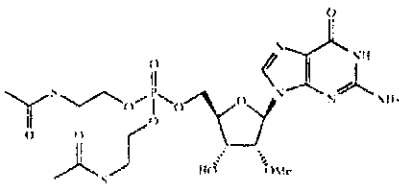


Compuesto I.

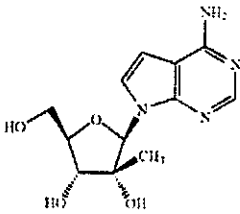
Adicionalmente, da a conocer a través de sus realizaciones preferidas los siguientes compuestos.



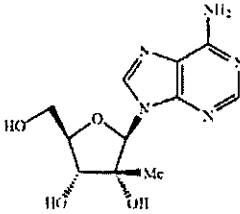
Ejemplo 129 (Pág 62, Par. [1217])



Ejemplo 73 (Pág. 45, Par. [1015])



Ejemplo 62 (Pág 41, Par. [0959])

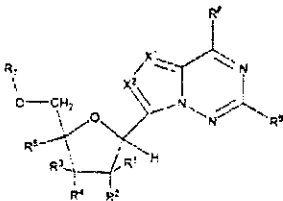


Ejemplo 52 (Pág 10, Par. [0941])

7. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

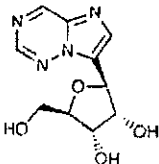
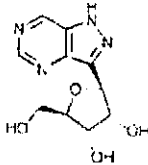
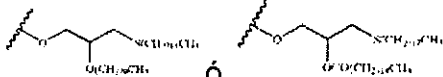
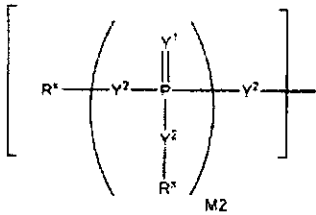
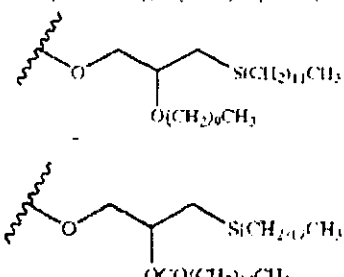
La reivindicación 1 corresponde a un compuesto de fórmula I.

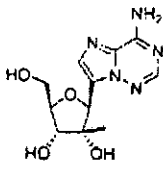
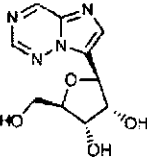
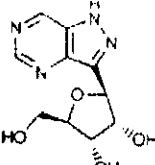
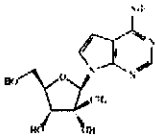
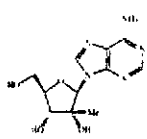
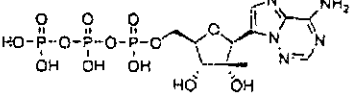
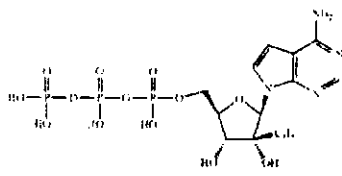
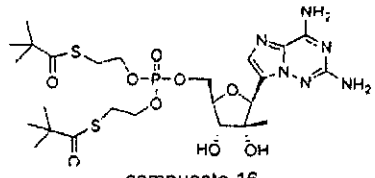
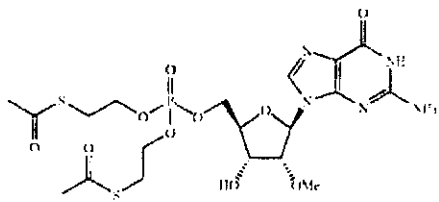


compuesto I

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Solicitud	D1	D2
Un compuesto de fórmula I compuesto I		Un compuesto de fórmula I compuesto I donde B es donde A, F y D son N ó CH y R¹³ es hidrógeno

$R^1, R^2, R^3, R^4 \text{ ó } R^5$ Al menos un R^1, R^2, R^3, R^4 o R^5 es $N(R^a)_2$, N_3, CN, NO_2, $S(O)_nR^3$, halógeno, alquilo (C_1-C_8), (C_4-C_8) carbociclitilalquil, alquilo(C_1-C_8)sustituido, alquénilo(C_2-C_8), alquénilo(C_2-C_8)sustituido, alquinilo (C_2-C_8), alquinilo(C_2-C_8) sustituido a alquilnil o arilo-alquilo (C_1-C_8) y cada restantes R^1, R^2, R^3, R^4 o R^5 es, independientemente, H, OR^a, $N(R^a)_2$, N_3, CN, NO_2, $S(O)_nR^a$, halógeno, alquilo(C_1-C_8), carbociclitilalquil (C_4-C_8), alquilo(C_1-C_8)sustituido, alquénilo(C_2-C_8), alquénilo(C_2-C_8)sustituido, alquinilo (C_2-C_8), alquinilo(C_2-C_8) sustituido a alquilnil o arilo-alquilo (C_1-C_8) ó cualquier dos R^1, R^2, R^3, R^4 o R^5 carbono adyacente átomos si se toman juntos son - $O(CO)O$ - ó cuando se toma junto con los átomos de carbono del anillo al que van unidos forman un enlace doble.	Un compuesto 3  Compuesto 3 Indica que el 3-β-D-ribofuranósido de la nueva imidazo[2,1-f][1,2,4]triazina (compuesto 3). Es isomérico e isoelectrónico con el nucleósido deaminoformicina (compuesto 1)  Compuesto 1	$R^1, R^2, R^3, R^4 \text{ ó } R^{12}$ R^1 es hidrógeno, alquilo (C_1-C_4), alquénilo(C_2-C_4) y alquinilo(C_2-C_4) opcionalmente sustituido por amino, hidroxí ó 1 a 3 átomos de fluór y uno de R^2 y R^3 es hidroxí o alcoxi (C_1-C_4) y el otro de R^2 y R^3 es seleccionado del grupo hidrógeno, hidroxí, halógeno, alquilo (C_1-C_4) opcionalmente sustituido por 1 a 3 átomos de fluór, alcoxi (C_1-C_4) opcionalmente sustituido por 1 a 3 átomos de fluór, C_2-C_6alquénilo, alquiltio (C_1-C_4), alquilcarboniltio (C_1-C_8), ariloxicarbonil, azido, amino, alquilamino(C_1-C_4) y dialquil (C_1-C_4) amino. R^2 es hidrógeno, alquilo (C_1-C_4), alquénilo(C_2-C_4) y alquinilo(C_2-C_4) opcionalmente sustituido por amino, hidroxí ó 1 a 3 átomos de fluór y uno de R^1 y R^3 es hidroxí o alcoxi (C_1-C_4) y el otro de R^1 y R^3 es seleccionado del grupo hidrógeno, hidroxí, halógeno, alquilo (C_1-C_4) opcionalmente sustituido por 1 a 3 átomos de fluór, alcoxi (C_1-C_4) opcionalmente sustituido por 1 a 3 átomos de fluór, C_2-C_6alquénilo, alquiltio (C_1-C_4), alquilcarboniltio (C_1-C_8), ariloxicarbonil, azido, amino, alquilamino(C_1-C_4) y dialquil (C_1-C_4) amino. R^4 es hidrógeno, OH, SH, amino, alquilamino(C_1-C_4), dialquil(C_1-C_4)amino, cicloalquil(C_3-C_6)amino, halógeno, alquil(C_1-C_4), alcoxi(C_1-C_4) ó CF_3 R^{12} es hidrógeno, metil, hidroximetil o fluorometil.	
R^7 H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)OR^{11}$, $S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, o 		Y H, C_{1-16}alquilcarbonil, $P_3O_5H_4$, $P_2O_4H_3$, o $P(O)R^9R^{10}$	
$Y \text{ o } Y^1$ Cada uno son O, S, NR, $*N(O)(R)$, $N(OR)$, $*N(O)(OR)$, o $N-NR_2$;		R^9 hidroxí, $OCH_2CH_2SC(=O)$alquiloC_1-C_4, $OCH_2CH_2SC(=O)$OalquiloC_1-C_4, $OCH_2O(=O)$OalquiloC_1-C_4, $NHCHMeCO_2Me$, OCH_2 (alquiloC_1-C_4), $O(C=O)$alquiloC_1-C_4.  Ó	
$W^1 \text{ y } W^2$ al ser tomados juntos, son $-Y^3/C(R^1)_2Y^2-$; o uno de W^1 o W^2 junto con R^3 o R^4 es $-Y^3-$ y el otro de W^1 ó W^2 es fórmula Ia; o W^1 y W^2 cada uno, son de forma independiente, un grupo de la fórmula Ia:  Formula Ia donde: cada Y^2 independientemente es un enlace, O, CR_2, NR, $*N(O)(R)$, $N(OR)$, $*N(O)(OR)$, $N-NR_2$, S, S-S, $S(O)$ o $S(O)_2$; cada Y^3 es independientemente O, S o NR.		R^{10} hidroxí, $OCH_2CH_2SC(=O)$alquiloC_1-C_4, $OCH_2CH_2SC(=O)$OalquiloC_1-C_4, $OCH_2O(=O)$OalquiloC_1-C_4, $NHCHMeCO_2Me$, OCH_2 (alquiloC_1-C_4), $O(C=O)$alquiloC_1-C_4.  Ó	

Solicitud	D1	D2
Realizaciones preferidas	Compuestos divulgados	Realizaciones preferidas
 compuesto 1	 Compuesto 3  Compuesto 1	 Ejemplo 62 (Pág 38)  Ejemplo 54 (Pág 36)
 compuesto 10		 Ejemplo 129 (Pág 62, Par. [1217])
 compuesto 16		 Ejemplo 73 (Pág. 41)

El documento D1 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1 porque un derivado 3-β-D-ribofuranósido imidazo[2,1-f][1,2,4]triazina inhibidores de la enzima desaminasa relacionada con adenosina ADA de interés como potencial fungicida y en las quimioterapias virales y del cáncer.

