1,3-Dipolar cycloaddition approach to the construction of new bis-heterocycles from thymine as potential non-nucleoside reverse transcriptase inhibitors

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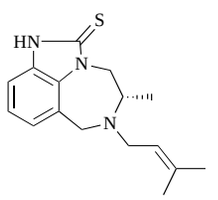
In the search for new anti-HIV agents, a synthetic route to novel acyclic (flexible) and tricyclic bis-heterocycles has been explored involving in the key steps the [3 + 2] cycloaddition reaction of the N-3 thymine-substituted enamines 34, 36 and 39 with the nitrile oxide 11, and the ring closure of the isoxazole amide derivatives 49 and 51 to the diazepine 10a, and the diazocine 10b. A number of competing reactions were also encountered during the construction of compounds 10. These include a fragmentation process wherein the 1-azadienes 38 and 46 are formed, and base-promoted rearrangement of the isoxazole ring in intermediates 50 and 59 to give the bicyclic thymine derivative 53 and the tricyclic succinimide derivative 60, respectively. Radical cyclisation of the guanidine amide 52 to isoxazole 57 on reaction with isoamyl nitrite in warm DMF was also observed.

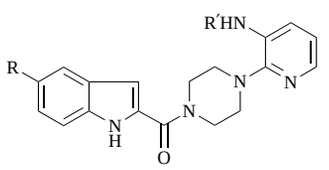
Introduction

Following the discovery of HIV-1 as the causative agent of AIDS[1,2] enormous efforts have been made to gain a detailed understanding of the mechanism of replication of this virus and thereby to define biochemical targets for selective interaction with chemotherapeutic agents. Reverse transcriptase (RT), the HIV encoded polymerase, and an integral feature of the intact virus particle, was one of the first HIV components to be identified as a target for the development of anti-AIDS drugs.[3] Initial efforts in the search for effective RT inhibitors were largely focused upon an evaluation of nucleoside analogues. From this research AZT,[4] ddI,[5] ddC,[6] and certain other 2′,3′-dideoxynucleosides have emerged.[7] These compounds, as their triphosphate derivatives, are competitive inhibitors of RT and/or alternative substrates. In the latter case they act as chain terminators upon incorporation into the growing DNA strand.[8]

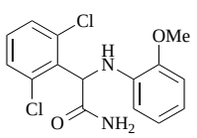
Further broad screening has subsequently revealed that a number of structurally diverse heterocycles, unrelated to nucleosides, are highly potent non-competitive inhibitors of RT. TIBO **1**,[9] BHAP **2**,[10] the APA **3**,[11] the 2-pyridone L-697,661 **4**,[12] and nevirapine **5**[13] are representative of this class of molecules, and all bind to HIV-1 RT (RT_1) at an 'allosteric' site adjacent to the catalytic site for DNA synthesis. The pronounced selectivity of these non-nucleoside reverse transcriptase inhibitors (NNRTIs) toward RT_1, and, in particular, their very low toxicities suggests that, in contrast to AZT, they do not show any affinity for human DNA polymerases. Although HIV strains resistant to NNRTIs have emerged rapidly in monotherapeutic clinical trials (due to point mutations within the allosteric site),[14] the results of an increasing number of biochemical and clinical studies in which different NNRTIs are employed in combination with each other or with AZT *etc.* are highly encouraging.[15] Further development of this strategy will require the continued discovery of new NNRTIs, particularly those which are active against the mutant HIV strains and HIV-2.



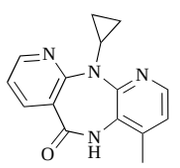
TIBO **1**



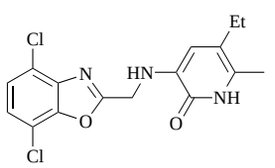
BHAP **2**



APA **3**



Nevirapine **5**



2-Pyridone L-697,661 **4**

A cursory look at the structure of NNRTIs reveals: (i) the presence of one or more heterocyclic rings containing or connected to an amide (thioamide) function, and (ii) that active molecules may either be conformationally constrained as in TIBO and nevirapine or possess heterocyclic rings linked by a more flexible acyclic spacer (*e.g.* L-697,661, BHAP and APA). In the search for new compounds which interact with the allosteric binding domain of RT, we initiated a programme to prepare novel bis-heterocyclic systems which incorporate these basic features in their structure. The synthetic strategy developed in this work is based upon the use of [3 + 2] cycloaddition reactions of different 1,3-dipoles with thymine deriv-

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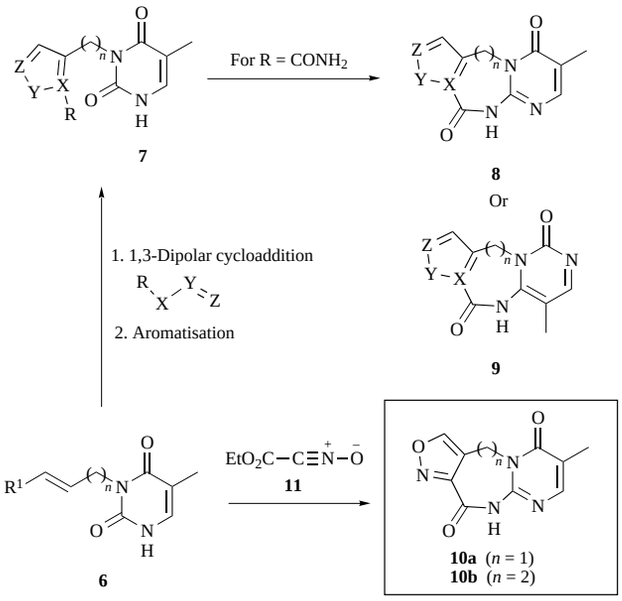


Scheme 1

atives such as **6** (Scheme 1). In this way flexible molecules of type **7**, and constrained systems represented by **8** and **9**, can be accessed from a common starting material, and the potential exists to vary widely the structure of one of the heteroaromatic ring components.

In this paper the discussion is specifically focused upon preparative studies directed toward the tricyclic isoxazoles **10a** ($n = 1$), and **10b** ($n = 2$) by 1,3-dipolar cycloaddition of the ethoxycarbonyl-substituted nitrile oxide **11** (generated from ethyl chloro(hydroxyimino)acetate[16]) with N-3 allyl and homoallyl thymine derivatives followed by B ring closure. A number of competing reaction processes encountered during the construction of these nevirapine-like compounds are also discussed.

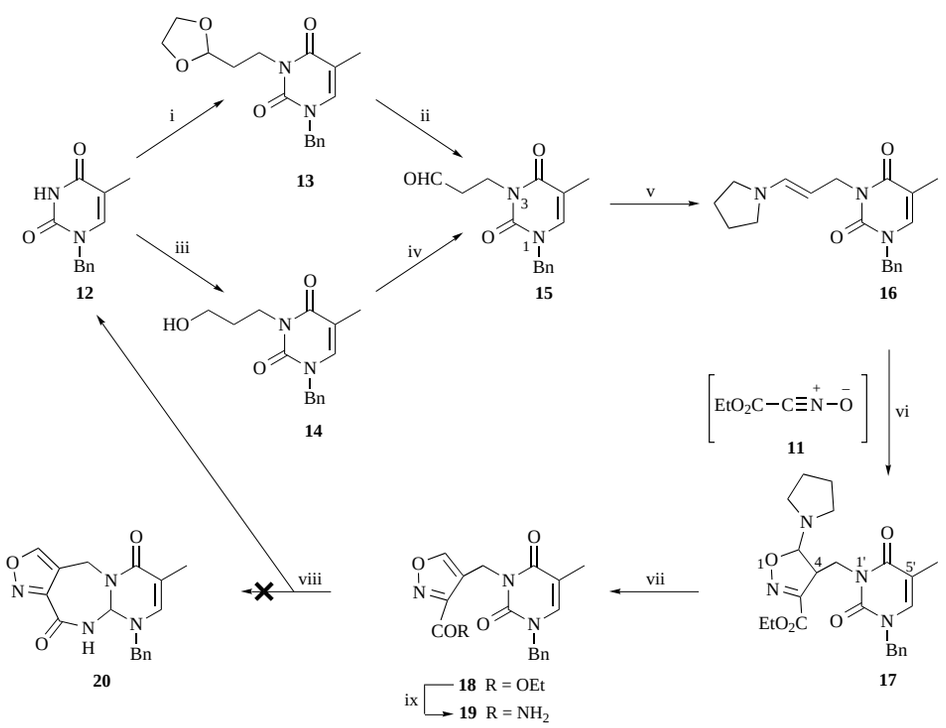
Results and discussion

To synthesize compounds **10** according to the plan in Scheme 1 necessitates: (i) selective introduction of the olefinic side chain at N-3 of thymine, (ii) control of the regiochemistry in the cycloaddition step, and (iii) activation of the C-2 position of the thymine ring such that the intramolecular condensation process which creates the *N*-acylguanidine system in the target molecule can occur under non-destructive conditions.

Within the context of the project to construct both acyclic and constrained bis-heterocyclic RT inhibitors, the reaction of nitrile oxides with the isolated double bond of N^3-allylthymine derivatives of type **6** ($R^1 = H$) was observed to lead to exclusive formation of 3,5-disubstituted dihydroisoxazole products. In contrast, cycloaddition reactions of the corresponding enamines (type **6**, $R^1 = NR_2$) proceed with the reverse orientation of the dipole relative to the dipolarophile to afford the regioisomeric 3,4-disubstituted isoxazoles required for the preparation of compounds **10**.[17] For example, the N^1-benzylthymine derived enamine **16** reacts with nitrile oxide **11** to give the dihydroisoxazole **17** as the unique product, isolated in 82% yield after flash column chromatography (Scheme 2).

To obtain enamine **16**, thymine was selectively converted into its *N*-benzyl derivative **12**,[18] *via* a Vorbrüggen-type reaction of its persilylated derivative with benzyl bromide, and subsequently elaborated to aldehyde **15**. This was initially achieved by conversion of substrate **12** to acetal **13** through reaction with 2-(2-bromoethyl)-1,3-dioxolane, and cleavage of the acetal unit (BBr_3–CH_2Cl_2; 30%).[19] However, the route involving alkylation of the anion of compound **12** with 3-bromopropanol followed by Dess–Martin oxidation[20] of the primary alcohol function in compound **14** gave aldehyde **15** in higher overall yield. The sensitive enamine **16** was prepared by reaction of aldehyde **15** with pyrrolidine in the presence of 4 Å molecular sieves, and was used immediately in the cycloaddition step.

