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Pyrimidines과 pyrimidine의 헤테로고리의 합성

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Synthesis of Pyrimidines and Heteroannulated Pyrimidine Ring Systems

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요 약. Imine 화합물 **1**을 hydrazine hydrate와 같은 nitrogenous 시약과 반응시켜서 치환된 pyrimidines 화합물을 합성하였다. 얻어진 화합물 **2**를 다양한 반응조건, 즉 propionic acid, formic acid, ethyl chloroformate, acdetic anhydride, carbon disulphide, cyanogene bromide, triflauroacetic acid 및 ethyl chloroacetate와 반응시켜서 대응하는 화합물을 좋은 수율로 얻었으며, 반응은 Dimroth-type 자리옮김 반응을 통하여 진행되었다.
주제어: 피리미딘, 트리아졸로피리미딘, 트리아지노피리미딘, 벤조피란 유도체

ABSTRACT. We have involved the imine compound **1** in condensations with various nitrogenous reagents including hydrazine hydrate to construct differently substituted pyrimidines. One of the pyrimidines so obtained was further subjected to interactions with different reagents such as propionic acid, formic acid, ethyl chloroformate, acdetic anhydride, carbon disulphide, cyanogene bromide, triflauroacetic acid and ethyl chloroacetate which resulted in the formation of annulated heterocyclic systems as pairs of isomers in most cases as a result of Dimroth-type rearrangement.
Keywords: Pyrimidine, Triazolopyrimidine, Triazinopyrimidine, Benzopyran derivatives

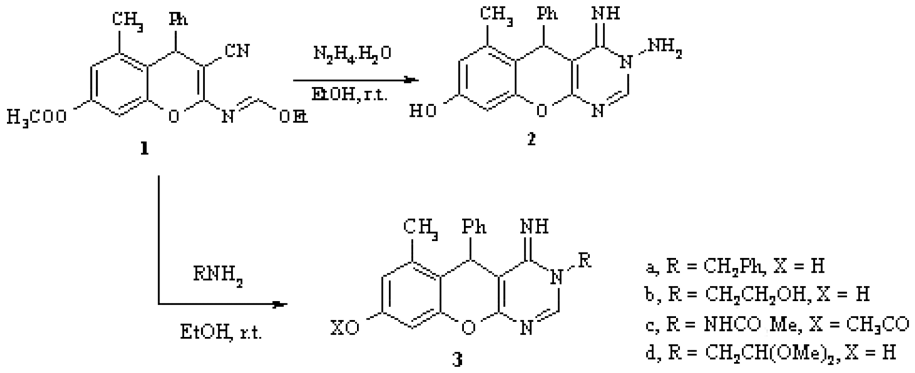
INTRODUCTION

Synthetic heterocycles have widespread interest as herbicides, insecticides, dyes, organic conductors and drugs. Nitrogen-containing heterocycles are of broad pharmaceutical interest and this justifies continuing efforts in the development of structural-activity relationship in this series and of new synthetic strategies.[1]

Our focused goal here is to approach synthetic routes for several heterocyclic systems based on benzopyran and expected to have biological applications. These heterocycles include pyrrole, pyridine, pyrimidine, oxazine, and triazole residues. Compounds containing fused pyrimidine ring have significant biological activity,[2-4] particularly in anti-cancer and antiviral research.[2]

RESULTS AND DISCUSSION

The condensation between compound **1** and hydrazine hydrate in ethanol at room temperature delivered the pyimidines **2** in 61% yield (*Scheme* 1). Structural evidence for the reaction product is based on the spectroscopic data. The IR spectrum revealed stretching vibrations at 3332 cm^{-1} (very br) (OH, NH_2, NH) and 1650 cm^{-1} for C=N. The ^1H NMR spectrum showed signals 2.20 (3H, s, CH_3), 5.28 (1H, s, 5-H), 6.36 (1H, d, J 0.9, 7-H), 6.51 (1H, d, J 0.9, 9-H), 6.90 (2H, br s, NH_2) and 9.78 (1H, br s, OH). Consequently, the imine compound **1** was further condensed with other amines including benzylamine, ethanolamine, methyl carbazate and 2-aminoacetaldehyde dimethyl acetal in absolute ethanol at room temperature and gave the substituted pyrimidines **3a-d** in moderate to good yields (*Scheme* 1). The structures of compounds **3a-d** were generally proven on the basis of spectroscopic data and in one case by X-ray crystallography. On examination of the ^1H NMR spectrum of compound **3b**, it was expected to show two triplets corresponding to the two methylene groups but surprisingly, the spectrum was more complicated and gave four different resonances (each integrating for one proton) indicating the presence of diastereotopic hydrogens from two pairs of hydrogens. A suggested explanation is the formation of an additional ring but X-ray crystal-



***Scheme* 1.**

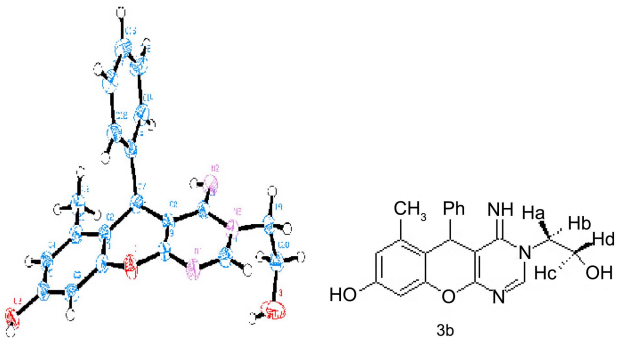


***Fig.* 1.** X-ray Crystallographic Analysis. 3-(2-Hydroxyethyl)-4-imino-6-methyl-5-phenyl-4,5-dihydro-3H-chromeno[2,3-d]pyrimidin-8-ol, 3b.

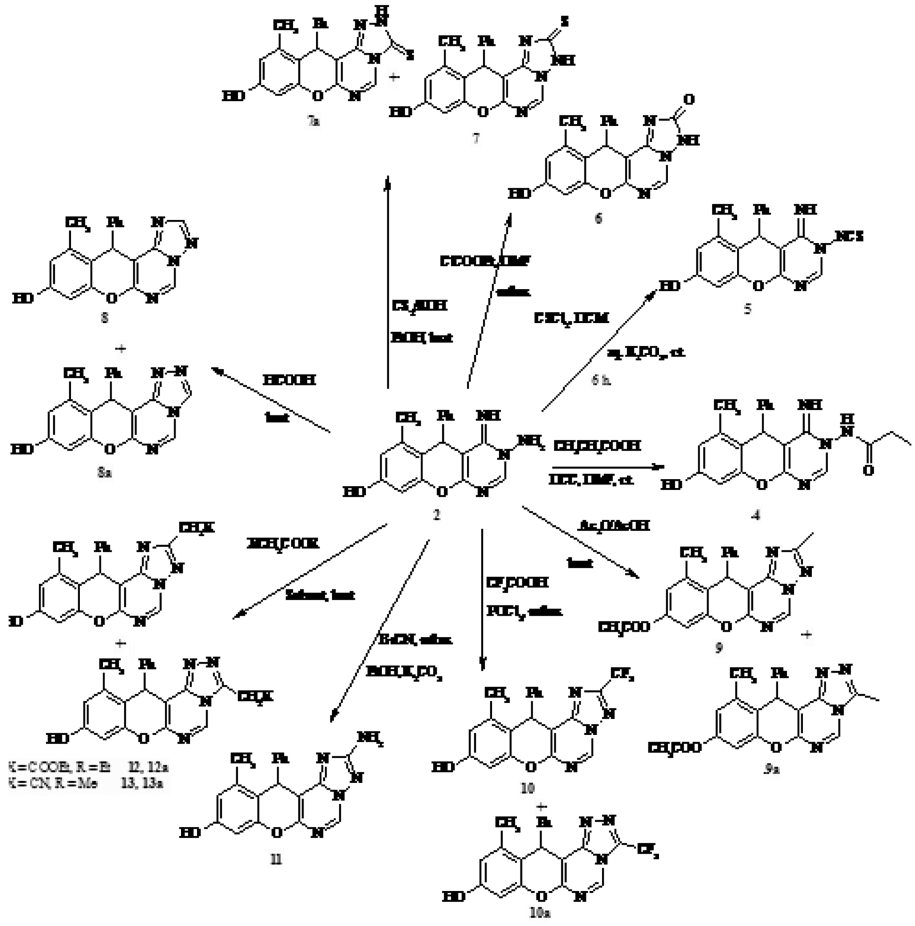
lographic analysis proved that the structure **3b** is the correct one. An explanation for the presence of diastereotopic hydrogens is presumably due to restricted rotation caused by formation of hydrogen bonds which might formed in solution but not in solid state.

The aminopyrimidine **2** could be used as a key intermediate in heterocyclic synthesis and for substituted heterocyclic systems. Therefore, the coupling between compound **2** and carboxylic acids such as propionic acid (2 equivalents) in DMF using the coupling reagent dicyclohexyl carbodimide (DCC), at room temperature, gave the amide **4** in 64% yield (*Scheme* 2). An easy and efficient method for preparation of isothiocyanates, important intermediates for organic synthesis, is the reaction between amines and thiophosogene.[5] Thus, aminopyrimidine **2** was converted into the isothiocyanate **5** when treated with thiophosogene in dichloromethane in the presence of saturated aqueous potassium carbonate at room temperature for 6 hours and resulted in 59% yield (*Scheme* 2). IR, ^{1}H NMR, and ^{13}CNMR are all consistent with the proposed structures **4** and **5**.