La diferencia entre la invención, definida en la reivindicación 1 y el compuesto I del documento D1 corresponde a que 1.) La invención define en la posición 5 del anillo [2,1-f][1,2,4]triazina un grupo de sustituyentes que incluyen (halógeno,amino,ciano, entre otros) y el documento D1 refiere un sustituyente hidrógeno.

La diferencia entre la invención, definida en la reivindicación 2 y el compuesto I del documento D2 corresponden a 1.) La invención define como sustituyente en la posición 2 de anillo tetrahidrofurano una base nitrogenada seleccionada entre imidazo[2,1-f][1,2,4]triazina y [1,2,4]triazolo[3,4-f][1,2,4]triazina y el documento D1 refiere como sustituyente un grupo de base nitrogenada que incluyen 9H-purina, 3H-pirazolo[4,3-d]pirimidina, 1H-pirazolo[3,4-d]pirimidina y 7H-pirrolo[3,2-d]pirimidina.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: “cómo modificar los sustituyentes del compuesto 3 del documento D1 para así obtener nuevos compuestos alternativos útiles para el tratamiento de infecciones por virus de la familia *flaviviridae*

Sin embargo, dado que el documento D1 refiere que el 3-β-D-ribofuranósido de una nueva imidazo[2,1-f][1,2,4]triazina (compuesto 3). Es isomérico e isoelectrónico con el nucleósido deaminoformicina (compuesto 1), por lo cual una persona versada en la materia entendería que el anillo imidazo[2,1-f][1,2,4]triazina es isomérico e

isoelectrónico al anillo 3H-pirazolo[4,3-d]pirimidina para los ribofuranósidos y que estos poseen actividad antiviral y que el documento D2 refiere que el anillo 3H-pirazolo[4,3-d]pirimidina puede ser sustituyente de una serie de compuestos análogos a nucleósidos inhibidores de la RNA-polimerasa viral dependiente de RNA en especial inhibidores de la replicación del virus de la hepatitis C (HCV) perteneciente a la familia *flaviviridae*.

En consecuencia, una persona del oficio normalmente versada en la materia, estaría motivada o tendría suficientemente expectativa de éxito modificar los sustituyentes del compuesto 3 del documento D1 para así obtener nuevos compuestos alternativos útiles para el tratamiento de infecciones por virus de la familia *flaviviridae* de la manera que está sugerida en el documento D2. Por lo cual la reivindicación 1 se considera obvia.

Puesto que las reivindicaciones dependientes 2-18 no mencionan características inventivas adicionales tampoco se pueden considerar inventivas.

8. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	J. Chem. Soc., Perkin Trans. 1, 1999, 2929–2936	1-18	Nivel Inventivo
D2	US 20040067901	1-18	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante (60 días) y presentarla por escrito.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.


JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 30 OCT. 2012

Elaborado por: Lenin Roberto Guerrero. 
Revisado Por: Consuelo Leguizamón Leguizamón. 
Aprobado por: José Luis Salazar López.



Synthesis of C-ribosyl imidazo[2,1-*f*][1,2,4]triazines as inhibitors of adenosine and AMP deaminases

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^a AgrEvo UK Limited, Chesterford Park, Saffron Walden, Essex, UK CB10 1XL

^b Department of Chemistry, Imperial College of Science, Technology and Medicine, London, UK SW7 2AY

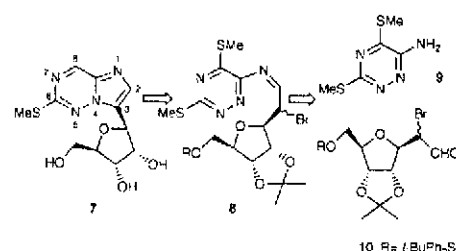
Received (in Cambridge, UK) 20th May 1999, Accepted 29th July 1999

The 3-β-D-ribofuranoside **6** of the new imidazo[2,1-*f*][1,2,4]triazine **27** is isomeric and isoelectronic with the nucleoside deaminomycin **1** which is a good inhibitor of adenosine deaminase (ADA) while its 5'-monophosphate **2** is a good inhibitor of adenosine 5'-monophosphate deaminase (AMPDA). The 6-methylsulfanyl derivative **7** of **6** is synthesized by condensation of the monocyclic 1,2,4-triazine **9** with bromo aldehyde **10**, which is accompanied by cyclization to give the protected C-nucleoside **21**; the 8-methylsulfanyl group of **21** is removed by replacement by hydrazine and oxidation. The 1,2,4-triazine **9** cyclizes similarly with chloroacetaldehyde or its dimethyl acetal to give 6,8-bis(methylsulfanyl)imidazo[2,1-*f*][1,2,4]triazine **17**, which is converted into the parent heterocycle **27** by two routes, and into mono- and di-substituted derivatives (**19**, **20**, **24**, **25**, **28–30**) of the new ring system. Riboside **7** is an inhibitor of mammalian ADA (IC_{50} 40 μM).

Inhibitors of the enzyme adenosine 5'-monophosphate deaminase (AMPDA, EC 3.5.4.6) have potential for use as herbicides¹ and in the treatment of ischaemia.² Inhibitors of the related enzyme adenosine deaminase (ADA, EC 3.5.4.4) are of interest as potential fungicides³ and in cancer and viral chemotherapy.⁴ Deaminomycin **1** and the corresponding 5'-phosphate derivative **2** have recently been shown to be good inhibitors of ADA and AMPDA, respectively.⁵ The isomeric ADA inhibitor, purine riboside **3**, binds to the enzyme as the covalent hydrate **4**⁶ and it is believed that an analogous hydration also occurs upon binding of **1** and **2** to ADA and AMPDA. Calculation of the heats of formation differences between the N7-H and N8-H tautomers of the pyrazolo-pyrimidine ring system and their corresponding covalent hydrates indicated that the less stable N8-H tautomer **5** formed the more stable hydrate.⁵ Thus, in an effort to improve inhibitory potency we have attempted to design new non-tautomeric heterocycles possessing similar electronic properties to structure **5**. Simple exchange of C-4 and N-8 of the pyrazolo-pyrimidine ring gives the furanosyl imidazo[2,1-*f*][1,2,4]triazine **6** as a new target molecule. Calculations suggested that this 10π aromatic system would readily undergo covalent hydration as

desired for biological activity.⁷ This heterocyclic ring system was unknown although various physical chemical properties of some of its derivatives have been calculated,⁸ and some related fused benzimidazo derivatives have been reported.⁹

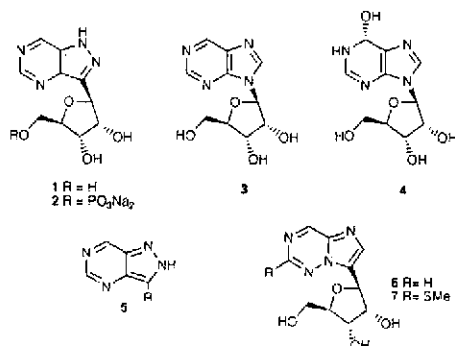
We now describe the synthesis of the imidazo[2,1-*f*][1,2,4]triazine ring system, including the parent **27**, and our biological target, the C-nucleoside **7**. The presence of the 6-methylsulfanyl group in **7** facilitated the synthesis and, based on the results of studies with substituted purines,¹⁰ should be compatible with achieving inhibition of ADA and AMPDA. Disconnection of the C3–N4 bond of **7**, with introduction of a second methylsulfanyl group for synthetic convenience, leads to the imine **8** which could be constructed from the aminotriazine **9** and the bromo aldehyde **10** (Scheme 1).



Scheme 1

Results and discussion

The bromo aldehyde **10** was synthesized from D-ribose by adapting the method used by Clingerman and Secrist in their synthesis of the related compound **10a**.¹¹ (Scheme 2). We found that whereas tritylation of the acetonide of D-ribose afforded the protected D-ribose **11a** in only modest yield (48%), silylation with *tert*-butyldiphenylsilyl chloride gave **11** in good yield (75%). Wittig reaction of the masked aldehyde **11** with the stabilized phosphorus ylide, ethyl bromo(triphenylphosphoranyliden)acetate,¹² followed by addition of DBU to aid

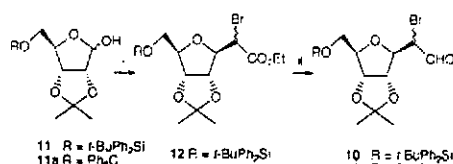


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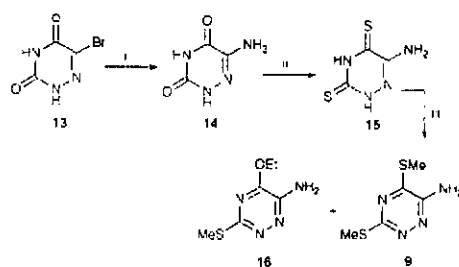
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cyclization of the open-chain compound formed, gave a good yield of the ester 12 (82%). Reduction of this ester with DIBAL-H in dry toluene at low temperature gave the desired bromo aldehyde 10 (58%) (Scheme 2).