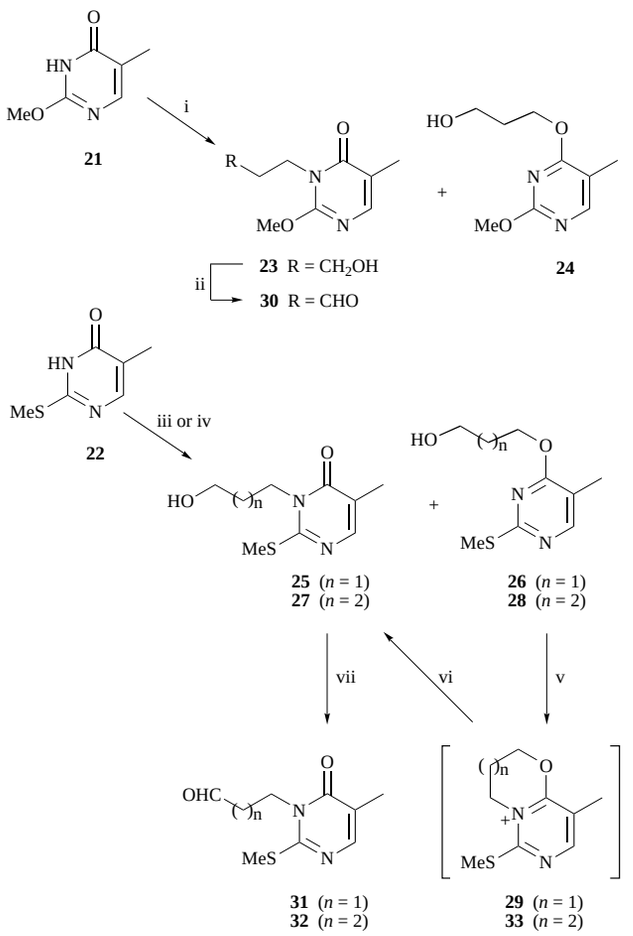
Dihydroisoxazole **17** was aromatised to the bis-heterocycle **18** by treatment with HCl in EtOH (reflux, 12 h, 89%), and to the corresponding amide derivative **19** by reaction with NH_3 in MeOH (quantitative). Having obtained the isoxazole **19**, a brief series of experiments was conducted to determine the feasibility



Scheme 2 *Reagents and conditions:* i, 2-(2-bromoethyl)-1,3-dioxolane, K_2CO_3, DMF, 25 °C (71%); ii, BBr_3, CH_2Cl_2, −78 °C (30%); iii, $Br[CH_2]_3OH$, NaH, DMF, 25 °C (63%); iv, Dess–Martin periodinane, CH_2Cl_2, 25 °C (86%); v, pyrrolidine, 4 Å molecular sieves, toluene; vi, ethyl chloro(hydroxyimino)acetate, Et_3N, THF, 25 °C (82% from **15**); vii, HCl, EtOH, 80 °C (89%); viii, toluene, reflux; ix, NH_3, MeOH, 0 °C (100%)

of direct cyclisation of amide **19** to tricycle **20**. Interestingly, however, compound **19** proved unstable to boiling toluene (12 h), undergoing cleavage to give a mixture of products from which *N*-benzylthymine **12** could be isolated in 50% yield. The thermal instability of this molecule is thought to result from a 'gramine'-type fragmentation[21] involving the isoxazole oxygen atom, and the thymine N-3 anion as a good leaving group.

Rather than attempt at this point to activate the C-2 position of the thymine ring in compound **19** with respect to ring closure, the synthesis of target molecules **10a,b** was explored using the 2-methoxypyrimidinone **21**[22] and the 2-(methylthio)thymine derivative **22**[23] as starting materials (Scheme 3). For the



Scheme 3 *Reagents and conditions:* i, $Br[CH_2]_3OH$, NaH, DMF, 25 °C (75% **23** + 15% **24**); ii, Dess–Martin periodinane, CH_2Cl_2, 25 °C (85%); iii, for $n = 1$: $Br[CH_2]_3OH$, KOH, DMF, 25 °C (49% **25** + 46% **26**); iv, for $n = 2$: $I[CH_2]_4OTBDMS$, KOH, DMF, 25 °C; then HF, aq. CH_3CN, 0 °C (29% **27** + 60% **28**); v, $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, 0 °C ⟶ reflux; vi, K_2CO_3, water–CH_2Cl_2, reflux (56% for **25** from **26**; 52% for **27** from **28**); vii, Dess–Martin periodinane, CH_2Cl_2, 25 °C (97% for **31**; 93% for **32**)

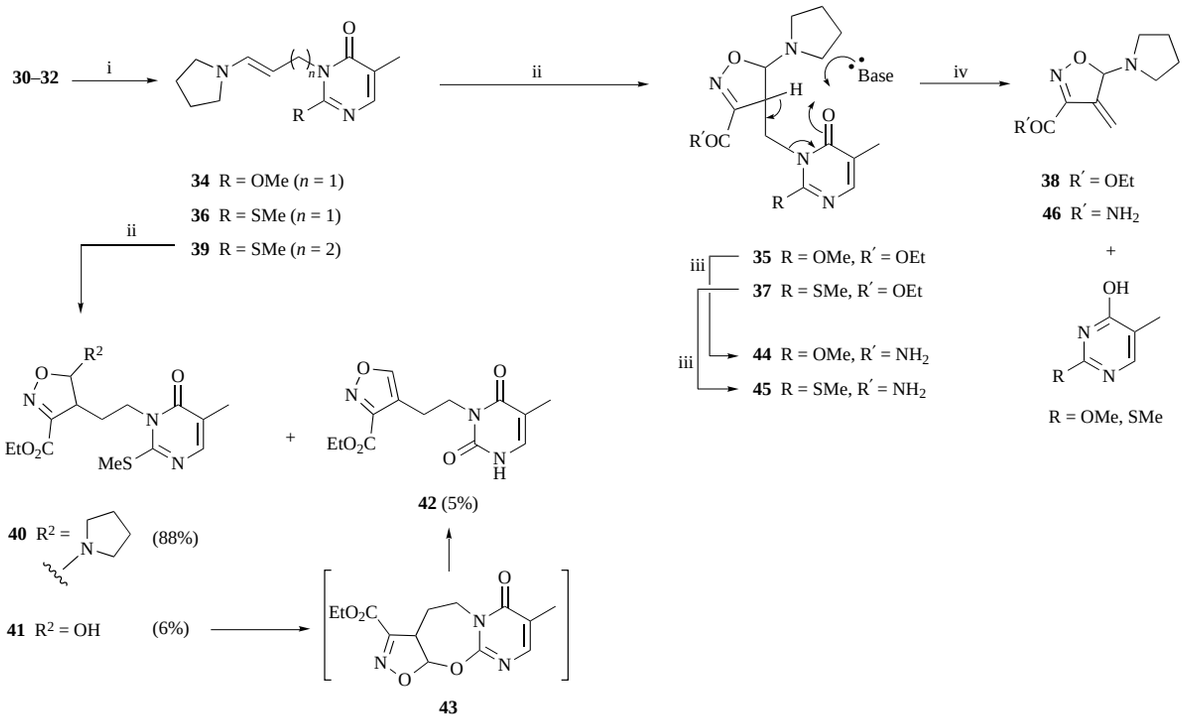
alkylation of the 2-methoxy derivative **21** it was found that, although in the presence of base reaction at N-1 is suppressed, its N-3 anion reacts with 3-bromopropan-1-ol to give a 5:1 mixture of the desired alcohol **23** and the O-4 alkylated product **24** (90% yield). For the alternative substrate **22**, it is reported that alkylation with benzyl chloromethyl ether occurs selectively at N-3 (>70% yield),[24] whereas treatment with 3-bromopropan-1-ol under basic conditions affords an approximately 1:1 mixture of N-3- and O-4-alkylated products **25** and **26** in only moderate yield.[25] In our hands, varying the base and solvent used in this latter reaction resulted in a significant improvement in the product yield, but the **25**:**26** ratio remained the same. The homologous alcohols **27** and **28** were similarly obtained in high yield by reaction of **22** with 4-iodobutyl *tert*-butyldimethylsilyl (TBDMS) ether.[26] In this case also a study of different reaction conditions [LiOH,[27] NaOH, NaH, potassium hexamethyldisilazide (KHMDS) in tetrahydrofuran (THF),[24] MeOH or CH_2Cl_2] did not permit inversion of the O/N product ratio (2:1) in favour of the desired N-3-alkylated compound **27**. Fortunately, even for large-scale preparations, compounds **25** and **27** are readily separated by column chromatography. Moreover, migration of the hydroxy-bearing side-chain in compounds **26** and **28** from O-4 to N-3 is possible by reaction with trifluoromethanesulfonic anhydride followed by treatment of their respective pyrimidinium trifluoromethanesulfonate intermediates **29** and **33** with aqueous base (50–60%, non-optimised). Oxidation of alcohols **23**, **25** and **27** using the Dess–Martin periodinane reagent provided the corresponding aldehydes **30**, **31** and **32** in excellent yields (85–97%).

As was the case with compound **15**, these aldehydes were treated with pyrrolidine in the presence of molecular sieves, and the sensitive enamine products were treated in crude form with an eight-fold excess of nitrile oxide **11** generated *in situ* (Scheme 4). In this way dihydroisoxazole **35** was obtained in 87% overall yield from aldehyde **30**, along with 2-methoxypyrimidinone **21** (10%), *via* intermediate **34**. In the cycloaddition of the methylthiopyrimidine enamine **36**, compound **37** was obtained in lower yield (56%) due to formation of larger quantities of the corresponding cleavage products **22** and thymine (18% total). With regards formation of these secondary products (**21**, **22** and thymine), two plausible mechanisms for their origin include: (i) a retro-Michael reaction of the starting enamines in the reaction medium (or the enol form of their aldehyde precursors), and (ii) a β-elimination process in cycloadducts **35** and **37** wherein azadiene **38** is also produced. Note that the dihydroisoxazole ring H-4 in compounds **35** and **37** is relatively acidic (imine–enamine tautomerism), and that thymine is a better leaving group than pyrrolidine in the olefin-forming reaction, even though the latter is located at the anomeric centre (assistance by oxygen), and its loss would lead to aromatisation of the dihydroisoxazole ring.

As both the postulated processes are related to the length of the N-3 side chain, it was not surprising that fragmentation products were not detected in the dipolar cycloaddition reaction of the homologous enamine **39** (Scheme 4). However, the production of cycloadduct **40** (88%) was accompanied by small amounts of compounds **41** and **42**. Formation of alcohol **41** may result from pyrrolidine/OH exchange in the presence of adventitious water in the reaction medium, and it is possible that compound **42** arises by a mechanism involving the cyclic ether **43**.

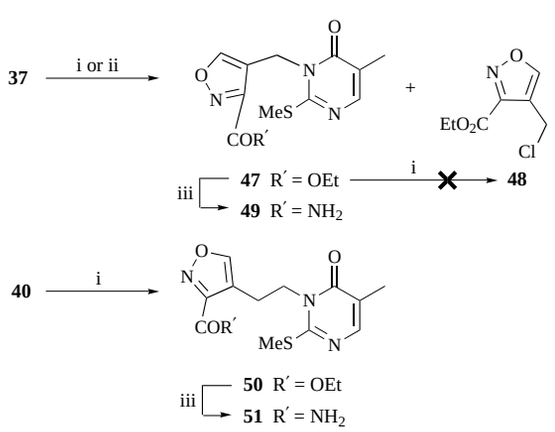
With the key esters **35** and **37** in hand, their conversion to the corresponding primary amides was studied, followed by experiments to effect ring closure at the dihydroisoxazole level. Transformation of ester **35** into amide **44** was readily achieved with methanolic ammonia (98%). In contrast, compound **37** was considerably more sensitive to these conditions, giving target amide **45** together with the corresponding product in which pyrrolidine has been exchanged by NH_2 (66% combined yield). A significant amount (22%) of the cleavage product **22** was also formed. In an attempt to bring about ring closure of amide **44**, treatment with NaH/dimethylformamide (DMF) at room temperature led to formation of the 2-methoxypyrimidinone **21** (35%) and the elusive azadiene **46** (13%). These observations strongly suggest that the β-elimination pathway, proposed above for fragmentation of esters **35** and **37**, is operative (Scheme 4). Azadiene **46** proved stable enough to be isolated and characterised by mass and ^1H NMR spectroscopy (olefinic resonances at δ_H 6.18 and 6.45).[28,29] Similar results were obtained when the *S*-methyl amide **45** was treated with base (NaH–DMF or K_2CO_3–DMF), or on simple heating. In the latter instance a mechanism analogous to that for the E_1 pyrolytic acetate elimination may be operative.[30]

The ease with which these fragmentations took place con-



Scheme 4 *Reagents and conditions:* i, pyrrolidine, 4 Å molecular sieves, toluene; ii, ethyl chloro(hydroxyimino)acetate, Et_3N, THF, 25 °C (87% for **35** from **30**; 56% for **37** from **31**); iii, NH_3, MeOH, 0 °C (98% for **44**; 44% for **45**); iv, NaH, DMF, 25 °C

vinced us that aromatisation of the dihydroisoxazole ring should be effected before considering closure of the central ring. This study was carried out on the methylsulfanylpyrimidinone **37** because, in principle, the sulfur leaving group of the pseudourea system could be further activated through sulfonium salt or sulfone formation if the final ring closure to tricycle **10a** were to present a problem. Contrary to expectation, elimination of pyrrolidine from ester **37** by reaction with HCl in $CHCl_3$ (60 °C) led to formation of isoxazole **47** in only 19% yield, the major component in the product mixture being ethyl 4-(chloromethyl)isoxazole-3-carboxylate **48** (52%) (Scheme 5).