The aminopyrimidine **2** proved to be highly reactive towards various reagents and underwent numerous chemical transformations, resulting in the formation of a wide range of annulated chromenopyrimidine systems.

The synthesis of [1,2,4]triazol-2-one **6** could be accomplished through the interaction of the aminopyrimidine **2** and ethyl chloroformate[6] in anhydrous DMF at reflux temperature for 1h and resulted in 69% yield (*Scheme* 2). Treatment of compound **2** with carbon disulfide in an alcoholic solution of potassium hydroxide at reflux gave the triazolthione **7**[6-9] in a poor yield (*Scheme* 2). The structure was established by the compatible spectroscopic data with the proposed structure. From the ^{1}H NMR spectrum, the product was obtained as a pair of isomers (**7** and **7a**) (77:23) presumably as a result of Dimroth- type rearrangement.[10-12] As mentioned, the reaction was subjected to conditions which strongly favour formation of the thermodynamically more stable isomer (strong base and heat for long time) which could enhance the isomerization to give only one isomer but still the two isomers were seen; hence this should be the thermodynamic mixture. It worth to mention that the structure **7** was probably the major isomer, this is based on the fact that it is more conjugated and looks like a tetraene; on the other hand structure **7a** looks like a triene.

The condensation between the aminopyrimidine **2** and formic acid under reflux temperature readily, after aqueous workup, furnished the expected triazole product as two isomers (**8** and **8a**), again generated by Dimroth-type rearrangement (*Scheme* 2). In this case, the two isomers were produced in a 1:1 ratio according to ^{1}H NMR data, the hot acidic conditions used should also generate a thermodynamic mixture **8** and **8a** have quite similar chromophores. The ^{1}H NMR data of the reaction product (**8** and **8a**) displayed signals at 8.55 and 8.75 ppm, which related to the resonances of 5-H in the two structures, a more characteristic proton is 2-H that showed two chem-



***Scheme* 2.**

ical shift values for both structures at 9.57 and 9.59 ppm.

An additional synthetic pathway for constructing triazoles based on the aminopyrimidine compound **2** was established using readily available reagents (a mixture of acetic anhydride and acetic acid) to convert the pyrimidin-8-ol **2** into triazolo[1,5-c]pyrimidin-9-ylacetate **9** which resulted in 83% yield (*Scheme* 2).

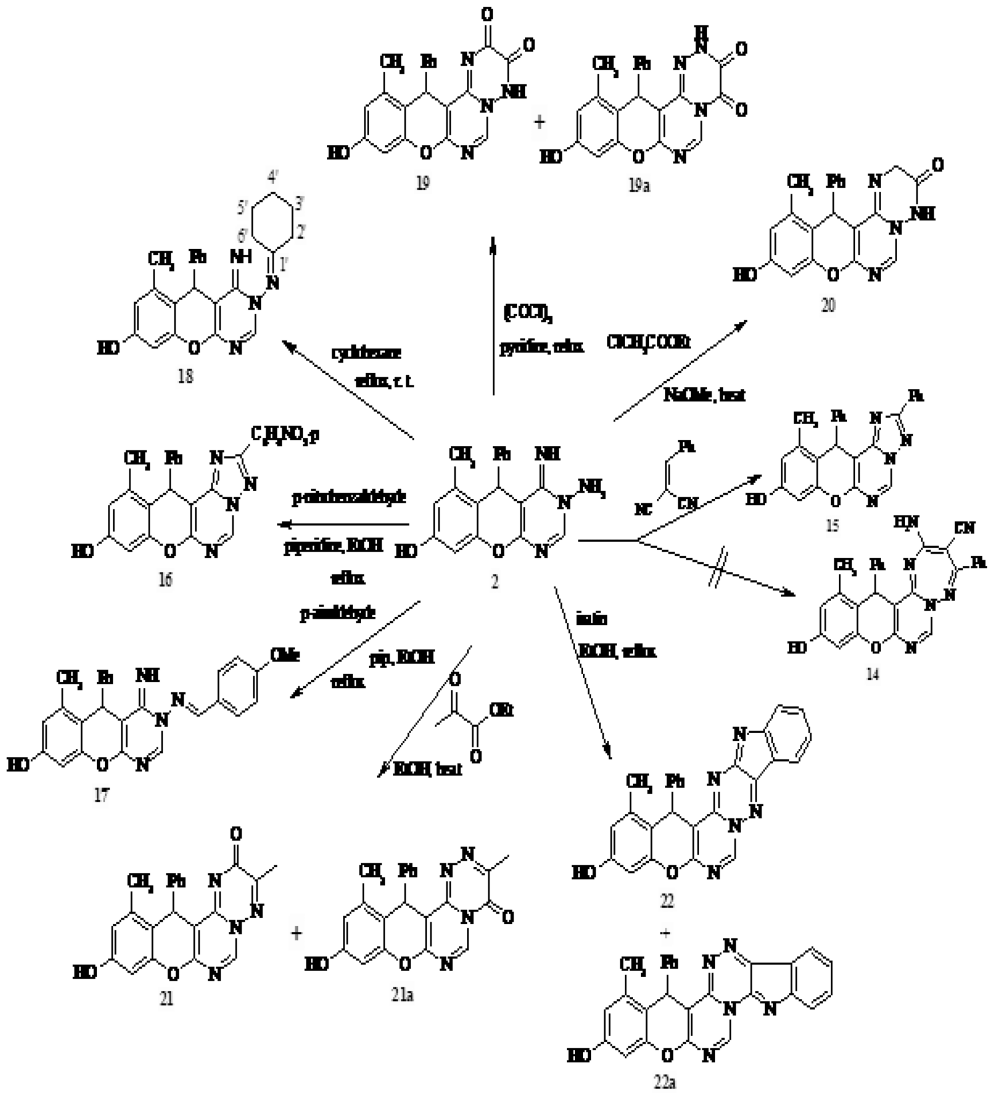
Interestingly, Dimroth rearrangement worked again and the result was a 1:1 mixture of structures **9** and **9a**, strongly thermodynamic conditions were used (acetic anhydride and acetic acid under reflux). Again, very similar chromophores in both isomers so might expect 1:1 mixture under these thermodynamic conditions so perhaps no surprise. Structure assignment for the reaction products was given from the spectroscopic data.

Therefore, an easy access to trifluoromethyl derivative **10** was carried out by the condensation of aminopyrimidine **2** and trifluoroacetic acid in the presence of phosphorous oxychloride under reflux conditions for 7 hours.[13-14] The product was obtained as a pair of isomers (**10** and **10a**) in the ratio 61:29 (based on ^{1}H NMR data) in 40% combined yield (*Scheme* 2). The structures proposed for the reaction products were confirmed with the aid of spectroscopic data. ^{13}C NMR showed a signal for a quaternary carbon at 160.1 ppm most likely to be related to the carbon attached to the trifluoromethyl group.

Moreover, reaction of **2** with cyanogen bromide (2 equiv.) in absolute ethanol containing anhydrous potassium carbonate under reflux afforded 2-amino-triazolo [1,5-c]pyrimidin-9-ol **11** as single isomer (*Scheme* 2).[7] The formation of a single isomer perhaps is due to the fact that the reaction was not hot enough in addition to the heterogeneous base (K_2CO_3).

When the reaction between compound **2** and diethyl malonate[15] was conducted in DMF under reflux conditions, elimination of water and ethanol occurred and gave the acetate derivatives as two isomers **12** and **12a** (about 66:33) in 86% yield (*Scheme* 2).

Similarly, condensation between compound **2** and methyl cyanoacetate in refluxing ethanol resulted in formation of



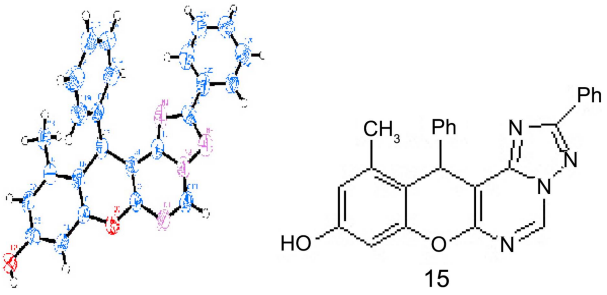
Scheme 3.

the acetonitrile derivative as an isomeric mixture **13** and **13a** (77:23) in 49% yield (*Scheme* 2). The identities of both compounds were confirmed on the basis of spectroscopic data. For the acetate derivative **12**, an IR spectrum showed stretching vibration frequencies at 3421, 1737 and 1631 cm^{-1} corresponding to OH, CO and C=N respectively. The ^1H NMR data displayed the expected pattern for the ethoxy group at 1.16 ppm (3H, t, J 7.1, CH_3) and at 4.10 (2H, q, J 7.1, CH_2O), also a signal at 3.95 ppm (2H, s, CH_2CO) and the 5-H chemical shift was found to be at 9.55 ppm which is more downfield than the corresponding one in compound **2** (at 8.05 ppm).