Scheme 2 Reagents and conditions (and yields): (i) $\text{Ph}_3\text{P-CBrCO}_2\text{Et}$, reflux, 7 h; then DBU (82%); (ii) DIBAL-H, PhCH_3 , -100°C , 15 min (58% 10).

A key feature of this synthesis of the C-nucleoside 7 is the availability of aminotriazine 9 in gram quantities by a rapid and reliable method (Scheme 3).¹² 6-Azauracil was brominated in

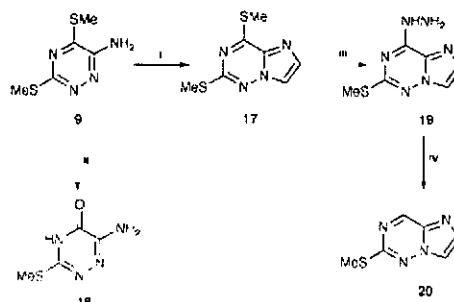


Scheme 3 Reagents and conditions (and yields): (i) NBr_3 , Cu_2O , autoclave, 80°C , 2 d (74%); (ii) P_2S_5 , py, S_d , reflux, 5 h; (iii) (a) MeI, 1M NaOH, EtOH, RT (43%); 9, 7% (16); (b) Hünig's base, MeI, DCM, RT, 16 h (52% 9 from 14).

high yield to give 13, from which the bromine was displaced by liquid ammonia in an autoclave in the presence of copper powder at 80°C to give the amine 14 in 74% yield. Attempts to simplify this procedure by working at atmospheric pressure or in a Carius tube, and with ammonium acetate in place of ammonia, all gave much lower yields of 14. Thiation was accomplished with phosphorus pentasulfide and pyridine in the presence of sulfur, but after extensive purification the dithione 15 was isolated in very low yield. Methylation of 15 with iodomethane and aqueous sodium hydroxide in ethanol gave amine 9 together with a small amount of ethoxy compound 16, though the latter could be avoided by using Hünig's base in DCM for the methylation reaction. The tedious and wasteful purification of the dithione 15 could be avoided by methylation of the crude material before purification.

The 1,2,4-triazine 9 was first converted into the heterocyclic aglycone of the C-nucleoside target for use in model desulfurization reactions. Treatment of 9 with chloroacetaldehyde and 4 Å molecular sieves at ambient temperature gave 6,8-bis-(methylsulfanyl)imidazo[2,1-f][1,2,4]triazine 17 (65%); chloroacetaldehyde dimethyl acetal in toluene with a catalytic amount of toluene-*p*-sulfonic acid at the same temperature gave a 75% yield. Desulfurization of the bis-sulfide 17 with Raney nickel¹⁴ in boiling ethanol or with nickel boride generated *in situ*¹⁵ failed to give the parent heterocycle 27. Similar reductive desulfurization of the triazine 9 with Raney nickel in boiling water resulted only in hydrolysis of the 8-methylsulfanyl group to give 18 (62%), presumably as a consequence of the electrophilicity of the triazine 5-position. With the failure of reductive desulfurization we turned to the hydrazine-oxidation method

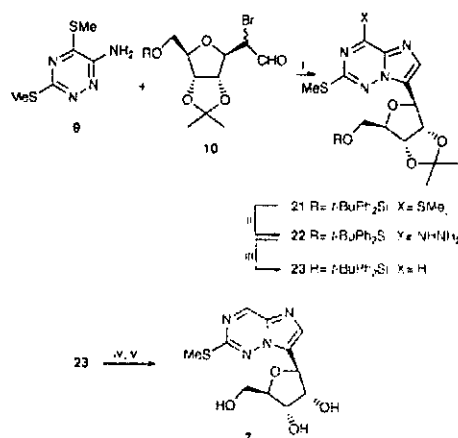
which has been used, for example, in the removal of a phenylthio group from a purine¹⁶ and a methylthio group from a 1,2,4-triazine.¹⁷ With two equiv. of hydrazine monohydrate in refluxing ethanol for 1 h, bis-sulfide 17 gave the monohydrazine 19 in high yield, an excess of hydrazine in refluxing ethanol for 12 h still gave only the monohydrazine. Subsequent experiments showed that conversion of 17 into 19 (89%) required only 1 h at room temperature. The hydrazine group was readily removed by oxidation with yellow mercuric oxide (HgO) in refluxing ethanol for 5 min to give 6-(methylsulfanyl)imidazo[2,1-f]-[1,2,4]triazine 20 (66%) (Scheme 4).



Scheme 4 Reagents and conditions (and yields): (i) $\text{C}_6\text{H}_5\text{CHO}$, 4 Å MS, RT (65%); 1 or $\text{C}_6\text{H}_5\text{CH}_2\text{CHO}$, PhCH_3 , PTSA, 60°C , 24 h (75%); (ii) R_a , H_2O , reflux, 12 h (62%); (iii) $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$, EtOH, RT, 1 h (89%); (iv) HgO , EtOH, reflux, 5 min (66%).

We now planned to apply this removal of the 8-methylsulfanyl group in the synthesis of the C-nucleoside 7, following coupling of the amine 9 with the aldehyde 10. Condensation of 9 with 10 in toluene in a Dean-Stark apparatus for 24 h was accompanied by spontaneous cyclization to give the protected C-nucleoside 21 (56%) in reasonable yield (Scheme 5). The silyl derivative gave a much cleaner reaction than the analogous trityl derivative, but it only worked well on a small scale (up to 200 mg), the yield being much reduced on a 1 g scale. However, with a mixture of toluene and HMPA as solvent at 100°C a reasonable yield of 21 (62%) was reinstated on the larger scale. The homogeneity of the ^1H and ^{13}C NMR spectra indicated that the condensation reaction gave only the β -isomer of 21. The ^{13}C data were fully consistent with the assigned stereochemistry and in particular the chemical shifts of the isopropylidene methyl groups and the quaternary carbon (δ_C 26, 28 and 115 ppm, respectively) agreed with the values reported for 1 β -substituted ribose derivatives.¹⁸ The ^1H NMR signals, at 270 MHz, for the isopropylidene methyl groups appeared at δ_H 1.37 and 1.62 ($\Delta\delta > 20$ Hz) which also supports β -stereochemistry, and $J_{1,2}$ was 3.70 Hz (usually about 0 Hz for *u*-forms). This assignment was subsequently verified by X-ray diffraction analysis of a related derivative 7 (below). Synthesis of the protected C-nucleoside 21 was now reproducible on a 1 g scale, and we next studied the removal of the 8-methylsulfanyl group. Treatment of 21 with hydrazine hydrate in refluxing ethanol for 1 h gave the monohydrazine 22 (87%), which was oxidized with yellow mercuric oxide in refluxing ethanol to give the 8-unsubstituted protected C-nucleoside 23 (72%). In contrast with the model reactions above, both of these reactions required boiling ethanol and a longer reaction time for completion. The NMR spectra of 22 and 23 were both in agreement with the β -configuration (Scheme 5).

Our first attempt at deprotection of 23 involved simultaneous removal of both protecting groups with aqueous trifluoroacetic acid,¹⁹ which proceeded only in low yield. Better was to remove the silyl group with tetrabutylammonium fluoride (TBAF) in



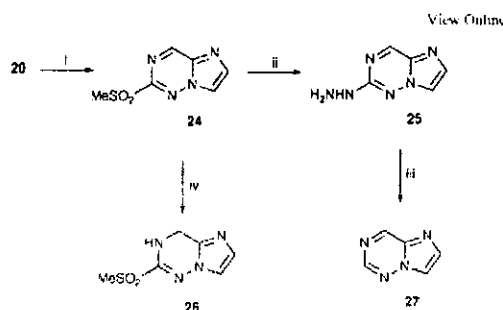
Scheme 5 Reagents and conditions (and yields): (i) PhCH_3 , K_2CO_3 , Dean Stark 24 h (56%) or PhCH_3 , HMPA, 100°C , 24 h (62%); (ii) $\text{N}_3\text{H}_4 \cdot \text{H}_2\text{O}$, EtOH, reflux, 1 h (87%); (iii) HgO , EtOH, reflux, 2 h (72%); (iv) TBAF, THF, RT, 30 min (90%), (v) 60–80% AcOH, RT, 18 h (60%).