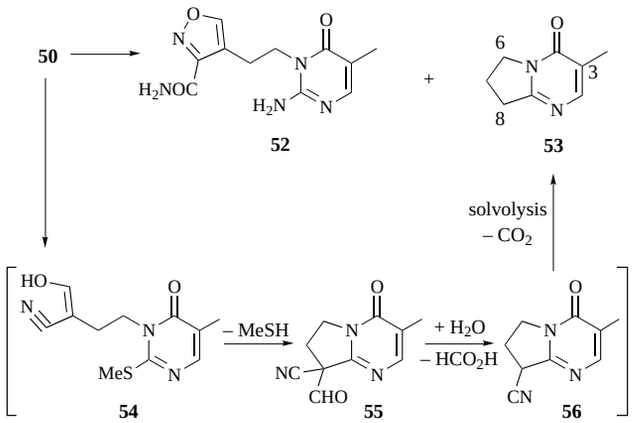


Scheme 5 *Reagents and conditions:* i, HCl, $CHCl_3$, 60 °C (19% **47** + 52% **48** from **37**; 68% **50** from **40**); ii, toluene, reflux (68% for **47**); iii, NH_3, MeOH, 25 °C (90% for **49**; 98% for **51**)

It was thus apparent that fragmentation of compound **37** can also occur under acidic conditions. Indeed, protonation of the pyrimidine ring[31] would most probably render the cleavage reaction very favourable. The alternative pathway to compound **48**, *via* a gramine-type fragmentation to give a conjugated oxonium ion species which subsequently picks up chloride, was discarded by the observation that the isoxazole product **47** is stable to heating in HCl–$CHCl_3$. The outcome of this reaction in contrast to that of *N*-benzylthymine analogue **17**, where elimination of pyrrolidine furnished isoxazole **18** in good yield, may be accounted for by the solvent employed and the more aromatic character of the liberated thymine component. In any event, ester **37** was efficiently transformed into isoxazole **47** on simple heating overnight in toluene, and thence converted into amide **49** in methanolic ammonia (90%). In ester **40**, the extended-chain homologue of compound **37**, the thymine and dihydroisoxazole rings are separated by an ethylene linker which prevents occurrence of fragmentation reactions. Thus, compound **40** was readily elaborated *via* ester **50** to amide **51** which resembles the anti-HIV pyridinone **4** (68% overall yield).

The intramolecular condensation of an amide anion with the thiourea system in 2-(methylthio)pyrimidinones to give bicyclic guanidine amides has been reported in the literature for systems using NaH–THF.[25b] Unfortunately, when compound **51** was subjected to these conditions only starting material was recovered. This was thought to be due mainly to the difficulty in closing an eight-membered ring. Thus, efforts were made to prepare both the sulfonium salt derivative of this compound, and the corresponding sulfone. However, reaction with MeI in DMF, with and without added base, and with H_2O_2 or *m*-chloroperbenzoic acid (MCPBA) led only to decomposition.

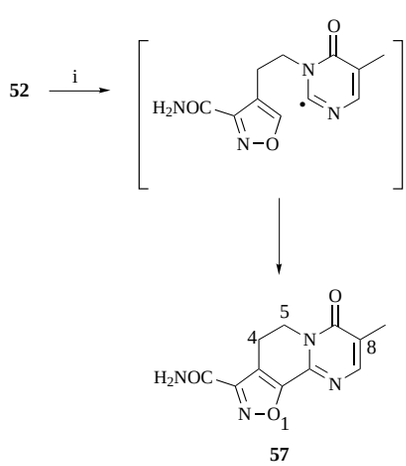
For this reason amino-for-methylthio exchange was carried out by reaction of ester **50** with NH_3 in *tert*-butyl alcohol at elevated temperature. After ten days at 137 °C (steel bomb) the guanidine–amide intermediate **52** was obtained in 29% yield together with amide **51** (45%) in which exchange of the methylthio group had not occurred (Scheme 6). Interestingly, on occasions when the autoclave was not completely sealed the escape of NH_3 gas from the solution was accompanied by a build up of the bicyclic pyrimidine derivative **53** (0–30%). The structure of product **53** was deduced from the spectral data, and in particular the presence of three CH_2 resonances at δ_C 19, 32 and 46. A plausible route to this compound involves initial hydrolysis of the ester function in compound **50** by traces of water present in the alcohol solvent, followed by a decarboxylative ring opening of the isoxazole ring to α-cyano aldehyde



Scheme 6

intermediate **54**‡ which ultimately reacts in its enol form with the SMe-bearing centre of the pyrimidine ring to give bicycle **55**.[32] Subsequent deformylation (formal addition of water and loss of formic acid) followed by solvolysis of the nitrile and decarboxylation then leads to the observed product. In support of this rationale, the cyano-substituted intermediate **56** was isolated in 58% yield from a related experiment in which we attempted to condense methylthiopyrimidine **50** with dimethyl malonate (Bu^{t}OH, Bu^{t}OK, reflux).

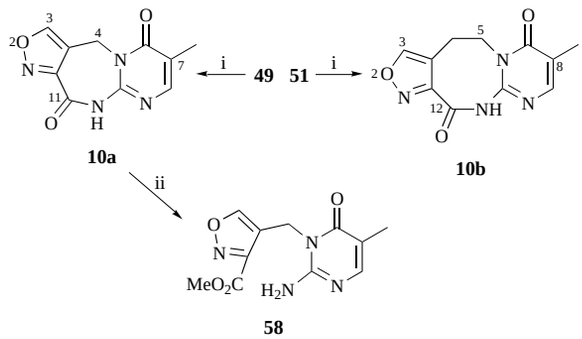
Among the various attempts to effect cyclisation of guanidine–amide **52**, one naïve idea was to convert substrate **52** into a diazonium salt which would decompose such that the derived carbonium ion would react with the amide function on the isoxazole ring to give the ring-closed product **10b**. Thus, intermediate **52** was treated with isoamyl nitrite in DMF.[33] From the structure of compound **57**, the major reaction product generated under these conditions, it appears that the diazonium species preferentially decomposed to a carbon-centred amidine radical (Gomberg process)[34] which reacted with the isoxazole ring at the C-5 position, a centre known to be receptive to radical additions (Scheme 7).[35] The pyrimidinedione



Scheme 7 *Reagents and conditions:* i, isoamyl nitrite, DMF, 80 °C (24%)

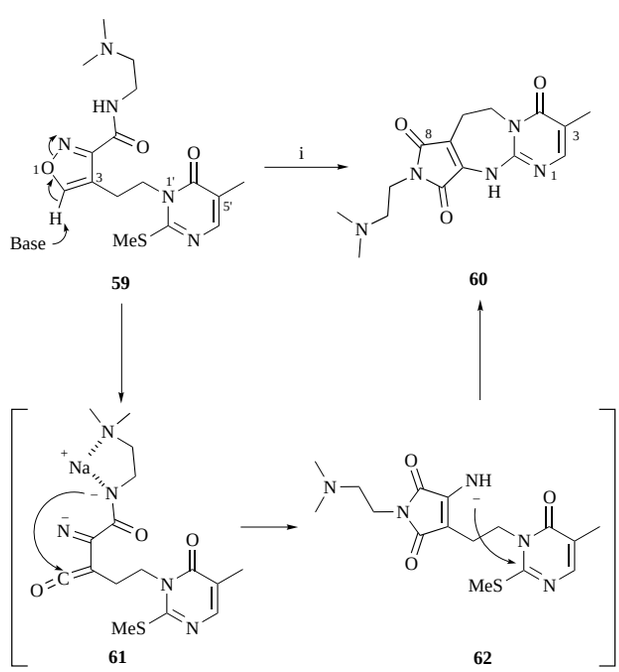
product issuing from the hydrolysis of the diazonium intermediate was also isolated from the mixture, albeit in small quantities.

Having explored these and other alternatives to the base-induced cyclisation of amide **51** we returned to the use of NaH in different solvents. It was gratifying that in a polar medium (DMF) the amide anion generated from compound **51** reacted with the pseudourea system to produce the target heterocycle **10b** with the eight-membered central ring in 61% isolated yield after flash column chromatography (Scheme 8). These conditions were then applied to the more fragile intermediate **49**. Again, cyclisation was observed and the nevirapine-type compound **10a** was isolated in up to 48% yield through selective precipitation of the product. Interestingly, on treatment with base in methanol this compound opens to give the guanidine ester **58**.



Scheme 8 *Reagents and conditions:* i, NaH, DMF, 25 °C (48% for **10a**; 61% for **10b**); ii, MeONa, MeOH, 25 °C (30%)

Finally, extension of this approach to the preparation of analogues bearing substituents on the amide nitrogen was looked into. Particularly interesting is the result observed on attempted ring closure of the dimethylaminoethyl-substituted amide **59**. In stark contrast to the reactivity of amide **49**, this molecule reacts with NaH in DMF to give the fragile succinimide derivative **60** as the major product in 25% yield (after repeated chromatography). From a long-distance correlation (HMBC) experiment carried out on compound **60**, the structural proximity of the C-8 and C-10 carbonyls to the N^9-methylene centre in the succinimide ring was established. An isoxazole ring fragmentation process is again invoked to explain formation of this rearrangement product.[36] As depicted in Scheme 9, this is believed to involve base-promoted ring open-



Scheme 9 *Reagents and conditions:* i, NaH, DMF, 25 °C (25%)

‡ Alternatively, base-catalysed transesterification of ethyl ester **50** (*tert*-butyl alcohol–ammonia) could give rise to the thermally labile *tert*-butyl ester analogue of **50** which might equally facilitate the decarboxylative ring opening of the isoxazole ring at elevated temperature.

ing to a ketene intermediate **61** which ring closes, first to the succinimide intermediate **62**, and subsequently to the observed product. The difference in reactivity of the chelated anion **59** compared with that derived from amide **49** is attributed to its altered base characteristics and increased steric bulk which makes approach to the thiourea carbon centre more difficult.

In conclusion, the [2 + 3] cycloaddition of thymine derived-enamines **36** and **39** with nitrile oxide **11** followed by aromatisation, ester-to-amide conversion, and ring closure represents an effective and concise strategy for the construction of the tricyclic bis-heterocyclic compounds **10a** (17% overall) and **10b** (36% overall) related to the potent RT_1 inhibitor nevirapine. *In vitro* evaluation of these compounds, as well as their precursor esters (**47** and **50**), and amides (**49** and **51**) as RT_1 inhibitors in cell culture (CEM SS cells; HIV-1 LAI strain)[2] revealed that they were inactive.[37] On the basis of recent structure–activity relationship (SAR) studies several reasons can be invoked to explain the inability of these compounds to block HIV-1 replication, perhaps the most important of which is the apparent necessity to conserve the hydrophobic character of the hetero-aromatic rings.[38–40] Future efforts will determine whether modification of the thymine component in compounds **10**, or its replacement by a less polar heterocycle, will produce active anti-HIV agents.

Experimental

General procedure

Mps were determined using a Reichert Thermovar apparatus and are uncorrected. Mass spectra were obtained on an MS-50 AEI (EI, 70 eV) or an MS-9 AEI (CI, isobutane) spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ (except where noted) on a Brüker spectrometer (200 or 250 MHz), using tetramethylsilane as internal standard.[13]C NMR spectra where recorded in $CDCl_3$ on the same instruments. Chemical-shift data are reported in parts per million (δ in ppm), and *J*-values are given in Hz. Flash column chromatography was performed using Merck aluminoxid 90 (activity II–III) or silica gel 60 (Art. 9385). In all cases the solvent system used for the chromatographic separations was chosen such that on TLC an R_F-value of 0.25–0.30 was observed for the compound to be isolated.