A trial to prepare the triazepine derivative **14** through the interaction between the aminopyrimidine **2** and benzylidenemalononitrile in a basic medium was unfortunately unsuccessful, but led interestingly to compound **15** which formed as the reactants were mixed together with few drops of acetone and left at room temperature for 30 min (*Scheme* 3). IR spectrum showed no absorption bands for NH_2 or CN groups; ^1H-NMR and ^{13}C-NMR and MS were consistent with proposed structure. Further proof was gained chemically when compound **2** was allowed to condense with benzaldehyde in acidic medium to furnish the same product **15**. X-ray crystallographic analysis finally proved the structure. A proposed explanation for the formation of compound **15** is that the reaction started first with the addition of the amino group lone pair to the double bond of benzylidenemalononitrile (Micheal type addition); since malononitrile is a good leaving group, it can be ejected by addition of the imino lone pair to the benzylic carbon followed by loss of hydrogen (aerial oxidation) to furnish compound **15**.

The condensation between aminopyrimidine compound **2** and aromatic aldehydes was studied next aiming to prepare analogues for compound **15** by an alternative route; the reaction was performed in ethanolic piperidine at reflux temperature. Two examples of aromatic aldehydes were chosen (*p*-nitrobenzaldehyde and p-anisaldehyde), in the case of first example the reaction proceeded through a condensation-addition protocol to furnish the triazolopyrimidine **16** as a single isomer in 71% yield (*Scheme* 3). The identity of compound **16** was proven based on its spectroscopic data which have close similarity to compound **15**. On the other hand, when *p*-anisaldehyde was allowed to react with compound **2**, unlike *p*-nitrobenzaldehyde, it only underwent a condensation reaction with the amino group without cyclization to afford the Schiff-base **17**. ^{1}H NMR data showed a singlet signal at 8.30 ppm (integrating for two protons) attributable to 5-H and CH=N protons and this assisting the uncyclized structure. In a similar manner, the condensation between amino-pyrimidine **2** and cyclohexanone (neat) under reflux[16] for 6 hours (TLC controlled) afforded the condensation product **18** as a fairly pure single isomer in 60% yield (*Scheme* 3).

With the aminopyrimidine **2** in hand, a series of fused pyrimidinotriazines could be obtained through a condensation pathway. Thus, when a mixture of compound **2** and oxalyl chloride was heated in pyridine for several hours, afforded the triazines **19** and **19a** as a pair of isomers (Dimroth-type rearramgment) in 84% combined yield (*Scheme* 3). The isomeric mixture was in a ratio of 6:5 (both isomers look to have similar chromophores and thus is not surprise to be obtained in this ratio) as indicated from the ^{1}H NMR spectrum which displayed all signals expected for the two isomers. Also, interaction between aminopyrimidine **2** and ethyl chloroacetate in sodium methoxide under reflux gave compound **20** as single isomer.[6] Spectroscopic data were consistent with proposed structure, for example, the ^{1}H NMR data revealed a resonance of CH_2 group to be at 6.58 ppm, in addition there are two resonances for two exchangeable protons at 9.30 and 9.91 ppm (OH and NH) which are reasonable chemical shifts for such protons.



15

***Fig.* 2.** X-ray Crystallographic Analysis. 11-Methyl-2,12-diphenyl-12H-chromeno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-9-ol 15.

The reaction between compound **2** and ethyl pyruvate and isatin in boiling ethanol afforded compounds **21, 21a** (ratio 1:1) and **22, 22a** (ratio 1:1) respectively according to ^{1}HNMR spectra (*Scheme* 3).

EXPERIMENTAL

All products were dried in an oven at 100 ºC then using high vacuum under pressure of 1 mm Hg. All melting points uncorrected and were determined on Stuart electric melting point apparatus and on a kolfer hot-stage apparatus. Infrared spectra were recorded on Bruker or Satellite 2000 spectrometer using KBr discs series Fourier Transform Infrared Spectrometer. ^{1}H NMR spectra were recorded at Bruker DX400 (unless stated) at 400 MHz and ^{13}C NMR spectra measured on the same instrument (unless stated) at 100.6 MHz. Mass spectra were determined on GC-MS (QP 1000 EX) SHIMADZU spectrometer. At an ionizing voltage of 70ev mass spectrometry.

General procedure for reaction between imine 1 and amines

To a stirred solution of the imine **1** (3.76 g, 10 mmol) in absolute ethanol (30 ml) was added appropriate amine (20 mmol, 2 equiv.). The mixture was stirred at room temperature and after 20 minutes, a solid started to precipitate; stirring was continued for an additional 2 h. The solid product was collected by filtration, washed with ethanol, then dried and crystallized from proper solvent to give *N-aminopyrimidine* **2** and the pyrimidines **3a-d**.

3-Amino-4-imino-6-methyl-5-phenyl-4,5-dihydro-3H-chromeno[2,3-d]pyrimidin-8-ol 2

Using the general procedure, reaction between imine **1** (3.76 g, 10 mmol) and hydrazine hydrate (1.25 g, 25 mmol, 2.5 equiv.) followed by crystallization from ethanol gave the *N-aminopyrimidine* **2** (1.95 g, 61%), as a colorless solid m.p. 260-261 ºC; IR, ν_{max}/cm^{-1}, 3332 (very br), 1650, 1591; ^{1}H NMR δ_H 2.20 (3H, s, CH_3), 5.28 (1H, s, 5-H), 6.36 (1H, d, J 0.9, 7- (or 9-) H), 6.51 (1H, d, J 0.9, 9- (or 7-)), 6.90 (2H, br s, NH_2), 7.12 (1H, t, J 7.4, 4-H-Ph), 7.23 (2H, t, J 7.4, 3- and 5-H-Ph), 7.32 (2H, d, J 7.4, 2- and 6-H-Ph), 8.05 (1H, s, 2-H), 9.78 (1H, br s, OH); ^{13}C NMR δ_C 19.2 (CH_3), 36.8 (5-CH), 101.1, 107.6 (7-and 9-CH), 110.0, 111.8, 114.2, (all ArC), 126.6, 128.3, 128.7 (all ArCH), 138.2 (ArC), 144.38 (2-CH), 155.2, 156.3, 157.1 (all ArC);

m/z [EI] 320 (M^+, 25%), 304 (100), 277 (8), 228 (30), 201 (27), 129 (10), 55 (54).

By a similar procedure, the imine **1** (0.94 g, 2.5 mmol) was reacted with other nitrogen nucleophiles (5 mmol) to furnish compounds **3a-d**.

3-Benzyl-4-imino-6-methyl-5-phenyl-4,5-dihydro-3H-chromeno[2,3-d]pyrimidin-8-ol 3a

Using the general procedure, reaction of compound **1** with benzylamine (0.54 ml, 5 mmol, 2 equiv.) followed by crystallization from ethyl acetate gave the *pyrimidine* **3a** (0.686 g, 69%) as a pale yellow solid, m.p. 265-267 ºC, IR, ν_{max}/cm^{-1}, 3355, 1639, 1623; ^{1}H NMR δ_H 2.18 (3H, s, CH_3), 5.01 (1H, d, J 14.9, H_a), 5.05 (1H, s, 5-H), 5.15 (1H, d, J 14.9, H_b), 6.30 (1H, s, 7- (or 9-) H), 6.42 (1H, s, 9- (or 7-) H), 6.76 (1H, br s, NH), 7.15-7.37 (10H, m, 10 x Ar-H), 8.29 (1H, s, 2-H), 9.73 (1H, br s, OH); ^{13}CNMR δ_C 21.3 (6-CH_3), 34.9 (5-CH), 50.0 (CH_2), 87.0, 100.0 (both ArC), 107.4 (ArCH), 109.6 (ArC), 112.1, 126.8, 127.8, 128.4 128.6, 128.8 (all ArCH), 137.3, 138.3, 144.4, 150.5 (all ArC), 151.6 (2-CH), 157.0 (ArC); MS [ES] [Found: $[M^+ + H]$, 396.1711. $C_{25}H_{22}N_3O_2$ requires *M*, 396.1712].

3-(2-Hydroxyethyl)-4-imino-6-methyl-5-phenyl-4,5-dihydro-3H-chromeno[2,3-d]pyrimidin-8-ol 3b

Using the general procedure, reaction of imine **1** with ethanolamine (0.305 g, 5 mmol, 2 equiv.) followed by crystallization from ethyl acetate gave the *pyrimidine* **3b** (0.4 g, 45%) as colorless crystals, m.p. 270 ºC, IR, ν_{max}/cm^{-1}, 3443 (very br), 1644, 1593, 1429; ^{1}H NMR δ_H 2.10 (3H, s, CH_3), 3.51 (1H, dt, J 4.3 and 13.5, H_a), 3.60 (1H, ddd, J 3.8, 6.9 and 13.4, H_b), 3.80 (1H, ddd, J 4.0, 6.9 and 13.4, H_c), 3.95 (1H, app. dt, J 4.4, 13.5, H_d), 4.13 (1H, br s, OH), 5.10 (1H, s, 5-H), 6.38 (1H, d, J 1.9, 7- (or 9-) H), 6.45 (1H, d, J 1.9, 9- (or 7-) H), 7.0 (1H, br s, NH), 7.15 (1H, t, J 7.4, 4-H-Ph), 7.23 (2H, t, J 7.4, 3- and 5-H-Ph), 7.33 (2H, d, J 7.4, 2- and 6-H-Ph), 7.98 (1H, s, 2-H), 9.10 (1H, br s, OH); ^{13}C NMR δ_C 19.4 (CH_3), 36.4 (5-CH), 50.5 (CH_2-N), 58.0 (CH_2-O), 100.4 (ArC), 101.1, 114.2 (7- and 9-CH), 114.3 (ArC), 126.9 (4-CHPh), 128.6 (4 x ArCH), 138.3, 144.3 (both ArC), 150.9 (ArCH), 151.8, 156.9, 157.1 (all ArC); MS [Found: $[M+H]^+$, 350.1496. $C_{20}H_{20}N_3O_3$ requires *M* 350.1505].