THF (90%) followed by hydrolysis (60%) of the acetonide with aqueous acetic acid, both at room temperature, to give the final target **7** (Scheme 5). Fortunately there was no sign of acid-catalyzed addition of water (covalent hydration²⁰) at the free 8-position of the imidazotriazine. The β -configuration of *C*-nucleoside **7** was again supported by the ¹H NMR spectrum in DMSO-*d*₆ which showed the H-1' signal as a doublet at δ_H 5.16 with a coupling constant of 6.23 Hz, similar to that for the related *C*-nucleoside deaminofomycin **1** (δ 5.08, *J* 7.5 Hz).^{3,21} The structure and stereochemistry was subsequently confirmed by single-crystal X-ray diffraction.²²

Imidazo[2,1-*f*][1,2,4]triazine 27

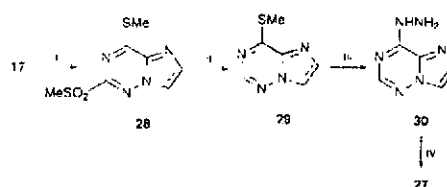
Having synthesized the C-nucleoside 7 we wished to remove the remaining methylsulfonyl group, though model studies suggested that this would be difficult. In the hope of providing a better leaving group, sulfide 20 was converted into its sulfone 24 by treatment with either *m*-chloroperoxybenzoic acid (MCPBA) in DCM or potassium permanganate in acetic acid. Both methods gave similar yields but oxidation with permanganate took only 30 min as opposed to 24 h for the peracid. Nucleophilic displacement of methylsulfonyl by hydrazine was very fast and virtually quantitative, and oxidation of the resulting hydrazine 25 with mercuric oxide gave the parent heterocyclic system, imidazo[2,1-*f*]][2,4]triazine 27 as a colourless oil in low yield (18%) (Scheme 6). Low yields are sometimes observed in the oxidation of hydrazines which afford products susceptible to covalent hydration since the hydrate can be oxidized by mercuric oxide to give the corresponding keto product, which is sometimes isolated.

We had hoped to replace the methylsulfonyl group in **24** by hydrogen in one step with NaBH_4 , following a related literature reaction,²¹ but similar treatment of **24** with NaBH_4 at room temperature gave the dihydro derivative **26** (Scheme 6) with the methylsulfonyl group intact. This parallels the ready reduction of monocyclic 1,2,4-triazines to their dihydro derivatives.²² We therefore returned to the bis-sulfide **17** and its oxidation with KMnO_4 in acetic acid: this gave only the monosulfone **28** (63%) in agreement with the exclusive oxidation of 3,5-bis(methylsulfonyl)-1,2,4-triazine to the 3-methylsulfone.²³ With both substrates the sulfur which is not oxidized is made less nucleophilic by the electron-withdrawing heteroatoms. Reduction of sulfone



Scheme 6 Reagents and conditions (and yields): (i) (a) MCPBA, DCM, RT, 24 h (52%) or KMnO_4 , AcOH, H_2O , RT, 30 min (58%), (ii) $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$, EtOH, RT, 1 min (97%); (iii) H_2O , EtOH, reflux, 10 min (18%), (iv) NaBH_4 , EtOH- CHCl_3 , RT, 10 min (34%).

28 with NaBH₄ under the Hitoshi conditions¹¹ gave the 6-unsubstituted imidazotriazine 29 (79%), no reduction of the heterocyclic ring being observed in the presence of the 8-methylsulfonyl group. This group was then removed with hydrazine hydrate in ethanol to give the hydrazine 30 (76%), followed by oxidation with mercuric oxide, to give the parent imidazotriazine 27, identical with that described above, but in slightly better yield (27%) (Scheme 7). We hope that the method



Scheme 7 Reagents and conditions (and yields): (i) KMnO_4 , AcOH , H_2O , RT, 30 min (63%); (ii) NaBH_4 , EtOH , CHCl_3 , RT, 5 min (79%); (iii) $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$, EtOH , RT, 2 h (76%); (iv) HgO , EtOH , reflux, 10 min (27%).

developed for the synthesis of **27** will be applied to the synthesis of ribofuranoside **6** in the future.

In the course of this work the new ring system, imidazo[2,1-*f*]-[1,2,4]triazine 27, has been prepared, together with several of its mono-, di- and tri-substituted derivatives including the ribofuranside 7. Preliminary biochemical studies indicate that 7 is an inhibitor of mammalian ADA (IC_{50} 40 μ M). Further details concerning biological activity will be published elsewhere.

Experimental

Tetrahydrofuran (THF) and toluene were used freshly distilled from sodium wire with benzophenone under nitrogen. All reactions were protected from moisture by calcium chloride drying tubes, unless carried out under a dry nitrogen atmosphere. Anhydrous magnesium sulfate was used for drying organic extracts, and volatiles were removed under reduced pressure. Ether refers to diethyl ether and light petroleum had boiling range 60–80 °C. All reactions and chromatography column eluents were monitored by TLC using commercial aluminium-backed thin-layer chromatography (TLC) plates (Merck Kieselgel 60 F₂₅₄). The plates were observed under UV light at 254 and 350 nm. Flash column chromatography refers to the technique described by Still²⁶ using medium pressure generated by a hand bellows or a small air compressor and was used throughout. Dry flash chromatography was carried out with suction using a water pump according to the technique described by Harwood.²⁷ Mps were determined using a Reichert

Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1710FT spectrometer and strong, medium and weak peaks are represented by s, m or w respectively. ^1H NMR spectra were recorded on JEOL GX 270 (at 270 MHz) and Bruker AM300WB (at 300 MHz) machines. ^{13}C NMR spectra were recorded on JEOL GX 270 (at 68 MHz) and Bruker AM300WB (at 76 MHz) machines. Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. Mass spectra were recorded on a VG Micromass 7070E or a VG Autospec "Q" mass spectrometer. FAB spectra were obtained using a glycerol matrix, and CI measurements were carried out using ammonia for ionization. Microanalyses were carried out on a Perkin-Elmer 2400 CHN Analyzer.

2,3-*O*-Isopropylidene-*D*-ribose²⁸

A solution of *D*-ribose (50 g, 0.33 mol) in dry acetone (800 ml) containing conc. hydrochloric acid (0.8 ml) and copper(II) sulfate monohydrate (45 g) was stirred overnight at 37 °C. The solution was neutralized by stirring with calcium hydroxide. The inorganic salts were filtered off and washed with dry acetone. The combined organic phase was concentrated *in vacuo* to give the crude product as pale yellow oil. Purification of the crude product by flash chromatography on silica gel (gradient elution: 20–30% ethyl acetate in light petroleum) gave the acetone (55.1 g, 87%) as a colourless oil; ν_{max} (NaCl/film)/ cm^{-1} 3391s (OH), 1462w, 1383s, 1327s, 1274s, 1243s, 1212s, 1116s, 1068s, 997w, 925w, 871s; δ_{H} (270 MHz; CDCl_3) 5.52 (1H, d, J 6.2 Hz, *H*-1), 5.38 (1H, s, OH), 4.77 (1H, d, J 5.8 Hz, *H*-2 or *H*-3), 4.54 (1H, d, J 6.0 Hz, *H*-3 or *H*-2), 4.35 (1H, m, *H*-4), 4.19 (1H, s, OH), 3.67 (2H, m, *H*-5), 1.45 (3H, s, CH_3), 1.29 (3H, s, CH_3); δ_{C} (76 MHz; CDCl_3) 112.19 (CCH_2), 102.75 ($\text{C}-1$), 87.66 ($\text{C}-4$), 86.72 ($\text{C}-2$), 81.51 ($\text{C}-3$), 63.49 ($\text{C}-5$), 26.35 (CH_3), 24.70 (CH_3); *m/z* (CI, NH_3) 208 (MNH_4^+ , 50%), 190 ($\text{MNH}_4^+ - \text{H}_2\text{O}$, 100), 175 ($\text{M}^+ - \text{CH}_3$, 22), 173 ($\text{M}^+ - \text{H}_2\text{O}$, 20), 68 (30) (Found: MNH_4^+ , 208.1189. Calc. for $\text{C}_5\text{H}_{10}\text{NO}_7$: MNH_4^+ , 208.1185).