1-Benzyl-3-[2-(1,3-dioxolan-2-yl)ethyl]-5-methylpyrimidine-2,4-(1*H*,3*H*)-dione 13

A mixture of N^1-benzylthymine **12**[18] (3.57 g, 16.5 mmol), potassium carbonate (6.85 g, 49.6 mmol) and 2-(2-bromoethyl)-1,3-dioxolane (3.88 cm^3, 33.1 mmol) in dry DMF (120 cm^3) was stirred under nitrogen at 25 °C for 48 h. The reaction mixture was then concentrated under reduced pressure, and taken up in a small quantity of $CHCl_3$. The precipitated salts were removed by filtration, and the concentrated filtrate was subjected to flash column chromatography (silica gel; 60% EtOAc–heptane). *Compound* **13** was obtained as an oil (3.71 g, 71%); δ_H 1.95 (3 H, s, 5-CH_3), 2.10 (2 H, m, CH_2-2′), 3.75–4.05 (4 H, m, OCH_2), 4.15 (2 H, t, *J* 5 , CH_2N^3), 5.00 (2 H, s, CH_2N^1), 5.05 (1 H, t, *J* 6, H-3′), 7.10 (1 H, s, H-6) and 7.35 (5 H, m, Ar); δ_C 12.4 (5-CH_3), 31.3 (CH_2-2′), 36.3 (CH_2N^3), 51.2 (CH_2N^1), 64.2 (OCH_2), 102.3 (CH-3′), 109.4 (C-5), 127.1 (Ph CH), 127.5 (Ph CH), 128.3 (Ph CH), 135.4 (Ph C), 137.5 (CH-6), 151.0 (C-2) and 162.9 (C-4); ν_{max}(neat)/cm^{-1} 2975, 2888, 1731, 1700, 1669, 1638 and 1469; *m/z* (CI) 317 (MH^+) (Found: C, 64.13; H, 6.31; N, 8.91. $C_{17}H_{20}N_2O_4$ requires C, 64.54; H, 6.37; N, 8.85%).

1-Benzyl-3-(3-hydroxypropyl)-5-methylpyrimidine-2,4-(1*H*,3*H*)-dione 14

In the same manner as for **13**, compound **14** was prepared from N^1-benzylthymine (1.47 g, 6.80 mmol), NaH (190 mg, 7.90 mmol) and 3-bromopropan-1-ol (0.95 cm^3, 10.2 mmol) in dry DMF (75 cm^3). *Compound* **14** was obtained as a solid (1.17 g, 63%) after flash column chromatography (silica gel; 75% EtOAc–heptane); δ_H 1.90 (5 H, m, 5-CH_3 and CH_2-2′), 3.52 (2 H, m, CH_2-3′), 4.14 (2 H, t, *J* 6 , CH_2N^3), 4.94 (2 H, s, CH_2N^1), 7.08 (1 H, s, H-6) and 7.27–7.37 (5 H, m, Ph); δ_C 13.0 (5-CH_3), 30.5 (CH_2-2′), 38.0 (CH_2N^3), 52.1 (CH_2N^1), 58.6 (CH_2-3′), 110.3 (C-5), 127.8 (Ph CH), 128.4 (Ph CH), 129.0 (Ph CH), 135.5 (Ph C), 138.3 (CH-6), 152.1 (C-2) and 164.2 (C-4); ν_{max}(neat)/cm^{-1} 3462, 3017, 1696, 1669 and 1636; *m/z* (CI) 275 (MH^+) (Found: C, 65.82; H, 6.54; N, 10.12. $C_{15}H_{18}N_2O_3$ requires C, 65.68; H, 6.61; N, 10.21%).

1-Benzyl-3-(3-oxopropyl)-5-methylpyrimidine-2,4-(1*H*,3*H*)-dione 15

By deprotection of acetal 13. BBr_3 in hexane (1 M; 6 cm^3, 6 mmol) was added to a solution of the dioxolane **13** (240 mg, 0.76 mmol) in dry CH_2Cl_2 (40 cm^3) at −78 °C (under nitrogen), and the stirred resulting mixture was brought to room temperature over a period of 2 h. The reaction was then neutralised by the addition of saturated aq. $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and concentrated. *Aldehyde* **15** was obtained as a solid (60 mg, 30%) after flash column chromatography (silica gel; 50% EtOAc–heptane), mp 96–97 °C (EtOAc); δ_H 1.89 (3 H, s, 5-CH_3), 2.77 (2 H, t, *J* 5, CH_2-2′), 4.35 (2 H, t, *J* 5, CH_2N^3), 4.90 (2 H, s, CH_2N^1), 7.00 (1 H, s, H-6), 7.27–7.37 (5 H, m, Ph) and 9.82 (1 H, s, CHO); δ_C 12.9 (5-CH_3), 35.5 (CH_2-2′), 42.1 (CH_2N^3), 51.9 (CH_2N^1), 110.1 (C-5), 127.8 (Ph CH), 128.3 (Ph CH), 129.0 (Ph CH), 135.5 (Ph C), 138.2 (CH-6), 151.4 (C-2), 163.4 (C-4) and 200.1 (CHO); ν_{max}(neat)/cm^{-1} 3066, 2974, 1719, 1702, 1664, 1637 and 1466; *m/z* (CI) 273 (MH^+) (Found: C, 65.87; H, 5.90; N, 10.28. $C_{15}H_{16}N_2O_3$ requires C, 66.16; H, 5.92; N, 10.29%).

By oxidation of alcohol 14. To a solution of alcohol **14** (0.92 g, 3.35 mmol) in CH_2Cl_2 (25 cm^3) under nitrogen at 25 °C was added the Dess–Martin periodinane reagent[20] (1.65 g, 3.89 mmol). The reaction mixture was stirred for 16 h, then diluted with CH_2Cl_2 (200 cm^3), and quenched by the successive addition of saturated aq. $NaHCO_3$ (50 cm^3) and 1 M aq. $Na_2S_2O_3$ (50 cm^3). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and concentrated. As above, aldehyde **15** was obtained as a solid (0.78 g, 86%) after flash column chromatography (silica gel; 50% EtOAc–heptane).

4-[(3-Benzyl-5-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-1-yl)methyl]-5-pyrrolidino-4,5-dihydroisoxazole-3-carboxylic acid ethyl ester 17

Finely powdered, activated 4 Å molecular sieves (900 mg) and pyrrolidine (220 mm^3, 2.64 mmol) were added to a solution of aldehyde **15** (598 mg, 2.20 mmol) in dry toluene (2.5 cm^3); the mixture was stirred under nitrogen at 25 °C for 90 min. Although the derived enamine **16** could be isolated (by filtration and evaporation off of the solvent) and characterised [δ_H 1.80 (4 H, m, CH_2CH_2), 1.85 (3 H, s, 5-CH_3), 3.05 (4 H, m, CH_2NCH_2), 4.20–4.40 (1 H, m, CH-2′), 4.55 (2 H, d, *J* 12, CH_2N^3), 4.95 (2 H, s, CH_2N^1), 6.70 (1 H, d, CH-3′), 7.00 (1 H, s, H-6) and 7.35 (5 H, m, Ph)], it was generally engaged directly in the cycloaddition step. This involved the addition of THF (100 cm^3) and Et_3N (2.48 cm^3, 8.80 mmol), followed by the dropwise addition of a solution of ethyl chloro(hydroxyimino)acetate (2.66 g, 8.80 mmol)[16] in THF (120 cm^3) over a period of 8 h (in the dark). After a further 5 h at room temperature the reaction mixture was filtered through a pad of Celite, and the solvent was evaporated off. *Cycloadduct* **17** was isolated by flash column chromatography of the residue (silica gel; 60% EtOAc–heptane) as a solid (813 mg, 82%); δ_H 1.25 (3 H, t, CH_3), 1.75 (4 H, m, CH_2), 1.95 (3 H, s, 5′-CH_3), 2.60 (2 H, m, NCH_2), 2.80 (2 H, m, NCH_2), 3.85 (1 H, m, H-4), 4.30 (2 H, q, OCH_2), 4.40 (2 H, dd, $N^{1\prime}CH_2$), 4.95 (2 H, s, PhCH_2), 5.75 (1 H, m, H-5), 7.00 (1 H, s, H-4′) and 7.30 (5 H, m, Ph); δ_C 13.0 and 14.1 (CH_3),

24.0 (CH_2), 41.3 ($N^{1'}CH_2$), 46.8 (CH_2N), 47.6 (CH-4), 51.9 ($N^{3'}CH_2$), 61.6 (OCH_2), 100.6 (CH-5), 110.2 (C-5′), 127.8 (Ph CH), 128.2 (Ph CH), 129.0 (Ph CH), 135.7 (Ph C), 138.4 (CH-4′), 151.1 (C-2′), 152.0 (C-3), 160.9 (CO) and 163.9 (C-6′); ν_{max}(neat)/cm^{-1} 2975, 1706, 1669, 1656, 1469 and 1237; *m/z* (CI) 441 (MH^+) (Found: C, 60.33; H, 6.25; N, 12.22. $C_{23}H_{28}N_4O_5$·5/6 H_2O requires C, 60.65; H, 6.56; N, 12.30%).

4-[(3-Benzyl-5-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-1-yl)methyl]isoxazole-3-carboxylic acid ethyl ester 18

To a solution of the isoxazoline **17** (183 mg, 0.4 mmol) in EtOH (20 cm^3) was added HCl (4 mmol, solution in EtOH), and the resulting mixture was heated at 80 °C in a sealed tube. After being stirred for 12 h, then cooling to room temperature, the solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2, and neutralised by addition of solid Na_2CO_3. After filtration and removal of solvent the *isoxazole* **18** was obtained as a solid (132 mg, 89%). A sample was sublimed for analytical purposes; δ_H 1.44 (3 H, t, C*H*$_3$CH$_2$), 1.89 (3 H, s, 5′-CH$_3$), 4.48 (2 H, q, OCH$_2$), 4.91 (2 H, s, PhC*H*$_2$), 5.29 (2 H, s, NCH$_2$), 7.00 (1 H, s, H-4′), 7.36 (5 H, m, Ph) and 8.44 (1 H, s, H-5); δ_C 13.0 and 14.2 (CH$_3$), 33.6 (NCH$_2$), 52.0 (Ph*C*H$_2$), 62.3 (OCH$_2$), 110.4 (C-5′), 116.9 (C-4), 128.0 (Ph CH), 128.5 (Ph CH), 129.1 (PhCH), 135.5 (Ph C), 138.4 (CH-4′), 151.4 (C-2′), 153.9 (CO), 159.4 (CH-5), 160.2 (C-3) and 163.2 (C-6′); *m/z* (CI) 370 (MH^+) (Found: C, 61.86; H, 5.06; N, 11.30. $C_{19}H_{19}N_3O_5$ requires C, 61.78; H, 5.18; N, 11.38%).

4-[(3-Benzyl-5-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-1-yl)methyl]isoxazole-3-carboxamide 19

Ammonia gas was passed through a solution of ester **18** (130 mg, 0.35 mmol) in dry MeOH (100 cm^3) at 0 °C during 2 h. Amide **19** was obtained pure (^{1}H NMR) as an oil (137 mg, 100%) after evaporation of the mixture. For analytical purposes a sample of this product was sublimed under vacuum; δ_H 1.90 (3 H, s, 5′-CH$_3$), 4.92 (2 H, s, PhC*H*$_2$), 5.34 (2 H, s, NCH$_2$), 5.95 (1 H, s, NH), 7.02 (2 H, s, H-4′ and NH), 7.29 (5 H, m, Ph) and 8.37 (1 H, s, H-5); δ_C 13.1 (5′-CH$_3$), 34.0 (NCH$_2$), 52.1 (Ph*C*H$_2$), 110.5 (C-5′), 116.7 (C-4), 128.0 (Ph CH), 128.5 (Ph CH), 129.2 (Ph CH), 135.5 (Ph C), 138.5 (CH-4′), 151.6 (C-3), 154.9 (C-2′), 159.1 (CH-5), 161.2 (CO) and 163.4 (C-6′); *m/z* (CI) 341 (MH^+) (Found: C, 57.35; H, 4.76; N, 15.53. $C_{17}H_{16}N_4O_4$·19/20 H_2O requires C, 57.12; H, 5.05; N, 15.67%).