4-Imino-3-(methoxycarbonylamino)-6-methyl-5-phenyl-4,5-dihydro-3H-chr-omeno [2,3-d]pyrimidin-8-yl acetate 3c

Using the general procedure, reaction of compound **1** with methyl carbazate (0.45 g, 5 mmol, 2 equiv.) followed by crystallization from methanol gave *the carbamate* **3c** (0.5 g, 47%) as colorless crystals, m.p. 186 ºC, IR, ν_{max}/cm^{-1}, 3369, 3148, 1771, 1648, 1622; ^{1}H NMR δ_H 2.23 (3H, s, 6-CH_3), 2.26 (3H, s, CH_3CO), 3.35 (1H, br s, NHCO), 3.49 (3H, s, CH_3O), 5.63 (1H, s, 5-H), 6.88 (1H, d, J 2.0, 7- (or 9-) H), 7.08 (1H, d, J 2.0, 9- (or 7-) H), 7.18 (1H, t, J 7.4, 4-H-Ph), 7.30 (2H, t, J 7.4, 3- and 5-H-Ph), 7.40 (2H, d, J 7.4, 2- and 6-H-Ph), 8.45 (1H, s, 2-H), 8.60 (1H, br s, NH); ^{13}C NMR δ_C 19.0 (6-CH_3), 21.2 (CH_3CO), 51.7 (CH_3O), 99.4 (ArC), 109.08 (7- (or 9-) CH), 120.5 (ArC), 121.0 (9- (or 7-) CH), 127.8 (4-CH-Ph), 128.3 (2 x ArCH), 129.2 (2 x ArCH), 138.7, 142.1, 150.2, 150.2 (all ArC), 152.7 (ArCH), 154.1 (ArC), 158.4 (CO-NH), 169.4 (CO-O); MS [ES] [Found: $[M+H]^+$, 421.1499. $C_{22}H_{21}N_4O_5$ requires *M,* 421.1512].

3-(2,2-Dimethoxyethyl)-4-imino-6-methyl-5-phenyl-4,5-dihydro-3H-chromeno[2,3-d]pyrimidin-8-ol 3d

Using the general procedure, reaction of imine **1** with 2-aminoacetaldehyde dimethyl acetal (0.52 g, 5 mmol, 2 equiv.) followed by crystallization from methanol gave the *pyrimidine* **3d** (0.6 g, 61%) as pale yellow crystals, m.p. 270-272 ºC, IR, ν_{max}/cm^{-1}, 3345, 2954, 1626, 1411; ^{1}H NMR δ_H 2.19 (3H, s, 6-CH_3), 3.34 (3H, s, CH_3O), 3.36 (3H, s, CH_3O), 3.86 (1H, dd, J 6.0, 13.4, H_a), 3.95 (1H, dd, J 4.7, 13.4, H_b), 4.60 (1H, app. t, J 6.0, H_x), 5.04 (1H, s, 5-CH), 6.35 (1H, s, 7- (or 9-) H), 6.45 (1H, s, 9- (or 7-) H), 6.80 (1H, br s, NH), 7.15 (1H, t, J 7.5, 4-H-Ph), 7.23 (2H, t, J 7.5, 3- and 5-H-Ph), 7.33 (2H, d, J 7.5, 2- and 6-H-Ph), 7.95 (1H, s, 2-H), 9.75 (1H, br s, OH); ^{13}C-NMR δ_C 21.3 (6-CH_3), 34.8 (5-CH), 49.2 (CH_2), 54.8, 54.9 (both CH_3O), 99.4 (O-CH-O), 100.3 (ArCH), 107.7 (7- (or 9-) CH), 109.5 (ArC), 112.0 (9- (or 7-) CH), 126.8 (4-PhCH), 128.4 (2 x ArCH), 128.6 (2 x ArCH), 138321.4, 144.2, 150.4 (all ArC), 152.0 (ArCH), 155.2, 156.9 (both ArC); MS [ES] [Found: $[M+H]^+$, 394.1767. $C_{22}H_{24}N_3O_4$ requires *M*, 394.1751].

N-(8-Hydroxy-4-imino-6-methyl-5-phenyl-4,5-dihydro-3H-chromeno[2,3-d]pyramidin-3-yl)propionamide 4

To a solution of the *N*-amino-pyrimidine **2** (0.8 g, 2.5 mmol) in anhydrous DMF (10 ml) was added DCC (0.6 g, 3 mmol, 1.2 equiv.), the solution stirred at room temperature for 10 minutes, then propionic acid (0.37 ml, 5 mmol, 2 equiv.) was added and the reaction mixture stirred overnight. The precipitated dicyclohexylurea was removed by filtration, the filtrate was evaporated and the solid obtained washed with ether then crystallized from ethanol to furnish the *propionamide* **4** (0.6 g, 64%) as a colorless solid,

m.p. 227-229 ºC, IR, ν_{max}/cm^{-1}, 3331, 3165, 2923, 2854, 1677, 1649, 1542; ^{1}H NMR δ_H 0.80 (3H, t, J 7.5, CH_3), 2.10 (3H, s, 6-CH_3), 2.20 (2H, q, J 7.5, CH_2), 5.15 (1H, s, 5-H), 5.78 (1H, br s, NH), 6.40 (1H, d, J 2.2, 7- (or 9-) H), 6.50 (1H, d, J 2.2, 9- (or 7-) H), 7.12 (1H, t, J 7.7, 4-H-Ph), 7.23 (2H, t, J 7.7, 3- and 5-H-Ph), 7.43 (2H, t, J 7.7, 2- and 6-H-Ph), 8.10 (1H, s, 2-H); ^{13}C NMR δ_C 9.6 (CH_3), 19.2 (6-CH_3), 27.6 (CH_2), 36.6 (5-CH), 100.4 (ArC), 101.1 (7- (or 9-) CH), 113.8 (9- (or 7-) CH), 114.3 (ArC), 126.7 (4-PhCH), 128.4 (2 x PhCH), 128.6 (2 x PhCH), 137.8 (ArC), 144.2 (ArCH), 150.6, 150.9, 156.1, 157.2 (all ArC), 175.7 (CO); *m/z* [ES] 320 (M^+- CH_3CH_2CO, 100%).

4-Imino-3-isothiocyanato-6-methyl-5-phenyl-4,5-dihydro-3H-chromeno[2,3-d]pyrimidin-8-ol 5

To a suspension of compound **2** (0.4 g, 1.25 mmol) in dichloromethane (25 ml) was added saturated aqueous potassium carbonate (10 ml), followed by thiophosgene (0.18 ml, 2.5 mmol, 2 equiv.). The resulting mixture was stirred at room temperature for 6 h then quenched with water (40 ml). The organic layer was separated, washed with water (2 x) and brine, then dried over sodium sulphate and filtered. The solvent was evaporated and the residue crystallized from ethanol furnishing the *isothiocyanate derivative* **5** (0.270 g, 59%) as orange crystals, m.p. > 300 ºC, IR, ν_{max}/cm^{-1}, 3451, 1628, 1593; ^{1}H NMR δ_H 2.11 (3H, s, CH_3), 5.25 (1H, s, 5-H), 6.43 (1H, d, J 2.2, 7- (or 9-) H), 6.50 (1H, d, J 2.2, 9- (or 7-) H), 7.14 (1H, t, J 7.3, 4-H-Ph), 7.25 (2H, d, J 7.3, 3- and 5-H-Ph), 7.33 (2H, d, J 7.3, 2- and 6-H-Ph), 8.21 (1H, s, 2-H); ^{13}C-NMR δ_C 19.3 (CH_3), 38.2 (5-CH), 101.9 (7-CH), 115.1 (9-CH), 127.55 (4-PhCH), 128.8 (2 x PhCH), 129.0 (2 x ArCH), 172.5 (CS), (remaining quaternary carbons unclear); MS [ES] [Found: $[M+H]^+$, 363.0907. $C_{19}H_{15}N_4O_2S$ requires *M*, 363.0916].