5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-*D*-ribofuranose 11

A solution of 2,3-*O*-isopropylidene-*D*-ribose (4.19 g, 22.1 mmol) and imidazole (1.65 g, 24.3 mmol) in DCM (40 ml) at 0 °C was treated with *tert*-butyldiphenylsilyl chloride (6.67 g, 24.3 mmol). The reaction mixture was allowed to warm to 25 °C and was stirred for 24 h. After dilution with ether (120 ml) the reaction mixture was washed with water (50 ml) and brine (50 ml), dried (MgSO_4), concentrated, and purified by flash chromatography on silica gel (gradient elution: 5–10% ethyl acetate in light petroleum) to give the epimeric alcohols 11 (7.08 g, 75%) as a colourless oily 2:1 mixture; ν_{max} (NaCl/film)/ cm^{-1} 3431br s (OH), 3072w, 3050w, 2935s, 1590s, 1568w, 1488s, 1473w, 1429w, 1383w, 1313w, 1212w, 1212w, 1075s, 990w, 872w, 798w, 742w, 703s; δ_{H} (270 MHz; CDCl_3) 7.63–7.70 (4H, m, *ArH*), 7.39–7.48 (6H, m, *ArH*), 5.36 (1H, d, J 10.2 Hz, OH), 4.65–4.80 (2H, m, *H*-2 and *H*-3), 4.61 (1H, d, J 6.0 Hz, *H*-1), 4.27–4.50 (1H, m, *H*-4, major), 4.15–4.16 (1H, m, *H*-4, minor), 3.79–3.89 (1H, m, *H*-5a), 3.61–3.69 (1H, m, *H*-5b), 1.57 (3H, s, CH_3 , minor), 1.40 (3H, s, CH_3 , major), 1.48 (3H, s, CH_3 , minor), 1.32 (3H, s, CH_3 , major), 1.10 (9H, s, *t*-Bu); δ_{C} (76 MHz; CDCl_3) [135.76, 135.58, 130.44, 130.25, 128.13, 128.07, 127.92, 127.73] (*Ar* C), [113.04, 112.15] (CCH_2), [103.44, 98.04] ($\text{C}-1$), [87.36, 87.11] ($\text{C}-4$), [81.99, 81.68] ($\text{C}-2$), [81.30, 79.54] ($\text{C}-3$), [66.09, 65.53] ($\text{C}-5$), [26.92, 26.89] (CCH_3), [26.60, 24.71] (CH_3), [26.50, 25.00] (CH_3), [26.19, 19.16] (CCH_3); *m/z* (CI, NH_3) 446 (MNH_4^+ , 12%), 428 ($\text{MNH}_4^+ - \text{H}_2\text{O}$, 6), 411 ($\text{MNH}_4^+ - \text{H}_2\text{O}$, 10), 371 ($\text{M}^+ - \text{t}-\text{Bu}$, 2), 353 (10), 274 ($\text{M}^+ - 2\text{Ph}$), 241 (8), 221 (15), 216 (25), 199 (28), 181 (13), 161 ($\text{M}^+ - \text{OSiPh}_2\text{tBu}$, 100), 91 (28), 78 (30), 58 (24) (Found: C, 67.0; H, 7.7. $\text{C}_{34}\text{H}_{32}\text{O}_5\text{Si}$ requires C, 67.3; H, 7.5%).

Ethyl 3,6-anhydro-2-bromo-7-*O*-*tert*-butyldiphenylsilyl-2-deoxy-4,5-*O*-isopropylidene-*D*-glycero-*D*-allo- and -*D*-altro-heptonate 12

To a solution of 5-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropylidene-*D*-ribofuranose 11 (3.20 g, 7.48 mmol) in dry benzene (10 ml) was added ethyl bromotriphenylphosphoranylideneacetate¹² (4.47 g, 10.5 mmol) and the solution was heated to reflux. After 7 h, TLC indicated the disappearance of starting material 11 and the appearance of 3 new products. The reaction mixture was cooled to room temperature and DBU (1 drop) was added. After the mixture was stirred for 1 min at room temperature, TLC indicated only 2 compounds. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (gradient elution: 10–15% ether in light petroleum) to furnish a mixture of esters 12 (3.54 g, 82%) as a colourless oil; ν_{max} (NaCl/film)/ cm^{-1} 3072w, 3050w, 1746s ($\text{C}=\text{O}$, ester), 1590w, 1473s, 1429s, 1383s, 1372s, 1338w, 1264s, 1213s, 1185w, 1156s, 1114s, 1080s, 1028s, 966w, 864w, 742w, 703s; δ_{H} (270 MHz; CDCl_3) 7.68–7.74 (4H, m, *Ar* H), 7.38–7.47 (6H, m, *Ar* H), 4.73–4.83 (2H, m, *H*-4 and *H*-5), 4.54, 4.50 (1H, each d, J 3.00, 3.23 Hz, *H*-2), 4.39–4.42 (1H, m, *H*-3), 4.24–4.32 (3H, m, *H*-6 and $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.64–3.81 (2H, m, *H*-7), 1.59 (3H, s, CH_3 , major), 1.40 (3H, s, CH_3 , minor), 1.57 (3H, s, CH_3 , major), 1.38 (3H, s, CH_3 , minor), 1.30 (3H, s, CH_3 , minor), 1.11 (9H, s, *t*-Bu); δ_{C} (76 MHz; CDCl_3) 168.28 ($\text{C}=\text{O}$, ester), [135.70 (<3), 132.68, 130.04, 129.92, 127.94, 127.84] (*Ar* C), 113.59 (CCH_2), 86.05 ($\text{C}-6$), 85.91 ($\text{C}-4$), 84.29 ($\text{C}-3$ or $\text{C}-5$), 82.35 ($\text{C}-5$ or $\text{C}-3$), 64.90 ($\text{C}-7$), 62.12 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 44.59 (CHBr), 27.31 (CH_3), 27.01 (CCH_3), 25.51 (CH_3), 19.24 (CCH_3), 13.92 ($\text{CO}_2\text{CH}_2\text{CH}_3$); *m/z* (CI, NH_3) 596, 594 (MNH_4^+ , 85%), 520 ($\text{M}^+ - \text{t}-\text{Bu}$, 30), 516 ($\text{MNH}_4^+ - \text{Br}$, 100), 497 ($\text{M}^+ - \text{Br}$, 5), 441 (42), 421 (35), 383 (5), 295 (18), 274 (16), 216 (45), 196 (28), 169 (18), 91 (18), 58 (30) (Found: C, 58.9; H, 6.1. $\text{C}_{34}\text{H}_{32}\text{BrO}_5\text{Si}$ requires C, 58.2; H, 6.5). Found: MNH_4^+ , 594.1893. $\text{C}_{34}\text{H}_{32}\text{BrNO}_5\text{Si}$ requires MNH_4^+ , 594.1887).

3,6-Anhydro-2-bromo-7-*O*-*tert*-butyldiphenylsilyl-2-deoxy-4,5-*O*-isopropylidene-*D*-glycero-*D*-allo- and -*D*-altro-heptose 10

A solution of bromo ester 12 (1.14 g, 1.98 mmol) in dry toluene (10 ml) at –100 °C was treated with DIBAL-H (1.5 M in toluene; 2.63 ml, 3.95 mmol) added *via* a cannula and stirred at –100 °C for 15 min. The reaction was quenched with dry methanol (5 ml) and the resulting mixture was allowed to warm to 25 °C. A thick gelatinous mass was formed. This was filtered off (Celite pad) and washed with ether. The resulting filtrate was evaporated *in vacuo* and the residue was purified by flash chromatography on silica gel (gradient elution: 20–30% ether in light petroleum) to furnish the bromo aldehyde 10 (0.61 g, 58%) as a colourless oil; ν_{max} (NaCl/film)/ cm^{-1} 3072w, 3050w, 1732s ($\text{C}=\text{O}$, aldehyde), 1590w, 1568w, 1473s, 1463s, 1429s, 1383s, 1244w, 1214s, 1157s, 1114s, 1078s, 1008w, 999w, 971w, 920w, 824w, 742s, 705s; δ_{H} (270 MHz; CDCl_3) 9.50 (1H, d, J 2.7 Hz, CHO , major), 9.41 (1H, d, J 3.69 Hz, CHO , minor), 7.68–7.75 (4H, m, *ArH*), 7.40–7.48 (6H, m, *ArH*), 4.68–4.85 (2H, m, *H*-4 and *H*-5), 4.36–4.50 (2H, m, *H*-3 and *H*-2), 4.26–4.29 (1H, m, *H*-6), 3.70–3.88 (2H, m, *H*-7), 1.59, 1.41 (6H, each s, CH_3 , minor), 1.57, 1.39 (6H, each s, CH_3 , major), 1.12, 1.10 (9H, each s, *t*-Bu); δ_{C} (76 MHz; CDCl_3) [192.07, 190.66] (CHO), [135.72, 135.64, 132.66, 130.10, 130.02, 129.91, 129.84, 127.99] (*Ar* C), [114.73, 113.98] (CCH_2), [86.19, 85.34] ($\text{C}-6$), [84.29, 84.22] ($\text{C}-4$), [82.89, 82.73] ($\text{C}-3$ or $\text{C}-5$), [82.02, 81.44] ($\text{C}-5$ or $\text{C}-3$), [64.67, 63.95] ($\text{C}-7$), [55.95, 52.60] (CHBr), [27.51, 25.60] (CH_3), [27.38, 25.48] (CH_3), [27.05, 26.95] (CCH_3), 19.29 (CCH_3); *m/z* (CI, NH_3) 552, 550 (MNH_4^+ , 3%), 472 ($\text{MNH}_4^+ - \text{Br}$, 12), 397 (2), 377 (2), 295 (6), 241 (2), 199 (9), 181 (6), 161 (58), 129 (22), 108 (45), 91 (100), 73 (26), 61 (50), 44 (20) (Found: MNH_4^+ , 550.1631. $\text{C}_{34}\text{H}_{32}\text{BrNO}_5\text{Si}$ requires MNH_4^+ , 550.1624).

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48 (30), 43 (54) (Found: M^+ , 158.0280. $C_8H_6N_4OS$ requires M , 158.0262).