3-(3-Hydroxypropyl)-2-methoxy-5-methylpyrimidin-4(3*H*)-one 23 and 3-(2-methoxy-5-methylpyrimidin-4-yloxy)propan-1-ol 24

In the same manner as for **13**, compound **23** was prepared from 2-methoxy-5-methylpyrimidin-4(3*H*)-one **21**[22] (106 mg, 0.53 mmol), NaH (20 mg, 0.83 mmol), and 3-bromopropan-1-ol (76 mm^3, 0.60 mmol) in dry DMF (10 cm^3). The less polar O-alkylated product **24** (16 mg, 15%), and the *N-alkylated product* **23** (79 mg, 75%) were isolated as solids.

Compound 23. δ_H 1.90 (2 H, m, CH$_2$-2′), 2.05 (3 H, s, 5-CH$_3$), 3.51 (2 H, t, *J* 5.6, CH$_2$-3′), 3.85 (1 H, s br, OH), 4.00 (3 H, s, CH$_3$O), 4.18 (2 H, t, *J* 6.1, CH$_2$-1′) and 7.55 (1 H, s, H-6); δ_C 12.9 (5-CH$_3$), 30.7 (CH$_2$-2′), 38.2 (CH$_2$-1′), 55.4 (CH$_2$-3′), 58.4 (CH$_3$O), 116.5 (C-5), 148.7 (CH-6), 157.5 (C-2) and 164.2 (C-4); ν_{max}(neat)/cm^{-1} 3425, 2956, 1663, 1550 and 1475; *m/z* (CI) 199 (MH^+) (Found: C, 54.33; H, 6.90; N, 14.24. $C_9H_{14}N_2O_3$ requires C, 54.53; H, 7.12; N, 14.13%).

Compound 24.§ δ_H 2.00 (5 H, m, 5-CH$_3$ and CH$_2$-2′), 2.77 (1 H, t, *J* 5.2, OH), 3.76 (2 H, m, CH$_2$-3′), 3.92 (3 H, s, CH$_3$O) 4.52 (2 H, t, *J* 6, CH$_2$-1′) and 7.97 (1 H, s, H-6); δ_C 12.0 (5-CH$_3$), 32.2 (CH$_2$-2′), 54.7 (CH$_2$-3′), 59.3 (OCH$_3$), 63.7 (CH$_2$-1′), 111.1 (C-5), 157.3 (CH-6), 164.0 (C-2) and 169.4 (C-4); ν_{max}(neat)/cm^{-1} 3269, 1602, 1588 and 1483; *m/z* (CI) 199 (MH^+).

§ Pyrimidine assignments are given unprimed numbers and alkane assignments are given primed numbers.

3-(3-Hydroxypropyl)-5-methyl-2-(methylsulfanyl)pyrimidin-4(3*H*)-one 25 and 3-[5-methyl-2-(methylsulfanyl)pyrimidin-4-yloxy]propan-1-ol 26

To a solution of sulfide **22** (484 mg, 3.2 mmol)[23] in DMF (25 cm^3) at 25 °C was added KOH (236 mg, 4.20 mmol) followed by 3-bromopropan-1-ol (350 mm^3, 3.84 mmol), and the mixture was stirred at room temperature for 12 h under nitrogen. The solvent was then evaporated off under reduced pressure, and the residue was taken up in water and extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated. The less polar *O-alkylated product* **26** (270 mg, 46%) and the *N-alkylated product* **25** (290 mg, 49%) were isolated as solids after flash column chromatography (silica gel; 50% EtOAc–heptane).

Compound 25. δ_H 2.02 (2 H, m, CH$_2$-2′), 2.04 (3 H, s, 5-CH$_3$), 2.55 (3 H, s, SCH$_3$), 3.53 (2 H, t, *J* 5.4, CH$_2$-3′), 3.76 (1 H, s, OH), 4.26 (2 H, t, *J* 6.1, CH$_2$-1′) and 7.71 (1 H, s, H-6); δ_C 14.1 (5-CH$_3$), 15.7 (SCH$_3$), 31.4 (CH$_2$-2′), 41.9 (CH$_2$-1′), 59.1 (CH$_2$-3′), 119.0 (C-5), 150.5 (CH-6), 160.2 (C-2) and 164.3 (C-4); ν_{max}(neat)/cm^{-1} 1651 and 1510; *m/z* (CI) 215 (MH^+) [Found (EI): M^+, 214.0787. $C_9H_{14}N_2O_2S$ requires M, 214.0777].

Compound 26.§ δ_H 2.03 (5 H, m, 5-CH$_3$ and CH$_2$-2′), 2.37 (1 H, s, OH), 2.54 (3 H, s, CH$_3$S), 3.77 (2 H, m, CH$_2$-3′), 4.56 (2 H, m, CH$_2$-1′) and 8.06 (1 H, s, H-6); δ_C 12.3 (5-CH$_3$), 14.2 (SCH$_3$), 32.1 (CH$_2$-2′), 59.4 (CH$_2$-3′), 63.6 (CH$_2$-1′), 113.0 (C-5), 156.7 (CH-6), 167.4 (C-2) and 169.0 (C-4); ν_{max}(neat)/cm^{-1} 1589 and 1551; *m/z* (EI) 214 (M^+) (Found: M^+, 214.0787).

3-(4-Hydroxybutyl)-5-methyl-2-(methylsulfanyl)pyrimidin-4(3*H*)-one 27 and 4-[5-methyl-2-(methylsulfanyl)pyrimidin-4-yloxy]butan-1-ol 28

Alkylation of compound 22. Using the same protocol as for **25/26**, pyrimidinone **22** (1.5 g, 9.61 mmol) in DMF (90 cm^3) was treated with KOH (645 mg, 11.5 mmol) followed by 1-[(2,2-dimethylethyl)dimethylsiloxy]-4-iodobutane[26] (2.73 cm^3, 11.5 mmol). The *TBS ethers of alcohols* **27** (985 mg, 30%) and **28** (2.08 g, 63%; least polar) were isolated as oils after flash column chromatography (silica gel; 25% EtOAc–heptane).

TBS ether of compound ***27***.—δ_H 0.00 [6 H, s, (CH$_3$)$_2$Si], 0.88 [9 H, s, (CH$_3$)$_3$C], 1.62 (2 H, m, CH$_2$-2′), 1.81 (2 H, m, CH$_2$-3′), 2.00 (3 H, s, 5-CH$_3$), 2.51 (3 H, s, SCH$_3$), 3.64 (2 H, t, *J* 6.5, CH$_2$-4′), 4.05 (2 H, t, *J* 7.8, CH$_2$-1′) and 7.63 (1 H, s, 6-H); δ_C −4.4 [(CH$_3$)$_2$Si], 14.2 (5-CH$_3$), 15.7 (SCH$_3$), 19.2 [*C*(CH$_3$)$_3$], 25.2 (CH$_2$-2′), 26.9 [(CH$_3$)$_3$], 31.2 (CH$_2$-3′), 45.6 (CH$_2$-1′), 63.6 (CH$_2$-4′), 120.1 (C-5), 149.8 (CH-6), 160.9 (C-2) and 163.7 (C-4); ν_{max}(neat)/cm^{-1} 1680 and 1512; *m/z* (EI) 342 (M^+), 285 ($M - Bu^t$)$^+$ and 212 (M − OTBS)$^+$ (Found: C, 55.83; H, 8.45; N, 8.03. $C_{16}H_{30}N_2O_2SSi$ requires C, 56.09; H, 8.83; N, 8.17%).

TBS ether of compound ***28***.—δ_H 0.06 [6 H, s, (CH$_3$)$_2$Si], 0.90 [9 H, s, (CH$_3$)$_3$C], 1.66 (2 H, m, CH$_2$-3′), 1.82 (2 H, m, CH$_2$-2′), 2.06 (3 H, s, 5-CH$_3$), 2.53 (3 H, s, SCH$_3$), 3.68 (2 H, t, *J* 6.2, CH$_2$-4′), 4.40 (2 H, t, *J* 6.5, CH$_2$-1′) and 8.04 (1 H, s, H-6); δ_C −5.0 [(CH$_3$)$_2$Si], 11.6 (5-CH$_3$), 13.5 (SCH$_3$), 17.8 [*C*(CH$_3$)$_3$], 24.9 (CH$_2$-3′), 25.4 [(CH$_3$)$_3$], 28.8 (CH$_2$-2′), 62.2 (CH$_2$-4′), 65.8 (CH$_2$-1′), 112.4 (C-5), 155.8 (CH-6), 166.7 and 168.3 (C-2 and -4); ν_{max}(neat)/cm^{-1} 1587, 1552, 1463 and 1428; *m/z* (EI) 342 (M^+), 285 ($M - Bu^t$)$^+$ and 212 (M − OTBS)$^+$ (Found: C, 56.14; H, 8.53; N, 7.96%).

Deprotection of TBS ethers. To a solution of *O*-TBS-protected alcohol **27** (815 mg, 2.38 mmol) in acetonitrile (8 cm^3) at 0 °C was added a solution of HF [40% aq. HF (23.8 mmol) in 10 cm^3 of acetonitrile], and the mixture was stirred at 0 °C for 1.5 h. The mixture was then neutralised by the addition of solid $NaHCO_3$, and after 1 h the precipitate was removed, and the solvent was evaporated off under reduced pressure. *Alcohol* **27** was obtained as a solid (531 mg, 98%). In an identical manner *O*-TBS-protected alcohol **28** (1.58 g, 4.60 mmol) was converted into *free alcohol* **28** (0.99 g, 95%). Both compounds were carried through directly to the next step. However, for analytical purposes a sample of each compound was sublimed under vacuum.

Compound **27**.—δ_H 1.68 (2 H, m, CH_2-2′), 1.84 (2 H, m, CH_2-3′), 2.01 (3 H, s, 5-CH_3), 2.38 (1 H, s, OH), 2.54 (3 H, s, SCH_3), 3.71 (2 H, t, *J* 6.2, CH_2-4′), 4.08 (2 H, t, *J* 7.5, CH_2-1′) and 7.66 (1 H, s, H-6); δ_C 12.5 (5-CH_3), 14.1 (SCH_3), 23.4 (CH_2-2′), 29.0 (CH_2-3′), 43.7 (CH_2-1′), 61.4 (CH_2-4′), 118.5 (C-5), 148.4 (CH-6), 159.2 (C-2) and 162.3 (C-4); ν_{max}(neat)/cm^{-1} 3430, 1659 and 1518; *m/z* (CI) 229 (MH^+) (Found: C, 52.38; H, 7.06; N, 12.29. $C_{10}H_{16}N_2O_2S$ requires C, 52.61; H, 7.06; N, 12.27%).

Compound **28**§.—δ_H 1.72 (2 H, m, CH_2-2′), 1.89 (2 H, m, CH_2-3′), 2.06 (3 H, s, 5-CH_3), 2.53 (3 H, s, SCH_3), 3.73 (2 H, t, *J* 6.3, CH_2-4′), 4.42 (2 H, t, *J* 6.3, CH_2-1′), 8.05 (1 H, s, H-6); δ_C 12.0 (5-CH_3), 14.0 (SCH_3), 25.2 (CH_2-2′), 29.1 (CH_2-3′), 62.3 (CH_2-1′), 66.1 (CH_2-4′), 112.9 (C-5), 156.2 (CH-6), 167.1 (C-2) and 168.7 (C-4); *m/z* (CI) 229 (MH^+).

Conversion of O-alkylated compound 26 into its N-alkylated isomer 25

To a solution of the O-alkylated alcohol **26** (200 mg, 0.93 mmol) in dry CH_2Cl_2 (20 cm^3) at 0 °C under nitrogen were successively added pyridine (0.11 cm^3, 1.4 mmol) and trifluoromethanesulfonic anhydride (0.25 cm^3, 1.4 mmol). Stirring was continued at 0 °C for 1 h, at reflux for 1 h, and for a further 10 min after addition of aq. K_2CO_3 (0.5 M; 5 cm^3). The mixture was then decanted, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated. The N-alkylated product **25** (112 mg, 56%) was obtained after flash column chromatography (silica gel; 50% EtOAc–heptane).