9-Hydroxy-11-methyl-12-phenyl-3,12-dihydro-2H-chromeno[3,2-e][1,2,4]triazolo-[1,5-c]pyrimidin-2-one 6

A mixture of the *N*-amino-pyrimidine **2** (0.40 g, 1.25 mmol) and ethyl chloroformate (0.46 ml, 2.5 mmol, 2 equiv.) in anhydrous DMF (10 ml) was refluxed for 1 h. The mixture was then cooled, diluted with cold water (50 ml), the solid obtained collected by filtration, washed with cold water, then dried and crystallized from DMF to give the *triazolopyrimidinone* **5** (0.30 g, 69%) as a colorless solid, m.p. 288 ºC, IR, ν_{max}/cm^{-1}, 3249, 1632, 1595, 1564; ^{1}H NMR δ_H 2.08 (3H, s, CH_3), 5.60 (1H, s, 12-H), 6.52 (1H, d, J 2.3, 8- (or 10-) H), 6.60 (1H, d, J 2.3, 10- (or 8-) H), 7.15 (1H, t, J 7.3, 4-H-Ph), 7.23 (2H, t, J 7.3, 3- and 5-H-Ph), 7.32 (2H, d, J 7.3, 2- and 6-H-Ph), 8.58 (1H, s, 5-H), 9.60 (1H, s, NH), 9.79 (1H, s, OH); ^{13}C NMR δ_C 19.2 (CH_3), 37.6 (12-CH), 101.3 (8- (or 10-) CH), 103.7, 11.32 (both ArC), 114.9 (10- (or 8-) CH), 127.6 (4-PhCH), 128.5 (2 x ArCH), 128.7 (2 x ArCH), 138.6, 140.5 (both ArC), 143.5 (5-CH), 151.5, 152.2, 153.6, 156.8 (all ArC), 157.6 (CO); *m/z* [APCI] 331(M-NH, 100%).

9-Hydroxy-11-methyl-12-phenyl-3,12-dihydro-2H-chromeno[3,2-e][1,2,4]triazolo-[1,5-c]pyrimidine-2-thione 7 and 9-hydroxy-11-methyl-12-phenyl-2-H-chromeno [3,2-e][1,2,4]triazolo[4,3-c]pyrimidine-3(12H)-thione 7a

The *N*-amino-pyrimidine **2** (0.80 g, 2.5 mmol) was added to an alcoholic solution of potassium hydroxide (0.28 g, 5 mmol, 2 equiv. in 30 ml ethanol) followed by addition of carbon disulphide (2 ml, excess). The resulting mixture was refluxed for 18 h. After cooling, the precipitate was removed by filtration, the filtrate largely evaporated, the residue diluted with water (40 ml) and the resulting solution acidified with 2M HCl. The solid obtained was collected by filtration, washed several times with cold water, then dried and crystallized from methanol furnishing the *triazolopyrimidinthione* as a pair of isomers **7** and **7a** (77/23, major/minor) (0.320 g, 24%) as pale yellow crystals, m.p. 223-225 ºC, IR, ν_{max}/cm^{-1}, 3477, 3388, 1618, 1559, 1428; ^{1}H NMR δ_H 2.13 (3H, s, CH_3, major isomer), 2.18 (3H, s, CH_3, minor isomer), 5.22 (1H, s, 12-H, major isomer), 5.29 (1H, s, 12-H, minor isomer), 6.42 (1H, d, J 2.3, 8- (or 10-) H), 6.59 (1H, d, J 2.3, 10- (or 8-) H), 6.90 (1H, br s, NH, minor isomer), 7.0 (1H, br s, NH, major isomer), 7.15 (1H, t, J 7.3, 4-H-Ph), 7.23 (2H, t, J 3.7, 3-and 5-H-Ph), 7.32 (2H, d, J 7.7, 2-and 6-H-Ph), 8.05 (1H, s, 5-H, major isomer), 8.07 (1H, s, 5-H, minor isomer), 9.63 (1H, s, OH, major isomer), 9.78 (1H, s, OH, minor isomer); ^{13}C NMR, δ_C 20.5 (CH_3), 34.0 (12-CH), 97.2 (ArC), 109.9 (2 x 8-and 10-CH), 111.4 (ArC), 126.8 (4-PhCH), 128.4 (4 x ArCH), 143.7, 143.9, 152.3 (ArC), 156.8 (5-CH), 157.2, 162.5, 162.8 (all ArC).

11-Methyl-12-phenyl-12H-chromeno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-9-ol 8 and 11-methyl-12-phenyl-12H-chromeno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidin-9-ol 8a

The *N*-amino-pyrimidine **2** (0.40 g, 1.25 mmol) was dissolved in formic acid (10 ml) and the solution was refluxed for 12 h. The mixture was allowed to cool, then poured into ice cold water with stirring. The solid obtained was collected by filtration, washed with water, then dried and crystallized from ethanol furnishing the *tri-*

azolopyrimidine as a pair of isomers **8** and **8a** (51/49, major/minor) (0.30 g, 73%) as a colorless solid, m.p. 270 ºC, IR, ν_{max}/cm^{-1}, 3345, 3062, 1629, 1591, 1503; ^1H NMR δ_H 2.10 (3H, s, CH_3), 2.25 (3H, s, CH_3, minor isomer), 5.61 (1H, s, 12-H), 5.65 (1H, s, 12-H, minor isomer), 6.49 (1H, app. s, 8- (or 10-) H), 6.62 (1H, s, 10- (or 8-) H), 6.50 (1H, d, J 2.3, 8- (or 10-) H, minor isomer), 6.60 (1H, d, J 2.3, 10- (or 8-) H, minor isomer), 7.09-7.37 (10H (both isomers), m, 10 x Ar-H), 8.55 (1H, s, 5-H), 8.57 (1H, s, 5-H, other isomer), 9.57 (1H, s, 2-H), 9.59 (1H, s, 2-H, minor isomer), 9.90 (1H, br s, OH); ^{13}C NMR δ_C 19.2, 21.2 (CH_3, both isomers), 35.3, 37.5 (12-CH, 2 isomers), 101.3 (ArC), 103.4, 103.6 (8- (or 10-) CH, both isomers), 107.9, 108.1 (both ArC), 112.0, 112.4 (10- (or 8-) CH, both isomers), 114.8 (ArC), 126.9, 127.1 (4-PhCH, both isomers), 128.3, 128.5 (3- and 5-PhCH, both isomers), 128.6, 128.7 (2- and 6-PhCH, both isomers), 138.6, 139.0, 140.5 (all ArC), 143.5, 143.9 (both ArCH), 151.3, 151.5, 152.2, 152.3, 153.6, 154.3, 155.3 (all ArC), 156.8, 156.9 (both ArCH), 157.6 (ArC); MS [ES] [Found: $[M+H]^+$, 331.1188. $C_{19}H_{15}N_4O_2$ requires *M,* 331.1195].

2,11-Dimethyl-12-phenyl-12H-chromeno[3,2-e][1,2,4]triazolo-[1,5-c]pyrimidin-9-ylacetate 9 and 2,11-Dimethyl-12-phenyl-12H-chromeno[3,2-e][1,2,4]triazolo[4,3,-c] py rimidin-9-yl acetate 9a

Compound **2** (0.40 g, 1.25 mmol) was added to a mixture of acetic acid (20 ml) and acetic anhydride (5 ml) and the resulting mixture refluxed for 12 h. After cooling, the solvent was evaporated, the residue treated with ether, the solid formed filtered, washed with ether, then dried and crystallized from dichloromethane to give the *acetate* as a pair of isomers **9** and **9a** (51/49, major/minor) (0.40 g, 83%) as a colorless solid, m.p. 204 ºC, IR, ν_{max}/cm^{-1}, 3037, 1773, 1750, 1624, 1593; ^1H NMR δ_H 2.12 (3H, s, 11-CH_3), 2.17 (3H, s, 11-CH_3, other isomer), 2.23 (3H, s, 2-CH_3), 2.27 (3H, s, 2-CH_3, minor isomer), 2.38 (3H, s, CH_3CO), 2.42 (3H, s, CH_3CO, minor isomer), 5.45 (1H, s, 12-H), 5.62 (1H, s, 12-H, minor isomer), 6.73 (1H, app. s, 8- (or 10-) H), 6.79 (1H, app. s, 10- (or 8-) H), 7.0-7.32 (10H (both isomers), m, 10 x Ar-H), 9.50 (1H, s, 2-H), 9.52 (1H, s, 2-H- minor isomer); ^{13}C NMR δ_C 14.6, 19.0, 21.0, 21.2 (all CH_3, both isomers), 36.2, 37.7 (12-CH, both isomers), 101.7 (ArC), 102.7 (8- (or 10-) CH), 108.8 (ArC), 115.0 (10- (or 8-) CH), 119.5, 120.6 (both ArC), 127.3, 127.4 (4-PhCH, both isomers), 128.4, 128.6, 128.7, 128.9 (2,3,5,6-PhCH, both isomers), 139.0, 139.5, 140.0, 142.7 (all ArC), 150.2, 151.0 (both 5-CH), 166.5, 169.3 (both CO); MS [EI] [Found: $[M]^+$, 386.1369. $C_{22}H_{18}N_4O_3$ requires *M,* 386.1379].