8-Hydrazino-6-(methylsulfanyl)imidazo[2,1-*f*][1,2,4]triazine 19

To a solution of bis-sulfide 17 (100 mg, 0.47 mmol) in ethanol (4 ml) was added hydrazine monohydrate (47.2 mg, 0.94 mmol) and the mixture was stirred at 25 °C for 1 h. A white precipitate was collected, and washed with ethyl acetate. The precipitate was recrystallized from ethanol to give the *title compound* 19 (82 mg, 80%) as white crystals, mp 225–226 °C (from EtOH); $\nu_{\max}$ (NaCl)/cm⁻¹ 3442br w (NH), 3328w (NH), 3134w, 1694w, 1627w, 1604s, 1568w, 1498w, 1451s, 1404s, 1347s, 1314w, 1279w, 1215s, 1179w, 1142w, 1124w, 1098w, 971w, 922s, 867w, 754s, 739s, 722w; δ_H (300 MHz; CDCl₃) 10.26 (1H, br s, NH), 7.94 (1H, s, *H*-2 or *H*-3), 7.46 (1H, s, *H*-3 or *H*-2), 4.88 (2H, br s, NH₂), 2.50 (3H, s, SCH₃); δ_C (76 MHz; CDCl₃) [162.06, 149.94, 130.62, 126.49, 117.90] (Het C), 13.84 (SCH₃); *m/z* (EI) 196 (M^+ , 46%), 181 (12), 150 (2), 133 (5), 119 (2), 109 (8), 103 (2), 94 (40), 89 (26), 84 (7), 73 (25), 68 (7), 45 (100) (Found: C, 37.6; H, 3.8; N, 42.2%; M^+ , 196.0536. $C_8H_6N_4S$ requires C, 36.7; H, 4.1; N, 42.8%; M , 196.0531).

6-(Methylsulfanyl)imidazo[2,1-*f*][1,2,4]triazine 20

To a stirred solution of the hydrazine 19 (36 mg, 0.18 mmol) in ethanol (4 ml) was added yellow mercury(II) oxide (120 mg, 0.55 mmol) at 25 °C. The reaction mixture was heated to reflux for 5 min, cooled and the inorganic residue was removed (Celite pad), washed with ethanol and the filtrate was evaporated *in vacuo* to give a pale yellow solid. Purification of the solid by flash chromatography on silica gel (gradient elution: 30–40% ether in light petroleum) afforded the *title compound* 20 (20 mg, 66%) as crystals, mp 129–130 °C (from DCM–light petroleum); $\nu_{\max}$ (NaCl)/cm⁻¹ 1694w, 1629w, 1584w, 1316w, 1290w, 1116w, 910w, 755w, 740w, 662w; δ_H (300 MHz; CDCl₃) 9.02 (1H, s, *H*-5), 7.93 (1H, s, *H*-2 or *H*-3), 7.84 (1H, s, *H*-3 or *H*-2), 2.61 (1H, s, SCH₃); δ_C (76 MHz; CDCl₃) [163.42, 149.38, 135.41, 134.19, 117.52] (Het C), 14.22 (SCH₃); *m/z* (CI, NH₃) 184 (MNH₂⁺, 3%), 167 (MH⁺, 100), 153 (2), 138 (3), 121 (6), 96 (7), 69 (4), 45 (2) (Found: C, 43.7; H, 3.3; N, 33.6. $C_8H_6N_4S$ requires C, 43.4; H, 3.6; N, 33.7%).

3-(5'-*O*-*tert*-Butyldiphenylsilyl-2',3'-*O*-isopropylidene-β-D-ribofuranosyl)-6-bis(methylsulfanyl)imidazo[2,1-*f*][1,2,4]triazine 21

Method A. A mixture of bromo aldehyde 10 (664 mg, 1.25 mmol), amine 9 (234 mg, 1.25 mmol) and anhydrous K₂CO₃ (208 mg, 1.50 mmol) in dry toluene (80 ml) was stirred at reflux with azeotropic removal of water (Dean–Stark trap) for 24 h. After the solution was cooled to 25 °C, excess of solvent was removed *in vacuo* to give a dark residue. This was purified by flash chromatography on silica gel (gradient elution: 10–15% ether in light petroleum) to furnish the *title compound* 21 (434 mg, 56%) as pale yellow foam; $\nu_{\max}$ (NaCl)/cm⁻¹ 3071w, 1694w, 1631w, 1574w, 1516w, 1441s, 1372w, 1352w, 1214w, 1154s, 1114s, 1080s, 952w, 863w, 704s; δ_H (270 MHz; CDCl₃) 7.63–7.69 (4H, m, ArH), 7.60 (1H, s, *H*-2), 7.32–7.43 (6H, m, ArH), 5.39 (1H, d, *J* 4.9 Hz, *H*-1'), 4.97 (1H, dd, *J* 6.58, 4.85 Hz, *H*-2'), 4.82 (1H, dd, *J* 6.47, 3.70 Hz, *H*-3'), 4.24–4.27 (1H, m, *H*-4'), 3.84, 3.86 (2H, m, *H*-5'), 2.67 (3H, s, SCH₃), 2.52 (3H, s, SCH₃), 1.62 (3H, s, CH₃), 1.37 (3H, s, CH₃), 1.05 (9H, s, 'Bu); δ_C (76 MHz; CDCl₃) [163.47, 161.46, 135.63, 129.79, 127.74] (Het C), [135.63, 133.15, 131.42, 127.70] (Ar C), 114.58 (CCH₃), 84.87 (C-4'), 83.97 (C-3'), 82.14 (C-2'), 77.27 (C-1'), 64.07 (C-5'), 27.62 (CH₃), 26.86 [C(CH₃)₂], 25.62 (CH₃), 19.28 [C(CH₃)₂], 14.20 (SCH₃), 11.83 (SCH₃); *m/z* (FAB, NBA) 623 (MH⁺, 100%), 507 (7), 295 (25), 267 (4), 237 (6), 225 (12), 197 (19), 135 (42), 120 (6), 105 (7), 91 (14), 69 (17), 57 (29) (Found: C, 58.6; H, 5.5; N, 8.05. $C_{31}H_{36}N_4O_4S_2Si$

requires C, 59.8; H, 6.15; N, 9.0%. Found: MH⁺, 623.2182. $C_{31}H_{36}N_4O_4S_2Si$ requires M/H , 623.2111).

Method B. To a stirred solution of amine 9 (1.20 g, 6.38 mmol) in HMPA (6 ml) was added a solution of aldehyde 10 (1.40 g, 6.38 mmol) in dry toluene (16 ml). The reaction mixture was stirred at 100 °C for 18 h under nitrogen and then allowed cool to 25 °C. Excess of solvent was removed *in vacuo* to give a dark residue. This was dissolved in water and the aqueous solution was extracted with ethyl acetate (3 × 40 ml). The combined organic extract was washed successively with water and brine, dried (MgSO₄), and concentrated *in vacuo* to give the crude product. The residue was purified by flash chromatography on silica gel (gradient elution: 10–15% ether in light petroleum) to afford the *title compound* 21 (2.46 g, 62%) which was identical to that described above.

3-(5'-*O*-*tert*-Butyldiphenylsilyl-2',3'-*O*-isopropylidene-β-D-ribofuranosyl)-8-hydrazino-6-(methylsulfanyl)imidazo[2,1-*f*][1,2,4]triazine 22

To a solution of bis-sulfide 21 (50.9 mg, 0.08 mmol) in ethanol (2 ml) was added hydrazine monohydrate (0.02 ml, 0.70 mmol). The solution was stirred and heated under reflux for 1 h. The reaction mixture was allowed to cool to 25 °C and concentrated *in vacuo*. The residue was dissolved in DCM (6 ml), washed with water, dried (MgSO₄), concentrated *in vacuo* and purified by flash chromatography on silica gel (ether as eluent) to furnish the *title compound* 22 (43.1 mg, 87%) as a colourless foam; $\nu_{\max}$ (NaCl)/cm⁻¹ 3442br s (NH), 2931w, 2858w, 1694s, 1631s, 1603s, 1443s, 1428s, 1353s, 1265s, 1113s, 1079s, 863w, 703s; δ_H (270 MHz; CDCl₃) 7.63–7.69 (4H, m, ArH), 7.54 (1H, s, *H*-2), 7.31–7.40 (6H, m, ArH), 5.35 (1H, d, *J* 4.85 Hz, *H*-1'), 5.02 (1H, dd, *J* 6.47, 4.85 Hz, *H*-2'), 4.82 (1H, dd, *J* 6.47, 3.69 Hz, *H*-3'), 4.24–4.25 (1H, m, *H*-4'), 3.84, 3.86 (2H, m, *H*-5'), 2.48 (3H, s, SCH₃), 1.62 (3H, s, CH₃), 1.37 (3H, s, CH₃), 1.05 (9H, s, 'Bu); δ_C (76 MHz; CDCl₃) [162.60, 151.39, 135.59, 133.23, 129.70] (Het C), [135.59, 133.23, 127.65, 126.75] (Ar C), 114.46 (CCH₃), 84.75 (C-4'), 83.83 (C-3'), 82.20 (C-2'), 77.24 (C-1'), 64.11 (C-5'), 27.57 (CH₃), 26.81 [C(CH₃)₂], 25.59 (CH₃), 19.23 [C(CH₃)₂], 13.99 (SCH₃); *m/z* (FAB, NBA) 607 (MH⁺, 100%), 577 (4), 491 (4), 379 (15), 264 (4), 197 (22), 183 (4), 163 (12), 135 (54), 121 (12), 95 (18), 57 (58) (Found: MH⁺, 607.2537. $C_{30}H_{36}N_4O_4SSi$ requires M/H , 607.2523).