Conversion of O-alkylated compound 28 into its N-alkylated isomer 27

With the exception that pyridine was not added to the reaction mixture, the O-alkylated alcohol **28** (90 mg, 0.39 mmol) was converted into isomer **27** as for **26** by reaction with trifluoromethanesulfonic anhydride (95 mm^3, 0.59 mmol) in CH_2Cl_2 (10 cm^3). Compound **27** (47 mg, 52%) was obtained after flash column chromatography (silica gel; 33% EtOAc–heptane).

3-(3-Oxopropyl)-2-methoxy-5-methylpyrimidin-4(3*H*)-one 30

Following the protocol for the oxidation of **14**, alcohol **23** (273 mg, 1.37 mmol) was treated with the Dess–Martin periodinane reagent (672 mg, 1.58 mmol) in CH_2Cl_2 (10 cm^3). Aldehyde **30**, obtained as a solid (229 mg, 85%) after work-up, was carried through to the enamine-forming step; δ_H 2.00 (3 H, s, 5-CH_3), 2.83 (2 H, t , *J* 7, CH_2-2′), 3.98 (3 H, s, CH_3O), 4.35 (2 H, t, *J* 7, CH_2-1′), 7.50 (1 H, s, H-6) and 9.80 (1 H, s, CHO); δ_C 13.0 (5-CH_3), 35.5 (CH_2-2′), 42.2 (CH_2-1′), 55.6 (CH_3O), 117.1 (C-5), 148.4 (CH-6), 155.2 (C-2), 163.1 (C-4) and 199.5 (CHO); ν_{max}(neat)/cm^{-1} 2962, 1725, 1669 and 1556; *m/z* (CI) 197 (MH^+).

3-(3-Oxopropyl)-5-methyl-2-(methylsulfanyl)pyrimidin-4(3*H*)-one 31

Following the protocol for the oxidation of **14**, alcohol **25** (1.13 g, 5.28 mmol) was treated with the Dess–Martin periodinane reagent (3.36 g, 7.92 mmol) in CH_2Cl_2 (60 cm^3). *Aldehyde* **31** was obtained as a solid (1.09 g, 97%) after column chromatography (silica gel; 50% EtOAc–heptane); δ_H 2.01 (3 H, s, 5-CH_3), 2.55 (3 H, s, SCH_3), 2.92 (2 H, t, *J* 7.3, CH_2-2′), 4.37 (2 H, t, *J* 7.3, CH_2-1′), 7.66 (1 H, s, H-6) and 9.84 (1 H, s, CHO); δ_C 13.3 (5-CH_3), 15.0 (SCH_3), 38.9 (CH_2-2′), 41.8 (CH_2-1′), 119.4 (C-5), 149.4 (CH-6), 159.7 (C-2), 163.0 (C-4) and 199.1 (CHO); ν_{max}(neat)/cm^{-1} 1722, 1667 and 1511; *m/z* (CI) 213 (MH^+) (Found: C, 50.71; H, 5.67; N, 13.07. $C_9H_{12}N_2O_2S$ requires C, 50.92; H, 5.70; N, 13.19%).

3-(4-Oxobutyl)-5-methyl-2-(methylsulfanyl)pyrimidin-4(3*H*)-one 32

Following the protocol for the oxidation of **14**, alcohol **27** (1.45 g, 6.37 mmol) was treated with the Dess–Martin periodinane reagent (4.0 g, 9.56 mmol) in CH_2Cl_2 (120 cm^3). *Aldehyde* **32** was obtained as a solid (1.34 g, 93%) after flash column chromatography (silica gel; 50% EtOAc–heptane); δ_H 2.01 (3 H, s, 5-CH_3), 2.09 (2 H, m, CH_2-2′), 2.58 (5 H, m, CH_2-3′ and SCH_3), 4.10 (2 H, t, *J* 7.3, CH_2-1′), 7.66 (1 H, s, H-6) and 9.80 (1 H, s, CHO); δ_C 13.0 (5-CH_3), 14.6 (SCH_3), 20.0 (CH_2-2′), 40.8 (CH_2-3′), 43.5 (CH_2-1′), 119.0 (C-5), 148.9 (CH-6), 159.6 (C-2), 162.7 (C-4) and 200.6 (CHO); ν_{max}(neat)/cm^{-1} 1723, 1667 and 1516; *m/z* (CI) 227 (MH^+) (Found: C, 52.94; H, 6.01; N, 12.36. $C_{10}H_{14}N_2O_2S$ requires C, 53.08; H, 6.23; N, 12.38%).

4-[(2-Methoxy-5-methyl-6-oxo-1,6-dihydropyrimidin-1-yl)-methyl]-5-pyrrolidino-4,5-dihydroisoxazole-3-carboxylic acid ethyl ester 35 *via* enamine 34

As described for the preparation of cycloadduct **17**, aldehyde **30** (170 mg, 0.87 mmol) was converted into the corresponding enamine **34** through reaction with pyrrolidine (87 mm^3, 1.04 mmol) in toluene (3 cm^3) containing 4 Å molecular sieves (0.3 g). Subsequent reaction with ethyl chloro(hydroxyimino)acetate (1.05 g, 6.93 mmol) and Et_3N (0.98 cm^3, 6.93 mmol) in THF (110 cm^3) followed by flash column chromatography (silica gel; 75% EtOAc–heptane) provided title compound **35** as an oil (274 mg, 87%) and pyrimidinone **21** (12 mg, 10%; oil); δ_H 1.32 (3 H, m, CH_3), 1.75 (4 H, s, 2 × CH_2), 2.00 (3 H, s, 5′-CH_3), 2.62 and 2.80 (4 H, 2 × m, CH_2NCH_2), 3.65 (1 H, m, H-4), 3.96 (3 H, s, CH_3O), 4.30 (4 H, m, N^1CH_2 and OCH_2), 5.62 (1 H, d, *J* 3.8, H-5) and 7.18 (1 H, s, H-4′); δ_C 12.9 and 14.0 (2 × CH_3), 23.9 (2 × CH_2), 41.4 (N^1CH_2), 46.7 (CH_2NCH_2), 47.0 (CH-4), 55.4 (CH_3O), 61.8 (CH_2O), 100.6 (CH-5), 117.1 (C-5′), 148.4 (CH-4′), 150.6 (C-3), 155.1 (C-2′), 160.6 (CO) and 163.4 (C-6′); *m/z* (CI) 365 $(MH)^+$, 225 (M − pyrimidinone)$^+$ and 294 (M − pyrrolidine)$^+$.

4-[(5-Methyl-2-methylsulfanyl-6-oxo-1,6-dihydropyrimidin-1-yl)methyl]-5-pyrrolidino-4,5-dihydroisoxazole-3-carboxylic acid ethyl ester 37 *via* enamine 36

As described for the preparation of cycloadduct **17**, aldehyde **31** (400 mg, 1.89 mmol) was converted into the corresponding enamine **36** through reaction with pyrrolidine (190 mm^3, 2.27 mmol) in toluene (4 cm^3) containing 4 Å molecular sieves (0.8 g). Subsequent reaction with ethyl chloro(hydroxyimino)acetate (2.3 g, 15.12 mmol) and Et_3N (2.12 cm^3, 15.12 mmol) in THF (220 cm^3) followed by flash column chromatography (silica gel; 50% EtOAc–heptane) provided title compound **37** as an oil (400 mg, 56%), pyrimidinone **22** (10%) and thymine (8%); δ_H 1.35 (3 H, t, CH_3), 1.75 (4 H, m, 2 × CH_2), 2.05 (3 H, s, 5′-CH_3), 2.50 (3 H, s, SCH_3), 2.60 and 2.80 (4 H, 2 × m, CH_2NCH_2), 3.85 (1 H, m, H-4), 4.25 (2 H, m, OCH_2), 4.45 (2 H, m, N^1CH_2), 5.75 (1 H, d, *J* 3.8, H-5) and 7.65 (1 H, s, H-4′); δ_C 12.7 and 13.6 (2 × CH_3), 14.5 (SCH_3), 23.6 (2 × CH_2), 43.9 (N^1CH_2), 45.9 (CH-4), 46.3 (CH_2NCH_2), 61.5 (CH_2O), 100.5 (CH-5), 118.8 (C-5′), 148.5 (CH-4′), 149.8 (C-3), 159.3 (C-2′), 160.3 (CO) and 162.7 (C-6′); ν_{max}(neat)/cm^{-1} 1717 and 1670; *m/z* (CI) 381 (MH^+), 310 (MH − pyrrolidine)$^+$, 225 (MH − pyrimidinone)$^+$ and 157 (pyrimidinone + H)$^+$.

4-[2-(5-Methyl-2-methylsulfanyl-6-oxo-1,6-dihydropyrimidin-1-yl)ethyl]-5-pyrrolidino-4,5-dihydroisoxazole-3-carboxylic acid ethyl ester 40 and compounds 41 and 42 *via* enamine 39

As described for the preparation of cycloadduct **17**, aldehyde **32** (3.2 g, 14 mmol) was converted into the corresponding enamine **39** through reaction with pyrrolidine (1.3 cm^3, 15 mmol) in toluene (15 cm^3) containing 4 Å molecular sieves (7 g). Subsequent reaction with ethyl chloro(hydroxyimino)acetate (17 g, 112 mmol) and Et_3N (15.9 cm^3, 112 mmol) in THF (900 cm^3) followed by flash column chromatography (silica gel; 50% EtOAc–heptane) provided *title compound* **40** as a solid (4.85 g, 88%; least polar), *the alcohol* **41** (286 mg, 6%; solid) and compound **42** (205 mg, 5%; solid).

Compound 40. δ_H 1.38 (3 H, t, *J* 7.1, CH_3), 1.77 (4 H, m, 2 × CH_2), 1.97 (4 H, m, 5′-CH_3 and NCH_2CHH'), 2.22 (1 H, m,

NCH_2CHH'), 2.52 (3 H, s, SCH_3), 2.66 and 2.86 (4 H, 2 × m, CH_2NCH_2), 3.30 (1 H, m, H-4), 4.09 (2 H, m, $N^{1'}CH_2$), 4.38 (2 H, q, *J* 7.1, OCH_2), 5.70 (1 H, d, *J* 3.8, H-5) and 7.63 (1 H, s, H-4′); δ_C 12.3 and 13.3 (2 × CH_3), 13.9 (SCH_3), 23.3 (CH_2), 27.2 (CH_2), 45.1 (CH-4), 45.3 ($N^{1'}CH_2$), 46.0 (CH_2NCH_2), 61.1 (OCH_2), 101.6 (CH-5), 118.4 (C-5′), 148.2 (CH-4′), 150.5 (C-3), 158.6 (C-2′), 159.8 (CO ester) and 161.7 (C-6′); ν_{max}(neat)/cm^{-1} 1743, 1722 and 1666; *m/z* (CI) 395 (MH^+) [Found (EI): M^+, 394.1683. $C_{18}H_{26}N_4O_4S$ requires 394.1677].

Compound 41. δ_H 1.40 (3 H, m, CH_3), 1.82 (1 H, s large, OH), 1.89 (1 H, m, NCH_2CHH'), 2.01 (3 H, s, 5′-CH_3), 2.31 (1 H, m, NCH_2CHH'), 2.55 (3 H, s, SCH_3), 3.32 (1 H, m, H-4), 4.17 (2 H, m, NCH_2), 4.33 (2 H, m, OCH_2), 6.04 (1 H, d, *J* 1.6, H-5) and 7.68 (1 H, s, H-4′); δ_C 13.3 and 14.2 (2 × CH_3), 14.9 (SCH_3), 26.0 (CH_2), 42.1 (NCH_2), 51.5 (CH-4), 62.2 (OCH_2), 104.6 (CH-5), 119.2 (C-5′), 149.9 (CH-4′), 153.4 (C-3), 159.8 (C-2′), 160.2 (CO) and 163.3 (C-6′); ν_{max}(neat)/cm^{-1} 3419, 1725, 1656 and 1512; *m/z* (CI) 342 (MH^+) (Found: MH^+, 342.1123. $C_{14}H_{20}N_3O_5S$ requires *m/z* 342.1123).