11-Methyl-12-phenyl-2-(trifluoromethyl)-12H-chromeno[3,2-e][1,2,4]triazolo[1,-5-c]pyrimidin-9-ol 10 and 11-methyl-12-phenyl-3-(trifluoromethyl)-12H-chromeno-[3,2-e]- [1,2,4]triazolo[4,3-c]pyrimidin-9-ol 10a

Compound **2** (0.4 g, 1.25 mmol) was dissolved in trifluoroacetic acid (10 ml) followed by the addition of $POCl_3$ (5 ml) portionwise with shaking; the resulting hot mixture was refluxed for 7 h. After cooling, a sticky solution formed which was dissolved in DMF. Water (50 ml) was added and the mixture was neutralized with solid potassium carbonate. The solid formed was filtered off, washed with water, dried and crystallized from DCM to give the *triflouromethyltriazolopyrimidine* as a pair of isomers **10** and **10a** (69/21, major/minor) (0.20 g, 40%) as a colorless solid, m.p. 252-253 ºC, IR, ν_{max}/cm^{-1}, 3343 (br), 1650, 1484, 1428; ^1H NMR δ_H 2.05 (3H, s, CH_3-minor isomer) 2.09 (3H, s, CH_3-major isomer), 5.59 (1H, s, 12-H-minor isomer) 5.65 (1H, s, 12-H- major isomer), 6.48 (1H, d, J 2.3, 8- (or 10-) H,minor isomer), 6.50 (1H, d, J 2.3, 8- (or 10-) H, major isomer), 6.58 (1H, d, J 2.3, 10- (or 8-) H, minor isomer), 6.60 (1H, d, J 2.3, 10- (or 8-) H), major isomer), 7.12 (1H, t, J 7.2, 4-H-Ph), 7.25 (2H, t, J 7.2, 3- and 5-H-Ph), 7.33 (2H, d, J 7.2, 2- and 6-H-Ph), 9.60 (1H, s, 5-H, minor isomer), 9.71 (1H, s, 5-H, major isomer), 9.78 (1H, br s, OH-minor isomer), 9.85 (1H, br s, OH-major isomer); ^{13}C NMR δ_C 19.1 (CH_3), 38.7 (12-CH), 58.2 (C), 100.5 (8- (or 10-) CH), 112.8 (ArC), 114.2 (10- (or 8-) CH), 121.1 (ArC), 126.7 (4-PhCH), 127.3 (2 x 3- and 5-PhCH), 128.9 (2 x 2- and 6- PhCH), 138.1 (5-CH), 146.0, 150.3, 157.1, 160.1 (all ArC); ^{19}F NMR δ_F, -63.7 (3F, s, major isomer), -69.0 (3F, s, minor isomer); MS [EI] [Found: $[M+H]^+$, 399.1051. $C_{20}H_{14}F_3N_4O_2$ requires *M,* 399.1069].

2-Amino-11-methyl-12-phenyl-12H-chromeno[3,2-e][1,2,4]triazolo[1,5-c]pyramidin-9-ol 11

To a stirred solution of the *N*-amino-pyrimidine **2** (0.40 g, 1.25 mmol) in absolute ethanol (20 ml) was added anhydrous potassium carbonate (0.51 g, 3.75 mmol, 3 equiv.) followed by cyanogen bromide (0.53 g, 2.5 mmol, 2 equiv.). The reaction mixture was then refluxed for 15 h, cooled, diluted with water and acidified with 2M HCl. The solid obtained filtered, washed with water, then dried and crystallized from methanol to afford the *aminotriazolopyrimidine* **11** (0.395 g, 91%) as a pale brown solid, m.p. 182-184 ºC, IR, ν_{max}/cm^{-1}, 3482, 3358, 3227, 2923, 2854, 1632, 1597; ^1H NMR δ_H 2.17 (3H, s, CH_3), 5.40 (1H, s, 12-H), 6.48 (1H, d, J 2.1, 8- (or 10-) H), 6.62 (2H, s, NH_2), 6.58 (1H, d, J 2.1, 10- (or 8-) H), 7.12 (1H, t, J 7.3, 4-H-Ph), 7.20 (2H, t, J 7.3, 3-and 5-H-Ph), 7.25 (2H, d, 7.3, 2-and 6-

H-Ph), 9.05 (1H, s, 5-H), 9.74 (1H, br s, OH); ^{13}C NMR δ_C 19.2 (CH_3), 37.4 (12-CH), 100.8 (ArC), 101.3 (8- (or 10-) CH), 112.6 (ArC), 114.5 (10- (or 8-) CH), 127.0 (4-PhCH), 128.3 (2 x 3- and 5-PhCH), 128.7 (2 x 2- and 6-PhCH), 137.6 (ArC), 138.3 (5-CH), 143.8, 151.7, 152.6, 153.7, 155.5, 168.2 (all ArC); MS [EI] [Found: $[M]^+$, 345.1283. $C_{19}H_{15}N_5O_2$ requires *M*, 345.1283].

Ethyl 2-(9-hydroxy-11-methyl-12-phenyl-12H-chromeno[3,2-e][1,2,4]triazolo[1,5-c]-pyrimidin-2-yl)acetate 12 and Ethyl 2-(9-hydroxy-11-methyl-12-phenyl-12H-chromeno[3,2-e][1,2,4]triazolo[4, 3-c] pyrimidin-3-yl)acetate 12a

Diethyl malonate (0.189 ml, 1.25 mmol) was added to a solution of compound **2** (0.40 g, 1.25 mmol) in DMF (10 ml) and the resulting mixture refluxed for 24 h. The solvent was reduced, the residue diluted with cold water (40 ml), the precipitate formed collected by filtration then washed with water, dried and crystallized from DCM giving the *ester* as a pair of isomers **12** and **12a** as a pale yellow solid (0.450 g, 86%), m.p. 152-154 ºC, IR, ν_{max}/cm^{-1}, 3421, 1737, 1631, 1593; ^{1}H NMR δ_H 1.16 (3H, t, J 7.1, CH_3CH_2), 2.05 (3H, s, 11-CH_3-major isomer), 2.22 (3H, s,11-CH_3-minor isomer) 3.95 (2H, s, CH_2CO), 4.10 (2H, q, J 7.1, CH_2O), 5.57 (1H, s, 12-H,major isomer), 5.62 (1H, s, 12-H, minor isomer), 6.48 (1H, s, 8- (or 10-) H,minor isomer), 6.05 (1H, d, J 1.9, 8- (or 10-) H, major isomer), 6.61 (1H, d, J 1.9, 10- (or 8-) H, major isomer), 6.64 (1H, 10- (or 8-) H, minor isomer), 7.15-7.35 (10H, m, 10 x Ar-H, both isomers), 9.55 (1H, s, 5-H), 9.80 (1H, br s, OH- major isomer), 9.90 (1H, br s, OH-minor isomer); MS [EI] [Found: $[M]^+$, 416.1470. $C_{23}H_{20}N_4O_4$ requires *M,* 416.1485].

2-(9-Hydroxy-11-methyl-12-phenyl-12H-chromeno-[3,2-e][1,2,4]triazolo[1,5-c]pyramidin-2-yl)acetonitrile 13 and 2-(9-Hydroxy-11-methyl-12-phenyl-12H-chromeno[3,2-e]-[1,2,4]triazolo[4,3-c]-pyrimidin-3-yl) acetonitrile 13a

A mixture of compound **2** (0.40 g, 1.25 mmol) and methyl cyanoacetate (0.12 ml, 1.25 mmol) in absolute ethanol (20 ml) was heated under reflux overnight. The solvent was evaporated, the residue was suspended in ether (30 ml), the solid which crystallized out collected by filtration, washed with ether and finally purified by crystallization from DCM giving the *acetonitrile* as a pair of isomers **13** and **13a** (0.225 g, 49%) as a yellow solid, m.p. 202-204 ºC, IR, ν_{max}/cm^{-1} 3421,3330,1631, 1593. ^{1}H NMR δ_H 2.02 (3H, s, CH_3), 4.25 (2H, s, CH_2), 5.40 (1H, s, 12-H), 6.22 (1H, s, 8- (or 10-) H), 6.39 (1H, s, 10- (or 8-) H), 6.90 (1H, t, J 7.7, 4-H-Ph), 7.0 (2H, t, J 7.7, 3- and 5-H-Ph), 7.05 (2H, d, J 7.7, 2- and 6-H-Ph), 9.32 (1H, s, 5-H), 9.64 (1H, br s, OH); ^{13}C NMR δ_C 18.4 (CH_2), 21.3 (CH_3), 35.4 (12-CH), 103.5 (ArC), 108.0 (8- (or 10-) CH), 108.3 (ArC), 112.6 (10- (or 8-) CH), 117.0 (ArC), 127.1 (4-PhCH), 128.6 (2 x ArCH), 128.7 (2 x ArCH), 139.2 (ArC), 140.5 (5-CH), 143.9, 151.3, 153.4, 155.0, 155.1, 161.2 (all ArC); *m/z* [ES] 370 ((M+H$^+$), 100%).