3-(5'-*O*-*tert*-Butyldiphenylsilyl-2',3'-*O*-isopropylidene-β-D-ribofuranosyl)-6-(methylsulfanyl)imidazo[2,1-*f*][1,2,4]triazine 23

A solution of the hydrazine 22 (1.04 g, 1.72 mmol) in ethanol (60 ml) at room temperature was treated with yellow mercury(II) oxide (1.12 g, 5.15 mmol). The dark solution was heated to reflux for 2 h. After being cooled to 25 °C, the inorganic residue was removed through a pad of Celite and washed with ethanol, and the combined solution concentrated *in vacuo* to give the crude product as a yellow foam. This was purified by flash chromatography on silica gel (gradient elution: 5–10% ether in light petroleum) to furnish the *title compound* 23 (712 mg, 72%) as a colourless foam; δ_H (300 MHz; CDCl₃) 9.00 (1H, s, *H*-8), 7.80 (1H, s, *H*-2), 7.64–7.70 (4H, m, ArH), 7.33–7.44 (6H, m, ArH), 5.46 (1H, d, *J* 4.99 Hz, *H*-1'), 4.98 (1H, dd, *J* 6.38, 5.10 Hz, *H*-2'), 4.86 (1H, dd, *J* 6.10, 3.59 Hz, *H*-3'), 4.30–4.31 (1H, m, *H*-4'), 3.87–3.89 (2H, m, *H*-5'), 2.56 (3H, s, SCH₃), 1.65 (3H, s, CH₃), 1.39 (3H, s, CH₃), 1.07 (9H, s, 'Bu); δ_C (76 MHz; CDCl₃) [163.56, 149.36, 135.62, 129.85, 127.73] (Het C), [134.67, 134.13, 132.89, 128.00] (Ar C), 114.67 (CCH₃), 84.92 (C-4'), 83.94 (C-3'), 82.12 (C-2'), 77.25 (C-1'), 64.08 (C-5'), 27.62 (CH₃), 26.86 [C(CH₃)₂], 25.60 (CH₃), 19.29 [C(CH₃)₂], 14.27 (SCH₃); *m/z* (FAB, NBA) 577 (MH⁺, 100%), 549 (3), 519 (4), 461 (7), 369 (6), 313 (2), 290 (5), 273 (4), 249 (25), 221 (4), 197 (17), 150 (18), 135 (52), 120 (20), 105 (18),

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91 (36), 77 (40), 69 (74), 55 (68) (Found: M^+ , 577.2321. $C_{36}H_{17}N_4O_5S$ requires M^+ , 577.2305).

3-(2',3'-O-Isopropylidene- β -D-ribofuranosyl)-6-(methylsulfanyl)-imidazo[2,1-f][1,2,4]triazine

A solution of silyloxy compound 23 (211 mg, 0.37 mmol) in dry THF (12 ml) was treated with n -Bu₄NF (TBAF; 0.73 ml of a 1 M solution in THF, 0.73 mmol) and stirred at 25 °C for 30 min. After dilution of the mixture with ether (20 ml), water (20 ml) was added. The organic layer was separated, washed with brine (10 ml), dried (MgSO₄), concentrated, and purified by flash chromatography on silica gel (gradient elution: 60–70% ether in light petroleum) to give the title compound (111 mg, 90%) as a white solid, mp 92–93 °C (from DCM–light petroleum); ν_{max} (NaCl/film)/cm⁻¹: 3441w (OH), 2935w, 2876w, 1694w, 1628w, 1591s, 1531s, 1471s, 1422s, 1382s, 1342s, 1304s, 1274w, 1214s, 1157w, 1122s, 1078s, 921w, 862w, 763w, 735w, 662w; δ_H (270 MHz; CDCl₃) 8.99 (1H, s, H-8), 7.82 (1H, s, H-2), 5.31 (1H, d, J 5.54 Hz, H-1'), 5.16 (1H, dd, J 6.58, 5.54 Hz, H-2'), 4.96 (1H, dd, J 6.59, 3.70 Hz, H-3'), 4.25–4.27 (1H, m, H-4'), 3.89–3.90 (2H, m, H₂-5'), 2.91–3.22 (1H, m, OH), 2.62 (3H, s, SCH₃), 1.62 (3H, s, CH₃), 1.37 (3H, s, CH₃); δ_C (68 MHz; CDCl₃) [163.89, 149.65, 135.13, 135.05, 126.73] (Het C), 114.95 (CCH₃), 84.78 (C-4'), 82.51 (C-3'), 81.68 (C-2'), 77.72 (C-1'), 62.61 (C-5'), 27.54 (CH₃), 25.43 (CH₃), 14.25 (SCH₃); m/z (FAB, NBA) 339 (M^+ , 20%), 282 (24), 242 (100), 197 (6), 135 (22), 121 (15), 91 (50), 69 (42), 55 (48) (Found: M^+ , 339.1144. $C_{14}H_{19}N_4O_5S$ requires M^+ , 339.1127).

6-Methylsulfanyl-3- β -D-ribofuranosylimidazo[2,1-f][1,2,4]-triazine 7

A solution of 3-(2',3'-O-isopropylidene- β -D-ribofuranosyl)-6-(methylsulfanyl)imidazo[2,1-f][1,2,4]triazine (50.9 mg, 0.15 mmol) in a mixture of glacial acetic acid (2 ml) and water (1 ml) was stirred at 25 °C for 18 h. The solvent was removed *in vacuo* to dryness. The residue was recrystallized from ethanol to yield the title compound 7 (27 mg, 60%) as white crystals, mp 227–228 °C (from EtOH); ν_{max} (NaCl/Nujol)/cm⁻¹: 3441 (OH), 3202 (OH), 1693w, 1630w, 1595s, 1529w, 1311s, 1225s, 1172w, 1116s, 1069w, 1040w, 985w, 957w, 931w, 774w; δ_H (270 MHz; DMSO- d_6 + D₂O) 9.14 (1H, s, H-8), 7.97 (1H, s, H-2), 5.16 (1H, d, J 6.23 Hz, H-1'), 4.42 (1H, dd, J 6.00, 5.55 Hz, H-2'), 4.00–4.08 (1H, m, H-3'), 3.90–3.91 (1H, m, H-4'), 3.52–3.58 (2H, m, H₂-5'), 2.60 (3H, s, SCH₃); δ_C (76 MHz; DMSO- d_6) [163.29, 150.31, 135.37, 135.03, 129.26] (Het C), 85.20 (C-4'), 74.95 (C-1'), 73.79 (C-2'), 71.68 (C-3'), 62.19 (C-5'), 14.45 (SCH₃); m/z (FAB, NBA) 299 (M^+ , 40%), 273 (5), 242 (6), 192 (22), 165 (18), 150 (40), 135 (65), 124 (28), 120 (45), 105 (32), 89 (90), 77 (100), 69 (20), 63 (52), 51 (55) (Found: C, 44.3; H, 4.5; N, 18.7. $C_{11}H_{14}N_4O_5S$ requires C, 44.3; H, 4.7; N, 18.8%. Found: M^+ , 299.0809. $C_{11}H_{14}N_4O_5S$ requires M^+ , 299.0814).

6-(Methylsulfanyl)imidazo[2,1-f][1,2,4]triazine 24

Method A. A solution of sulfide 20 (50 mg, 0.30 mmol) in glacial acetic acid (1 ml) was added to a stirred solution of KMnO₄ (95 mg, 0.60 mmol) in a mixture of glacial acetic acid (0.5 ml) and water (0.5 ml) at 0 °C. The resulting mixture was allowed to warm to 25 °C and stirred vigorously for 30 min. The dark solution was extracted with ethyl acetate (3 $\times$ 10 ml) and the combined organic extract was washed successively with 1 M NaOH and brine. After drying (MgSO₄) and evaporation of volatiles *in vacuo*, the residue was purified by flash chromatography on silica gel (gradient elution: 30–40% ethyl acetate in light petroleum) to give the sulfone 24 (35 mg, 58%) as pale yellow crystals, mp 185–190 °C (from DCM–light petroleum); ν_{max} (NaCl/Nujol)/cm⁻¹: 1695s, 1591w, 1307s, 1264w, 1139s (SO₂), 1113w, 1074w, 899s, 779s, 750w; δ_H (300 MHz; CDCl₃) 9.41 (1H, s, H-8), 8.31 (1H, s, H-2 or H-3), 8.25 (1H, d, J 0.91

Hz, H-3 or H-2), 3.45 (3H, s, SO₂CH₃); δ_C (76 MHz; CDCl₃) [157.78, 151.07, 139.69, 135.11, 119.55] (Het C), 40.26 (SO₂CH₃); m/z (CI, NH₃) 216 (MNH_4^+ , 100%), 199 (M^+ , 98), 183 (M^+ – CH₃, 2), 138 (10), 130 (15), 121 (48), 96 (4), 88 (6), 69 (4) (Found: M^+ , 199.0296. $C_6H_7N_4O_2S$ requires M^+ , 199.0290).

Method B. A solution of the sulfide 20 (36 mg, 0.22 mmol) in DCM (1 ml) was added to a stirred suspension of MCPBA (172 mg of a 50% mixture with *m*-chlorobenzoic acid, 0.5 mmol) in DCM (2 ml) at 0 °C. The resulting mixture was allowed to warm to 25 °C and stirred vigorously for 24 h. The organic mixture was evaporated *in vacuo* and the residue was purified by flash chromatography on silica gel (gradient elution: 20–30% ethyl acetate in light petroleum) to give the sulfone 24 (22 mg, 52%) which was identical to that described above.