Compound 42. δ_H 1.44 (3 H, t, *J* 7.1, CH_3), 1.92 (3 H, s, 5′-CH_3), 3.06 (2 H, t, *J* 6.6, CH_2), 4.24 (2 H, t, *J* 6.6, $N^{1'}CH_2$), 4.48 (2 H, q, *J* 7.1, OCH_2), 7.13 (1 H, d, *J* 5.4, H-4′), 8.30 (1 H, s, H-5) and 9.99 (1 H, br d, *J* 4.9, NH); δ_C 12.2 and 13.4 (2 × CH_3), 19.9 (CH_2), 38.9 ($N^{1'}CH_2$), 61.4 (OCH_2), 109.3 (C-4), 116.7 (C-5′), 134.3 (CH-4′), 152.6 (C-3), 153.8 (C-2′), 157.2 (CH-5), 159.7 (CO ester) and 163.2 (C-6′); ν_{max}(neat)/cm^{-1} 3390, 1740, 1704, 1658 and 1632; *m/z* (CI) 294 (MH^+) (Found: C, 53.01; H, 5.29; N, 14.03. $C_{13}H_{15}N_3O_5$ requires C, 53.24; H, 5.15; N, 14.32%).

4-[(2-Methoxy-5-methyl-6-oxo-1,6-dihydropyrimidin-1-yl)-methyl]-5-pyrrolidino-4,5-dihydroisoxazole-3-carboxamide 44

Ammonia gas was bubbled for 2 h into a solution of ester **35** (198 mg, 0.54 mmol) in dry MeOH (100 cm^3) at 0 °C. *Amide* **44** was obtained pure (^{1}H NMR) as a solid (194 mg, 98%) after evaporation off of the solvent. For analytical purposes a sample of this product was sublimed under vacuum; δ_H 1.73 (4 H, m, 2 × CH_2), 1.96 (3 H, s, 5′-CH_3), 2.77 and 2.57 (4 H, 2 × m, CH_2NCH_2), 3.66 (1 H, td, *J* 6.3 and 3.4, H-4), 3.94 (3 H, s, CH_3O), 4.34–4.25 (2 H, m, $N^{1'}CH_2$), 5.63 (1 H, d, *J* 3.4, H-5), 6.08 (1 H, s, NH), 6.68 (1 H, s, NH) and 7.48 (1 H, s, H-4′); δ_C 13.1 (5′-CH_3), 24.0 (CH_2), 41.2 (N^1CH_2), 46.8 (CH_2NCH_2 and CH-4), 55.4 (CH_3O), 100.8 (CH-5), 117.0 (C-5′), 148.4 (CH-4′), 152.4 (C-3), 155.4 (C-2′), 161.9 (CO) and 163.6 (C-6′); ν_{max}(neat)/cm^{-1} 3331, 2964, 1672, 1556 and 1470; *m/z* (CI) 336 (MH^+) (Found: C, 53.92; H, 6.37; N, 20.65. $C_{15}H_{21}N_5O_4$ requires C, 53.72; H, 6.31; N, 20.88%).

4-[(5-Methyl-2-methylsulfanyl-6-oxo-1,6-dihydropyrimidin-1-yl)methyl]-5-pyrrolidino-4,5-dihydroisoxazole-3-carboxamide 45

Ammonia gas was bubbled for 2 h into a solution of ester **37** (50 mg, 0.13 mmol) in dry MeOH (30 cm^3) at 0 °C. Amide **45**, a solid (20 mg, 44%), was obtained together with the C-5 NH_2-substitution product (24%), compound **22** (22%) and the starting ester (20 mg) after flash column chromatography (silica gel; 50% EtOAc–heptane). Compound **45**: δ_H 1.62 (4 H, m, 2 × CH_2), 2.02 (3 H, s, 5′-CH_3), 2.61 (5 H, m, CH_2NCH_2, SCH_3), 2.80 (2 H, m, CH_2NCH_2), 3.89 (1 H, m, H-4), 4.35 (2 H, dd, *J* 7.5 and 14, $N^{1'}CH_2$), 5.41 (1 H, s, NH), 5.76 (1 H, d, *J* 4, H-5), 6.58 (1 H, s, NH) and 7.66 (1 H, s, H-4′); δ_C 13.4 (5′-CH_3), 15.1 (SCH_3), 24.2 (CH_2), 44.1 ($N^{1'}CH_2$), 46.3 (CH-4), 47.0 (CH_2NCH_2), 101.1 (CH-5), 119.4 (C-5′), 149.2 (CH-4′), 152.1 (C-3), 160.1 (C-2′), 162.0 (CO) and 163.5 (C-6′); ν_{max}(neat)/cm^{-1} 3323, 2970, 2933, 1679 and 1594; *m/z* (CI) 352 (MH^+). [For the C-5 NH_2-substituted component: Found: (CI) MH^+, 298.0975. $C_{11}H_{16}N_5O_3S$ requires M, 298.0974].

Fragmentation of amide 44 to 4-methylene-5-pyrrolidino-4,5-dihydroisoxazole-3-carboxamide 46 and pyrimidinone 21

An excess of NaH (38 mg, 1.6 mmol) was added to a solution of amide **44** (55 mg, 0.16 mmol) in dry DMF (10 cm^3), and the mixture was stirred under nitrogen for 10 min at 25 °C, then was filtered, and stirred under N_2 for a further 3 h. After this period the solvent was evaporated off under reduced pressure, and the residue was subjected to flash column chromatography (silica gel; EtOAc). Azadiene **46**, an oil (4 mg, 13%), and pyrimidinone **21** (8 mg, 35%) were obtained.

Compound 46. δ_H 1.73 (4 H, s, CH_2), 2.57–2.77 (4 H, m, CH_2NCH_2), 5.33 (1 H, br s, NH), 5.55 (1 H, br s, H-5), 6.18 (1 H, m, =CHH), 6.45 (1 H, m, =CHH) and 6.60 (1 H, br s, NH); *m/z* (CI) 196 $(MH)^+$.

4-[(5-Methyl-2-methylsulfanyl-6-oxo-1,6-dihydropyrimidin-1-yl)methyl]isoxazole-3-carboxylic acid ethyl ester 47

Isoxazoline **37** (3.9 g, 0.01 mol) was refluxed as a solution in toluene (75 cm^3) overnight. After removal of the solvent the residue was subjected to flash column chromatography (silica gel; 60% EtOAc–heptane). *Compound* **47** was obtained as a solid (2.2 g, 68%), mp 129 °C (EtOAc); δ_H 1.47 (3 H, t, *J* 7.1, CH_3), 2.06 (3 H, s, 5′-CH_3), 2.53 (3 H, s, SCH_3), 4.54 (2 H, q, *J* 7.1, OCH_2), 5.41 (2 H, s, $N^{1'}CH_2$), 7.70 (1 H, s, H-4′) and 8.37 (1 H, s, H-5); δ_C 13.3 and 14.3 (2 × CH_3), 15.0 (SCH_3), 37.5 ($N^{1'}CH_2$), 62.5 (OCH_2), 116.4 (C-4), 119.4 (C-5′), 149.6 (CH-4′), 153.3 (C-3), 159.0 (CH-5), 159.9 (C-2′), 160.3 (CO ester) and 162.8 (C-6′); ν_{max}(neat)/cm^{-1} 1731, 1667 and 1512; *m/z* (CI) 310 (MH^+) (Found: C, 50.46; H, 4.75; N, 13.62. $C_{13}H_{15}N_3O_4S$ requires C, 50.48; H, 4.89; N, 13.58%).

4-(Chloromethyl)isoxazole-3-carboxylic acid ethyl ester 48

A solution of isoxazoline **37** (800 mg, 2.10 mmol) in $CHCl_3$ (30 cm^3) saturated with HCl was heated and stirred in a sealed tube overnight at 60 °C. After removal of the solvent the residue was subjected to flash column chromatography (silica gel; 30% EtOAc–heptane). Compound **47** (126 mg, 19%) and the *less polar fragmentation product* **48** (205 mg, 52%; oil) were obtained. Compound **48**: δ_H($CDCl_3$) 1.44 (3 H, t, *J* 7.2, CH_3), 4.49 (2 H, q, *J* 7.2, OCH_2), 4.70 (2 H, s, CH_2Cl) and 8.59 (1 H, s, H-5); δ_C 14.2 (CH_3), 33.7 (CH_2Cl), 62.5 (CH_2O), 119.1 (C-4), 159.5 (C-3), 159.8 (CH-5) and 179.4 (CO); ν_{max}(neat)/cm^{-1} 1736; *m/z* (CI) 190 (MH^+) (Found: MH^+, 190.0312. $C_7H_9ClNO_3$ requires M, 190.0270).

4-[(5-Methyl-2-methylsulfanyl-6-oxo-1,6-dihydropyrimidin-1-yl)methyl]isoxazole-3-carboxamide 49

In a well sealed flask, a solution of ester **47** (163 mg, 0.52 mmol) in methanolic ammonia (45 g l^{-1} 20 cm^3) was stirred overnight at room temperature. After evaporation of the mixture, *amide* **49** was precipitated from heptane (solid; 131 mg, 90%), mp 232 °C (from EtOAc–heptane); δ_H[$(CD_3)_2SO$] 2.07 (3 H, s, 5′-CH_3), 2.62 (3 H, s, SCH_3), 5.36 (2 H, s, NCH_2), 7.94 (1 H, s, H-4′), 8.05 (1 H, s, NH), 8.33 (1 H, s, NH) and 8.91 (1 H, s, H-5); δ_C[$(CD_3)_2SO$] 12.6 (5′-CH_3), 14.4 (SCH_3), 37.5 (NCH_2), 115.3 (C-4), 118.4 (C-5′), 148.9 (CH-4′), 155.0 (C-2′), 158.8 (CH-5), 159.6 (C-3), 160.6 (CO) and 161.6 (C-6′); *m/z* (CI) 281 (MH^+) (Found: C, 47.23; H, 4.52; N, 19.87; S, 11.67. $C_{11}H_{12}N_4O_3S$ requires C, 47.14; H, 4.32; N, 19.99; S, 11.44%).

4-[2-(5-Methyl-2-methylsulfanyl-6-oxo-1,6-dihydropyrimidin-1-yl)ethyl]isoxazole-3-carboxylic acid ethyl ester 50

Isoxazoline **40** (3.87 g, 9.8 mmol) as a solution in $CHCl_3$ (75 cm^3) saturated with HCl was heated and stirred in a sealed tube overnight at 80 °C. The mixture was then diluted with CH_2Cl_2 (300 cm^3), washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was subjected to flash column chromatography (silica gel; 30% EtOAc–heptane). *Compound* **50** was obtained as a solid (2.12 g, 68%); δ_H 1.43 (3 H, t, *J* 7.1, CH_3), 1.99 (3 H, s, 5′-CH_3), 2.48 (3 H, s, SCH_3), 3.14 (2 H, t, *J* 7.2, CH_2), 4.30 (2 H, t, *J* 7.2, NCH_2), 4.48 (2 H, q, *J* 7.1, OCH_2), 7.63 (1 H, s, H-4′) and 8.32 (1 H, s, H-5); δ_C 13.1 (5′-CH_3), 14.1 (CH_3), 14.8 (SCH_3), 20.2 (CH_2), 44.1 (NCH_2), 62.1 (OCH_2), 116.9 (C-4), 119.2 (C-5′), 149.0 (CH-4′), 153.9 (C-2′), 158.1 (CH-5), 159.8 (C-3), 160.2 (CO) and 162.6 (C-6′); ν_{max}(neat)/

cm^{-1} 1729, 1669 and 1656; *m/z* (CI) 324 (MH^+) [Found: (EI) M^+, 323.0978. $C_{14}H_{17}N_3O_4S$ requires M, 323.0965].