11-Methyl-2,12-diphenyl-12H-chromeno[3,2-e][1,2,4] triazolo[1,5-c]pyrimidin-9-ol 15

The *N*-amino-pyrimidine **2** (0.40 g, 1.25 mmol) was mixed with benzylidenemalononitrile (0.145 g, 1.25 mmol.), to which was added a few drops of either ethanol or acetone. The mixture was shaken vigorously for 10 minutes then left at room temperature for 30 minutes. The resulting yellow solid was collected and crystallized from ethanol then ethyl acetate to furnish the *triazolopyrimidine* **15** (0.380 g, 74.8%) as pale yellow crystals, m.p.> 300 ºC, IR, ν_{max}/cm^{-1}, 3276, 1632, 1593, 1518; ^{1}H NMR δ_H 2.10 (3H, s, CH_3), 5.69 (1H, s, 12-CH), 6.55 (1H, d, J 2.1, 8- (or 10) H), 6.60 (1H, d, J 2.1, 10- (or 8-) H), 7.12 (1H, t, J 7.5, Ar-H), 7.27 (2H, t, J 7.5, 2 x Ar-H), 7.38 (2H, d, J 7.5, 2 x Ar-H), 7.55 (3H, m, 3 x Ar-H), 8.25 (2H, dd, J 2.7 and 7.7, 2 x Ar-H), 9.60 (1H, s, 5-H), 9.80 (1H, br s, OH); ^{13}C NMR δ_C 19.3 (CH_3), 37.7 (12-CH), 101.5 (8- (or 10-) CH), 103.4, 112.2 (both ArC), 115.0 (10- (or 8-) CH), 127.3, 127.7, 128.7, 128.9, 129.5 (all ArCH), 130.1 (ArC), 131.4 (ArCH) 138.7 (ArC), 140.4 (5-CH), 143.7, 151.7, 153.4, 153.9, 157.7, 165.8 (all ArC); MS [EI] [Found: $[M]^+$, 406.1431. $C_{23}H_{20}N_4O_4$ requires *M,* 406.1430].

General procedure for reaction of N-amino-pyrimidine 2 with aromatic aldehydes to give compounds 16 and 17

An appropriate aromatic aldehyde (1.25 mmol.) was added to a solution of the *N*-amino-pyrimidine **2** (0.40 g, 1.25 mmol) in absolute ethanol (15 ml) containing a few drops of piperidine, the resulting mixture refluxed for 5h. The solids formed on hot in case of compound **16** and after cooling in case of compound **17** were collected by filtration, washed with ether and crystallized from proper solvent.

11-Methyl-2-(4-nitrophenyl)-12-phenyl-12H-chromeno [3,2-e][1,2,4]triazolo[1,-c]pyrimidin-9-ol 16

Using the general procedure, reaction of compound **2** with *p*-nitrobenzaldehyde (0.188 g, 1.25 mmol) followed by crystallization from methanol to give the *triazolopyrimidine* **16** (0.40 g, 71%) as yellow crystals, m.p. >300 ºC,

IR, ν_{max}/cm^{-1}, 3313, 2963, 2846, 1628, 1591; ^1H NMR δ_H 2.11 (3H, s, CH_3), 5.62 (1H, s, 12-H), 6.47 (1H, d, J 2.2, 8- (or 10-) H), 6.60 (1H, d, J 2.2, 10- (or 8-) H), 7.15 (1H, t, J 7.5, 4-H-Ph), 7.25 (2H, t, J 7.5, 3- and 5-H-Ph), 7.37 (2H, d, J 7.5, 2- and 6-H-Ph), 8.32 (2H, d, J 8.0, 3- and 5-H-nitro ring), 8.50 (2H, d, J 8.0, 2- and 6-H-nitro ring), 9.56 (1H, s, 5-H), 9.78 (1H, br s, OH); ^{13}C NMR δ_C 19.3 (CH_3), 37.6 (12-CH), 101.5 (8- (or 10) CH), 103.6, 112.0 (both ArC), 115.1 (10- (or 8-) CH), 124.6 (2 x ArCH), 127.3 (4-PhCH), 128.6 (2 x ArCH), 128.7 (2 x ArCH), 128.9 (2 x ArCH), 135.9, 138.7 (both ArC), 140.7 (5-CH), 143.5, 149.0, 151.5, 153.6, 154.0, 157.7, 163.8 (all ArC); MS [EI] [Found: $[M]^+$, 451.1470. $C_{25}H_{17}N_5O_4$ requires *M,* 451.1485].

(E)-4-imino-3-(4-methoxybenzylideneamino)-6-methyl-5-phenyl-4,5-dihydro-3H-chromeno[2,3-d]pyrimidin-8-ol 17

Using the general procedure, reaction of compound **2** with *p*-anisaldehyde (0.17 g, 1.25 mmol) followed by crystallization from ethanol gave the *Schiff base* **17** (0.30 g, 55%) as a yellow solid, m.p. 276-278 ºC, IR, ν_{max}/cm^{-1}, 3175, 2952, 2836, 1633, 1596.3, 1564; ^1H NMR δ_H 2.25 (3H, s, 11-CH_3), 3.80 (3H, s, OCH_3), 6.05 (1H, s, NH), 6.48 (1H, d, J 2.2, 8-H), 6.55 (1H, d, J 2.2, 10-H), 7.02 (2H, d, J 9.8, 2- and 6-H-anisole), 7.10 (1H, t, J 7.2, 4-H-Ph), 7.21 (4H, d, J 7.2, 4 x Ar-H), 7.72 (2H, d, J 9.8, 3- and 5-H-anisole), 8.30 (2H, s, 5-H + CH=N-N), 9.73 (1H, br s, OH); ^{13}C NMR δ_C 19.2 (11-CH_3), 34.9 (12-CH), 55.7 (OCH_3), 101.5 (8- (or 10-) CH), 114.3 (10- (or 8-) CH), 114.6, 114.8 (both C), 114.9 (2 x ArCH), 127.1 (4-PhCH), 127.4 (ArC), 127.7 (2 x ArCH), 128.6 (2 x PhCH), 129.06 (2 x PhCH), 138.0 (ArC), 144.5 (5-CH), 151.2 (ArC), 156.5 (CH=N), 157.4, 161.0 (both ArC); MS [EI] [Found: $[M]^+$, 438.1685. $C_{21}H_{15}N_5O_2$ requires *M,* 438.1692].

3-(cyclohexylideneamino)-4-imino-6-methyl-5-phenyl-4,5-dihydro-3H-chromeno-[2,3-d]pyrimidin-8-ol 18

A mixture of *N*-amino-pyrimidine **2** (0.40 g, 1.25 mmol) and cyclohexanone (3 ml) was heated at 100 ºC until the reaction was complete (monitored by TLC; *ca*. 6 h). After cooling, the mixture was diluted with water, when an oily layer formed. The water was decanted and water (50 ml) added. The organic material was extracted into DCM (2 x) and the combined extracts washed with water and brine, then dried over sodium sulphate, filtered and the solvent evaporated. The residue was treated with ether, the solid obtained collected and crystallized from DCM to afford the *Schiff base* **18** (0.30 g, 60%) as a yellow solid, m.p. 238-240 ºC, IR, ν_{max}/cm^{-1}, 3292, 2952, 2846, 1622, 1585; ^1H NMR δ_H 0.80-0.88 (2H, m, 4'-CH_2), 1.25-1.33 (4H, m, 3'-and 5'-CH_2), 1.68 (2H, t, J 7.13, 2'-CH_2), 2.23 (3H, s, CH_3), 2.76 (2H, t, J 7.4, 6'-CH_2), 5.65 (1H, s, 12-H), 6.45 (1H, app. s, 8- (or 10-) H), 6.65 (1H, app. s, 10- (or 8-) H), 7.10 (1H, t, J 7.3, 4-H-Ph), 7.20 (2H, d, J 7.3, 3- and 5-H), 7.30 (2H, t, J 7.3, 2- and 6-H-Ph), 9.50 (1H, s, 5-H), 9.90 (1H, s, OH); ^{13}C NMR δ_C 21.4 (CH_3), 22.3, 27.4, 28.5, 31.3 (all CH_2), 35.3 (12-CH), 102.8, 108.1 (both ArC), 108.4 (8- (or 10-) CH), 112.4 (10- (or 8-) CH), 127.0 (4-PhCH), 128.3 (2 x ArCH), 128.6 (2 x ArCH), 139.1 (ArC), 140.0 (5-CH), 144.1, 151.5, 152.9, 154.4, 155.4, 170.1 (all ArC); MS [Found: $[M]^+$, 401.1988. $C_{24}H_{25}N_4O_2$ requires *M,* 401.1978].