6-Hydrazinoimidazo[2,1-f][1,2,4]triazine 25

To a stirred solution of sulfone 24 (20 mg, 0.10 mmol) in ethanol (0.5 ml) was added hydrazine monohydrate (6 mg, 0.10 mmol) at 25 °C. The reaction mixture was stirred for 1 min and excess of solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient elution: 2–5% MeOH in DCM) followed by recrystallization from EtOH to afford the hydrazine 25 (52 mg, 97%) as a white solid, ν_{max} (NaCl/film)/cm⁻¹: 3303br s (NH₂), 1667s, 1652s, 1623s, 1538w, 1481w, 1376w, 1142w, 993w, 761w, m/z (EI) 150 (M^+ , 100%), 135 (40), 121 (40), 93 (38), 80 (30), 67 (42), 43 (22) (Found: M^+ , 150.0647. $C_5H_6N_6$ requires M^+ , 150.0654).

6-Methylsulfonyl-7,8-dihydroimidazo[2,1-f][1,2,4]triazine 26

A solution of sulfone 24 (30 mg, 0.15 mmol) in a mixture of chloroform (0.5 ml) and EtOH (0.5 ml) at 25 °C was treated with NaBH₄ (8.63 mg, 0.23 mmol) in small portions. The reaction mixture was stirred for 10 min and then quenched with water (0.1 ml). Excess of solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (gradient elution: 2–5% MeOH in DCM) to afford the dihydro sulfone 26 (10 mg, 34%) as a white solid, δ_H (270 MHz; CDCl₃) 7.25 (1H, d, J 1.62 Hz, H-2 or H-3), 7.01 (1H, d, J 1.61 Hz, H-3 or H-2), 4.79 (2H, s, H₂-8), 3.31 (3H, s, SO₂CH₃); m/z 200 (M^+ , 76%), 165 (8), 151 (8), 121 (M^+ – SO₂CH₃, 20), 111 (35), 97 (52), 81 (95), 69 (78), 57 (100), 43 (82) (Found: M^+ , 200.0383. $C_6H_8N_4O_2S$ requires M^+ , 200.0368).

8-Methylsulfanyl-6-(methylsulfonyl)imidazo[2,1-f][1,2,4]-triazine 28

A solution of bis-sulfide 17 (166 mg, 0.78 mmol) in glacial acetic acid (1 ml) was added to a stirred solution of KMnO₄ (248 mg, 1.57 mmol) in a mixture of glacial acetic acid (1 ml) and water (8 ml) at 0 °C. The resulting mixture was allowed to warm to 25 °C and stirred vigorously for 30 min. The dark solution was extracted with ethyl acetate (3 $\times$ 20 ml) and the combined organic extract was washed successively with 1 M NaOH and brine. After drying (MgSO₄) and evaporation of solvent *in vacuo*, the residue was purified by flash chromatography on silica gel (gradient elution: 30–40% ethyl acetate in light petroleum) to give the sulfone 28 (120 mg, 63%) as pale yellow crystals, mp 202–203 °C (from DCM–light petroleum); ν_{max} (NaCl/Nujol)/cm⁻¹: 3020w, 2927w, 1693s, 1607w, 1566w, 1538w, 1467w, 1427s, 1406s, 1354w, 1315s, 1268w, 1190w, 1133s (SO₂), 1070w, 1041w, 967w, 883w, 665w; δ_H (270 MHz; CDCl₃) 8.04 (1H, d, J 1.15 Hz, H-2 or H-3), 7.90 (1H, d, J 0.92 Hz, H-3 or H-2), 3.39 (3H, s, SO₂CH₃), 2.80 (3H, s, SCH₃); δ_C (76 MHz; CDCl₃) [165.02, 153.78, 133.29, 131.11, 116.46] (Het C), 37.52 (SO₂CH₃), 9.99 (SCH₃); m/z (EI) 244 (M^+ , 45%), 165 (M^+ – SO₂CH₃, 100), 151 (2), 138 (7), 123 (60), 119 (25), 94 (30), 93 (45), 69 (15), 47 (8) (Found: C, 34.75; H, 3.0; N, 22.6%;

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M^+ , 244.0086. $C_7H_8N_4O_2S_2$ requires C, 34.4; H, 3.3; N, 22.9%; M , 244.0089).

8-(Methylsulfonyl)imidazo[2,1-*f*][1,2,4]triazine 29

A solution of sulfone 28 (36 mg, 0.15 mmol) in a mixture of chloroform (0.6 ml) and EtOH (0.6 ml) at room temperature was treated with $NaBH_4$ (11 mg, 0.30 mmol) in small portions. The reaction mixture was stirred for 5 min and then quenched with water (0.2 ml). Excess of solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (gradient elution; 5–15% ethyl acetate in light petroleum) to afford the sulfide 29 (19.5 mg, 79%) as a pale yellow solid, mp 114–116 °C (from DCM/light petroleum); $\nu_{max}(NaCl/NaClO_4)/cm^{-1}$ 1692s, 1607w, 1579w, 1538w, 1482w, 1430s, 1410s, 1370s, 1340w, 1314w, 1142w, 908w, 864w, 748w; δ_H (270 MHz, $CDCl_3$) 8.45 (1H, s, *H*-6), 7.88 (1H, d, *J* 1.15 Hz, *H*-2 or *H*-3), 7.74 (1H, d, *J* 0.93 Hz, *H*-3 or *H*-2), 2.70 (3H, s, SCH_3); δ_C (76 MHz, $CDCl_3$) [164.90, 146.92, 133.35, 132.69, 117.49] (HeI ϵ), 11.83 (SCH_3); m/z (EI) 166 (M^+ , 85%), 139 (10), 112 (10), 95 (30), 94 (60), 93 (100), 70 (55), 65 (20), 45 (22) (Found: M^+ , 166.0317. $C_8H_8N_4S$ requires M , 166.0313).

8-Hydrazinoimidazo[2,1-*f*][1,2,4]triazine 30

To a stirred solution of sulfide 29 (60 mg, 0.36 mmol) in ethanol (1 ml) was added hydrazine monohydrate (22 mg, 0.43 mmol) at 25 °C. The reaction was stirred for 2 h and excess of solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient elution; 2–5% MeOH in DCM) followed by recrystallization from EtOH to afford the hydrazine 30 (41 mg, 76%) as a white solid, mp 205–210 °C (decomp); $\nu_{max}(NaCl/NaClO_4)/cm^{-1}$ 3289w, 3116w, 3103 (NH), 1682w, 1682w, 1661w, 1608w, 1505w, 1417w, 1349s, 1274w, 1140w, 1089w, 1041w, 920w, 773w, 646s; δ_H (270 MHz, $DMSO-d_6$) 10.08 (1H, br s, NH), 8.12 (1H, s, *H*-6), 8.02 (1H, s, *H*-2 or *H*-3), 7.53 (1H, d, *J* 0.70 Hz, *H*-3 or *H*-2), 4.95 (2H, br s, NH_2); δ_C (76 MHz, $DMSO-d_6$) [151.56, 149.23, 130.92, 128.09, 118.07] (HeI ϵ); m/z (EI) 150 (M^+ , 70%), 121 (65), 105 (35), 94 (100), 77 (20), 67 (40), 53 (50), 43 (45).

Imidazo[2,1-*f*][1,2,4]triazine 27

Method A. A solution of the hydrazine 25 (50 mg, 0.33 mmol) in ethanol (1 ml) at room temperature was treated with yellow mercury(II) oxide (214 mg, 0.99 mmol). The dark solution was heated gently for 10 min. After being cooled to 25 °C, the inorganic residue was removed through a pad of Celite, washed with ethanol and the combined solution concentrated *in vacuo* to give the crude product as a yellow oil. This was purified by flash chromatography on silica gel (ether as eluent) to furnish the title compound 27 (7 mg, 18%) as an oil; $\nu_{max}(NaCl/NaClO_4)/cm^{-1}$ 1691s, 1608w, 1580w, 1482w, 1370s, 1314w, 1142w, 863w, 752w; δ_H (270 MHz, $CDCl_3$) 9.10 (1H, s, *H*-8), 8.52 (1H, s, *H*-6), 7.80 (1H, d, *J* 1.10 Hz, *H*-2 or *H*-3), 7.73 (1H, d, *J* 0.96 Hz, *H*-3 or *H*-2); m/z (EI) 120 (M^+ , 25%), 93 (100), 70 (32), 45 (22) (Found: M^+ , 120.1608. $C_7H_4N_4$ requires M , 120.1616).

Method B. A solution of the hydrazine 30 (35 mg, 0.23 mmol) in ethanol (1 ml) at room temperature was treated with yellow mercury(II) oxide (150 mg, 0.69 mmol). The dark solution was heated gently for 10 min. After being cooled to 25 °C, the inorganic residue was removed through a pad of Celite and washed with ethanol, and the combined solution concentrated *in vacuo* to give the crude product as a yellow oil. This was purified by flash chromatography on silica gel (ether as eluent)

to furnish the title compound 27 (8 mg, 27%) as an oil which was identical with that described above.

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