4-[2-(5-Methyl-2-methylsulfanyl-6-oxo-1,6-dihydropyrimidin-1-yl)ethyl]isoxazole-3-carboxamide 51

In a well sealed flask, a solution of ester **50** (200 mg, 0.62 mmol) in methanolic ammonia (45 g l^{-1} 50 cm^3) was stirred overnight at room temperature. After evaporation the residue was subjected to flash column chromatography (silica gel; 60% EtOAc–heptane). Amide **51** was obtained as a solid (185 mg, 98%), mp 213–214 °C (from EtOAc); δ_H 2.00 (3 H, s, 5′-CH_3), 2.49 (3 H, s, SCH_3), 3.19 (2 H, t, *J* 7.2, CH_2), 4.35 (2 H, t, *J* 7.2, NCH_2), 5.69 (1 H, s, NH), 6.78 (1 H, s, NH), 7.64 (1 H, s, H-4′) and 8.28 (1 H, s, H-5); δ_C 13.1 (5′-CH_3), 14.7 (SCH_3), 20.1 (CH_2), 44.0 (NCH_2), 115.9 (C-4), 118.5 (C-5′), 148.9 (CH-4′), 156.0 (C-2′), 158.9 (CH-5), 159.9 (C-3), 161.2 (CO) and 161.8 (C-6′); ν_{max}(neat)/cm^{-1} 1706 and 1662; *m/z* (CI) 295 (MH^+) (Found: C, 48.80; H, 4.93; N, 18.75. $C_{12}H_{14}N_4O_3S$ requires C, 48.97; H, 4.79; N, 19.03%).

Conversion of ester 50 to 4-[2-(2-amino-5-methyl-6-oxo-1,6-dihydropyrimidin-1-yl)ethyl]isoxazole-3-carboxamide 52 and 3-methyl-7,8-dihydropyrrolo[1,2-*a*]pyrimidin-4(6*H*)-one 53

A solution of ester **50** (100 mg, 0.31 mmol) in Bu^{t}OH saturated with NH_3 (57 g l^{-1}) was heated for 8 days in a steel autoclave at 137 °C. After cooling and evaporation of the mixture, the residue was preadsorbed onto silica gel and subjected to flash column chromatography (5% MeOH–CH_2Cl_2). *Guanidine-amide* **52**, a solid (24 mg, 29%), and amide **51** (45%) were obtained. On occasions when the autoclave was not properly sealed, and the NH_3 gas escaped, the *pyrrolo*[1,2-*a*]*pyrimidine* **53** (0–30%) was formed as the reaction product.

Compound 52. δ_H[$(CD_3)_2SO$] 1.89 (3 H, s, 5′-CH_3), 2.96 (2 H, m, CH_2), 4.16 (2 H, m, NCH_2), 7.18 (2 H, s, NH_2), 7.55 (1 H, s, H-4′), 8.17 (1 H, s, NH amide), 8.45 (1 H, s, NH amide) and 9.10 (1 H, s, H-5); δ_C[$(CD_3)_2SO$] 12.8 (5′-CH_3), 19.5 (CH_2), 40.6 (NCH_2), 108.7 (C-5′), 115.5 (C-4), 151.5 (CH-4′), 154.5 (C-3), 155.4 (C-2′), 159.2 (CH-5), 161.4 (CO) and 161.9 (C-6′); *m/z* (EI) 263 $(M)^+$, 219 $(M - CONH_2)^+$ and 125 (pyrimidine base)$^+$ (Found: M^+, 263.1017. $C_{11}H_{13}N_5O_3$ requires M, 263.1018).

Compound 53. δ_H 2.04 (3 H, s, CH_3-3), 2.23 (2 H, m, CH_2-7), 3.08 (2 H, t, *J* 7.9, CH_2-8), 4.13 (2 H, t, *J* 7.3, CH_2-6) and 7.72 (1 H, s, H-2); δ_C 12.6 (CH_3-3), 19.0 (CH_2-7), 32.0 (CH_2-8), 46.5 (CH_2-6), 121.3 (C-3), 150.5 (CH-2), 152.5 (C-8a) and 161.7 (C-4); ν_{max}(neat)/cm^{-1} 1662, 1606 and 1562; *m/z* (CI) 151 (MH^+) (Found: M^+, 151.0900. $C_8H_{10}N_2O$ requires M, 151.0871).

8-Methyl-7-oxo-4,5-dihydro-7*H*-isoxazolo[5′,4′ : 3,4]pyrido[1,2-*a*]pyrimidine-3-carboxamide 57

Isoamyl nitrite (226 cm^3, 1.9 mmol) and amide **52** (50 mg, 0.19 mmol) were heated in dry DMF (40 cm^3) at 80 °C for 4 h. After evaporation off of the solvent the residue was subjected to flash column chromatography (4% MeOH–CH_2Cl_2). *Tricycle* **57** was obtained as a solid (12 mg, 24%); δ_H 2.16 (3 H, s, CH_3-8), 3.28 (2 H, t, *J* 7.1, CH_2-4), 4.47 (2 H, t, *J* 7.1, CH_2-5), 5.71 (1 H, br s, NH), 6.77 (1 H, br s, NH) and 7.89 (1 H, s, H-9); δ_C[$(CD_3)_2SO$] 13.4 (CH_3-8), 17.2 (CH_2-4), 40.4 (CH_2-5), 119.5 (C-8), 124.7 (C-3a) 143.1 (C-10b), 147.9 (CH-9), 155.2 (C-3), 159.3 (C-10a), 159.5 (CO) and 160.3 (C-7); ν_{max}(neat)/cm^{-1} 3369, 1707, 1675, 1625 and 1537; *m/z* (CI) 246 (MH^+) (Found: MH^+, 246.0774. $C_{11}H_{11}N_4O_3$ requires M, 246.0753).

7-Methyl-10,11-dihydro-4*H*,6*H*-isoxazolo[3,4-*e*]pyrimido[1,2-*a*][1,3]diazepine-6,11-dione 10a

NaH (20 mg, 0.85 mmol) was added to a solution of amide **49** (100 mg, 0.36 mmol) in dry DMF (10 cm^3); the mixture was stirred at 25 °C for 20 min. The reaction was then quenched by the addition of conc. HCl (until acidic), and concentrated under reduced pressure. The residue was taken up in aq. MeOH, and the precipitated product was collected and dried. *Lactam* **10a** was thus obtained microanalytically pure (solid; 40 mg, 48%); δ_H[$(CD_3)_2SO$] 2.02 (3 H, s, CH_3-7), 5.42 (2 H, s, CH_2-4), 7.85 (1 H, s, H-8), 9.44 (1 H, s, H-3) and 11.62 (1 H, s, 10-NH); δ_C[$(CD_3)_2SO$] 13.1 (CH_3-7), 32.5 (CH_2-4), 115.6 (C-3a), 118.6 (C-7), 147.7 (C-11a), 148.9 (CH-8), 156.3 (C-9a), 158.1 (6-CO), 158.1 (CH-3) and 161.0 (11-CO); *m/z* (CI) 233 (MH^+); ν_{max}(KBr)/cm^{-1} 1703 and 1676; *m/z* (CI) 233 (MH^+) (Found: C, 51.43; H, 3.81; N, 24.02. $C_{10}H_8N_4O_3$ requires C, 51.73; H, 3.47; N, 24.13%).

8-Methyl-4,5,11,12-tetrahydro-7*H*-isoxazolo[3,4-*e*]pyrimido-[1,2-*a*][1,3]diazocine-7,12-dione 10b

NaH (20 mg, 0.85 mmol) was added to a solution of amide **51** (100 mg, 0.34 mmol) in dry DMF (10 cm^3); the mixture was stirred at 25 °C until the starting amide was consumed (TLC). The solvent was then evaporated off, and the residue was subjected to flash column chromatography (silica gel; 5% MeOH–CH_2Cl_2). *Lactam* **10b** was obtained as a solid (51 mg, 61%); δ_H[$(CD_3)_2SO$] 1.98 (3 H, s, CH_3-8), 3.12 (2 H, m, CH_2-4), 4.59 (2 H, m, CH_2-5), 7.81 (1 H, s, H-9), 8.95 (1 H, s, H-3) and 11.85 (1 H, s, 11-NH); δ_C[$(CD_3)_2SO$] 12.7 (CH_3-8), 19.6 (CH_2-4), 41.4 (CH_2-5), 112.2 (C-3a), 118.4 (C-8), 145.8 (C-12a), 148.3 (CH-9), 157.6 (C-10a), 158.6 (CH-3), 161.8 (7-CO) and 161.9 (12-CO); ν_{max}(neat)/cm^{-1} 1681 and 1556; *m/z* (CI) 247 (MH^+) (Found: C, 53.54; H, 4.23; N, 23.05. $C_{11}H_{10}N_4O_3$ requires C, 53.66; H, 4.09; N, 22.75%).

***N*-[(2-Dimethylamino)ethyl]4-[2-(5-methyl-2-methylsulfanyl-6-oxo-1,6-dihydropyrimidin-1-yl)ethyl]isoxazole-3-carboxamide 59**

Ester **50** (100 mg, 0.31 mmol) and 2-(dimethylamino)ethylamine (638 mm^3, 2.33 mmol) were heated in Pr^{i}OH (5 cm^3) at 90 °C for 3 days. After evaporation of the mixture, the residue was taken up in water and extracted with CH_2Cl_2. The combined organic phases were dried (K_2CO_3), and concentrated. The residue was subjected to flash column chromatography (silica gel; 2% MeOH–EtOAc). *Amine* **59** was obtained as a solid (87 mg, 76%); δ_H 2.00 (3 H, s, 5′-CH_3), 2.26 [6 H, s, $(CH_3)_2N$], 2.49 [5 H, m, SCH_3 and $CH_2N(CH_3)_2$], 3.19 (2 H, t, *J* 7.0, $N^{1\prime}CH_2CH_2$), 3.53 (2 H, m, CH_2NH), 4.37 (2 H, t, *J* 6.9, $N^{1\prime}CH_2$), 7.35 (1 H, br s, NH), 7.64 (1 H, s, H-4′) and 8.24 (1 H, s, H-5); δ_C 13.3 (5′-CH_3), 15.0 (SCH_3), 20.4 (CH_2), 36.9 (CH_2NH), 44.5 (N^1CH_2), 45.3 [$N(CH_3)_2$], 57.7 [$CH_2N(CH_3)_2$], 116.6 (C-4), 119.2 (C-5′), 149.1 (CH-4′), 155.6 (C-3), 157.8 (CH-5), 159 6 (C-2′), 160.4 (CO) and 161.0 (C-6′); ν_{max}(neat)/cm^{-1} 3349, 3103, 2944, 1669, 1596, 1556 and 1510; *m/z* (CI) 366 (MH^+) (Found: C, 52.71; H, 6.15; N, 18.95. $C_{16}H_{23}N_5O_3S$ requires C, 52.58; H, 6.34; N, 19.16%).

9-[2-(Dimethylamino)ethyl]-3-methyl-6,7,8,9,10,11-hexahydropyrimido[1,2-*a*]pyrrolo[3,4-*d*][1,3]diazepine-4,8,10-trione 60

NaH (5 mg, 0.19 mmol) was added to a solution of amide **59** (23 mg, 0.06 mmol) in dry DMF (50 cm^3); the mixture was stirred at 25 °C under nitrogen until all the starting material was consumed (TLC). The solvent was then evaporated off under reduced pressure, and the residue was subjected to flash column chromatography (silica gel; 2% MeOH–EtOAc). *Compound* **60** was obtained as a yellow oil (5 mg, 25%); δ_H 2.04 (3 H, s, 3-CH_3), 2.25 [6 H, s, $N(CH_3)_2$], 2.50 (2 H, t, *J* 6.3, CH_2-2′), 2.77 (2 H, m, CH_2-7), 3.65 (2 H, t, *J* 6.3, CH_2-1′), 4.50–4.70 (2 H, m, CH_2-6) and 7.60 (1 H, s, CH-2); δ_C[$(CD_3)_2SO$] 13.00 (CH_3), 23.70 (CH_2-7), 35.15 (CH_2-1′), 40.95 (CH_2-6), 44.90 [$N(CH_3)_2$], 56.50 (CH_2-2′), 112.65 (C-7a), 113.75 (C-3), 138.70 (C-10a), 146.60 (CH-2), 152.70 (C-11a), 162.55 (4-CO), 166.70 (10-CO) and 170.30 (8-CO); ν_{max}(neat)/cm^{-1} 1713, 1674 and 1551; *m/z* (FAB) 318 (MH^+) [Found: (CI) MH^+, 318.1573. $C_{15}H_{20}N_5O_3$ requires M, 318.1566].

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