10-Hydroxy-12-methyl-13-phenyl-13H-chromeno-[2,3-d]]pyrimidino[3,4-b][1,2,4]triazin-2,3-dione 19 and 10-Hydroxy-12-methyl-13-phenyl-13H-chromeno [2,3-d]]pyrimidino[4,3-c][1,2 ,4]triazin-3,4-dione 19a

Oxaloyl chloride (0.21 ml, 2.5 mmol, 2 equiv.) was added carefully to a solution of compound **2** (0.40 g, 1.25 mmol) in pyridine (10 ml) and the resulting mixture shaken at room temperature for 10 minutes then refluxed for 20 h. The solvent was reduced under vacuum, the residue poured into a mixture of crushed ice and 2M HCl. The solid precipitate was collected by filtration, washed with water, then dried and crystallized from ethanol to give the *trizindione* as apair of isomers **19** and **19a** (55/45, major/minor) (0.39 g, 83%) as whitish-grey crystals, m.p. 220 ºC, IR, ν_{max}/cm^{-1}, 3167 (very br), 1649, 1588, 1566, 1493.6; ^1H NMR δ_H 2.15 (3H, s, CH_3-major isomer), 2.20 (3H, s, CH_3-minor isomer), 5.55 (1H, s, 13-H-major isomer), 5.72 (1H, s, 13-H-minor isomer), 6.53 (1H, d, J 2.3, 9- (or 11-) H-major isomer), 6.56 (1H, s, 9- (or 11-) H-minor isomer), 6.60 (1H, app. s, 11- (or 9-) H-minor isomer), 6.62 (1H, d, J 2.3, 11- (or 9-) H-major isomer), 7.14 (2H, 2 overlaping t, J 7.5, 2 x Ar-H (both isomers)), 7.23 (2H, t, J 7.5, 2 x Ar-H-major isomer), 7.24 (2H, t, J 7.5, 2 x Ar-H, minor isomer), 7.36 (2H, d, J 7.4, 2 x Ar-H-major isomer), 7.42 (2H, d, J 7.4, 2 x Ar-H minor isomer), 8.65 (1H, s, 6-H-major isomer), 8.69 (1H, s, 6-H-minor isomer), 9.06 (1H, br s, NH-major isomer), 9.50 (1H, br s, NH-minor isomer), 9.95 (1H, br s, OH-major isomer), 10.25 (1H, s, OH-minor isomer); ^{13}C NMR δ_C 19.0 (CH_3), 21.2 (CH_3-other isomer), 33.2 (13-CH), 35.0 (13-CH-other isomer), 100.3 (9- (or 11-) CH-major isomer), 102.1 (9- (or 11-) CH-minor isomer), 107.5, 108.0 (both ArC), 112.9 (11- (or 9-) CH-major isomer), 113.0 (11- (or 9-) CH-minor isomer), 127.3, 128.2, 128.3, 128.6, 129.0 (all ArCH), 138.3 (ArC), 139.2 (6-CH), 142.5, 149.7, 150.1,153.2, 156.0, 157.7, 158.2, 162.0 (all

ArC); *m/z* for $C_{20}H_{14}N_4O_4$ (ES) M.

10-Hydroxy-12-methyl-13-phenyl-2H,13H-chromeno [2,3-d]]pyrimidinp[3,4-b][1,2-,4] triazin-3-one 20

Ethyl chloroacetate (0.26 ml, 2.5 mmol, 2 equiv.) was added to the *N*-amino -pyrimidine **2** (0.40 g, 1.25 mmol) in sodium methoxide solution (0.057 g Na in 30 ml methanol) and the reaction mixture refluxed for 12 h. After cooling, the mixture was diluted with cold water and acidified with 2 M HCl. The resulting solid product was filtered, washed with water, then dried and crystallized from methanol furnishing the *triazinone* **20** (0.350 g, 78%) as a yellow solid, m.p. ºC, IR, ν_{max}/cm^{-1}, 3380, 3203, 1628; ^{1}H NMR δ_H 2.15 (3H, s, CH_3), 5.60 (1H, s, 13-H), 6.50 (1H, d, J 2.3, 9- (or 11-) H), 6.58 (2H, s, CH_2), 6.62 (1H, d, J 2.3, 11- (or 9-) H), 7.20 (1H, t, J 7.4, 4-H-Ph), 7.30 (2H, t, J 7.4, 3- and 5-H-Ph), 7.42 (2H, d, J 7.4, 2- and 6-H-Ph), 8.62 (1H, s, 6-H), 9.30 (1H, br s, NH), 9.91 (1H, s, OH); ^{13}C NMR δ_C 19.3 (CH_3), 35.0 (13-CH), 64.9 (CH_2), 98.2 (ArC), 101.0 (9- (or 11-) CH), 106.6 (ArC), 113.5 (11- (or 9-) CH), 127.0 (4-PhCH), 128.2 (2 x ArCH), 128.8 (2 x ArCH), 139.5, 146.2, 148.0, 149.0, 153.3 (all ArC), 156.6 (6-CH), 172.1 (CO); *m/z* for $C_{20}H_{16}N_4O_3$ (ES) M.

10-Hydroxy-13-phenyl-3,12-dimethyl-2H,13H-chromeno[2,3-d]]pyrimidinp[3,4-b][1,2,4]triazin-2-one 21 and 10-Hydroxy-13-phenyl-3,12-dimethyl-2H,13H-chromeno[2,3-d]]pyrimidinp[4,3-c][1,2-,4]triazin-4-one 21a

To a stirred solution of compound **2** (0.40 g, 1.25 mmol) in absolute ethanol (15 ml) was added ethyl pyruvate (0.145 ml, 1.25 mmol) and the mixture refluxed for 3 h. The solid formed during heating and, after cooling, was collected by filtration, washed with ethanol, dried and crystallized from ethanol to give the *triazinone* as a pair of isomers **21** and **21a** (51/49, major/minor) (0.30 g, 64%) as a pale violet solid, m.p. >300 ºC, IR, ν_{max}/cm^{-1}, 3201, 2922, 1661, 1605, 1471; ^{1}H NMR δ_H 2.10 (3H, s, 12-CH_3-major), 2.20 (3H, s, 12-CH_3-minor isomer), 2.26 (6H, s, 2 x 3-CH_3-both isomers), 5.40 (1H, s, 13-H-major isomer), 5.51 (1H, s, 13-H-minor isomer), 6.43 (1H, s, 9- (or 11-) H-major isomer), 6.46 (1H,s, 11- (or 9-) H-major isomer), 6.57 (1H, s, 9- (or 11-) H-minor isomer), 6.60 (1H, s, 11- (or 9-) H-minor isomer), 7.12 (2H, t, J 7.6, 4-H-Ph-both isomers), 7.22 (4H, t, J 7.6, 2 x 3- and 5-H-Ph-both isomers), 7.30 (4H, d, J 7.6, 4 x 2- and 6-H-Ph-both isomers), 8.98 (1H, s, 6-H-major isomer), 9.02 (1H, s, 6-H-minor isomer), 9.83 (1H, s, OH-major isomer), 10.0 (1H, s, OH-minor isomer); ^{13}C NMR δ_C 18.1 (12-CH_3), 19.2 (12-CH_3-other isomer), 21.3 (2 x 3-CH_3-both isomers), 33.7, 36.0 (13-CH-both isomers), 101.5 (9- (or 11-) CH), 104.6, 104.9 (both ArC), 108.09 (ArCH), 109.1, 113.03 (both ArC), 115.4 (ArCH), 126.9, 127.1 (2 x 4-PhCH-both isomers), 128.5, 128.6 (2 x PhCH-both isomers), 128.7, 129.0 (2 x PhCH-both isomers), 138.5, 139.1, 143.4, 143.9 (all ArC), 148.4 (6-CH), 150.8, 151.0, 152.6, 152.8, 155.2, 157.3, 157.6, 157.9, 158.7, 159.8, 159.9 (all ArC); MS [ES] [Found: $[M+H]^+$, 373.1308. $C_{20}H_{17}N_4O_3$ requires *M,* 373.1301].

Reaction of compound 293 with isatin to furnish compounds 22 and 22a

A mixture of the *N*-amino-pyrimidine **293** (0.40 g, 1.25 mmol) and isatin (0.18 g, 1.25 mmol) in absolute ethanol (20 ml) was stirred and heated for 3 h. The solid formed during the reaction was filtered while hot, the filtrate was evaporated and the residue treated with ether to give an additional amount of the product which was combined and which crystallized from acetic acid to furnish the *hexacyclic* compound as a pair of isomers **320** and **320a** (51/49, major/minor) (0.45 g, 83%) as red crystals, m.p. >300 ºC, IR, ν_{max}/cm^{-1}, 3432, 3061, 1639, 1544; ^{1}H NMR δ_H 2.15 (3H, s, CH_3-major isomer), 2.22 (3H, s, CH_3-minor isomer), 5.68 (1H, s, 16-H-major isomer), 5.82 (1H, s, 16-H-minor isomer), 6.51 (2H, app. s, 12- and 14-H-major isomer), 6.66 (2H, d, 2.2, 12- and 14-H-minor isomer), 7.10 (2H, t, J 6.7, 4-H-Ph-both isomers), 7.15-7.24 (6H, m, 6 x Ar-H-both isomers), 7.39 (4H, d, J 7.9, 4 x Ar-H-both isomers), 7.52-7.61 (4H, m, 4 x Ar-H-both isomers), 8.0 (2H, t, J 7.9, 2 x 6-H-both isomers), 9.40 (1H, s, 9-H-major isomer), 9.45 (1H, s, 9-H-minor isomer), 10.20 (1H, br s, OH); ^{13}C NMR δ_C 19.1 (CH_3-major isomer), 21.2 (CH_3-minor isomer), 34.2, 36.4 (16-CH-both isomers), 101.4, 106.4 (both 12- (or 14-) CH-both isomers), 106.6, 107.9, 109.0 (all ArC), 112.9, 115.3 (both 14- (or 12-) CH-both isomers), 119.4, 119.5, 122.4, 123.6, 126.8, 127.0, 128.3, 128.6, 128.7, 129.0 (all ArCH), 134.7 (ArC), 138.3, 138.9 (both 9-CH-both isomers), 143.5, 144.0, 146.7, 146.9, 148.3, 149.0, 150.6, 150.8, 150.9, 150.7, 155.2, 156.4, 157.2, 157.5, 161.0 (all ArC); MS [EI] [Found: $[M]^+$, 432.1448. $C_{26}H_{17}N_5O_2$ requires *M,* 432.1461].

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