A captured room temperature stable Wheland intermediate as a key structure for the orthogonal decoration of 4-amino-pyrido[2,3-d]pyrimidin-7 (8H)-ones†

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Wheland intermediates are usually unstable compounds and only a few have been isolated at very low temperatures. During our work on tyrosine kinase inhibitors, we studied the bromination of 7 in order to obtain a dibromo substituted pyrido[2,3-d]pyrimidin-7(8H)-one which could be orthogonally decorated. Surprisingly, treatment of 7 with 3 equiv. of Br2 in acetic acid (AcOH) afforded 12, a captured room temperature stable Wheland bromination intermediate stabilized by the bromination of the imino tautomer of the amino group at C4 of the pyridopyrimidine skeleton. The structure was confirmed by crystal structure determination from powder X-ray diffraction data. Treatment of 12 with DMSO afforded the dibromo substituted compound 13 presenting a bromine atom at C6 and C5–C6 unsaturation. 13 was directly accessed by treating 7 with N-bromosuccinimide (NBS), a protocol extended to other compounds using NBS or N-iodosuccinimide (NIS) to afford 6-halo substituted systems. 26, bearing an iodine at C6 and a p-bromophenylamino at C2, allows the orthogonal decoration of pyridopyrimidines.

INTRODUCTION

Pyrido[2,3-d]pyrimidin-7(8H)-ones are bicyclic heterocyclic compounds for which very interesting inhibitory activities have been described in the field of protein kinase inhibitors. Thus, compounds of general structure 1 (Fig. 1) have shown IC50 values in the range of μM to nM against platelet-derived growth factor receptor (PDFGR), fibroblast growth factor receptor (FGFR), epidermal growth factor receptor (EGFR), and proto-oncogene tyrosine-protein kinase (c-Src), particularly when R2 is an aryl group.1–8 However, most of these promising C4-unsubstituted compounds did not reach the market due to solubility and toxicity issues.

In this context, our group has described in the past years several straightforward strategies for the synthesis of 4-amino and 4-oxo substituted pyrido[2,3-d]pyrimidin-7(8H)-ones 2 (R4 = NH2, OH) (Fig. 1) with up to 5 diversity centres and two possible degrees of unsaturation in the pyridone ring.9–12 Contrary to compounds 1, the presence of the 4-amino or 4-oxo substituents in such systems renders these compounds, in general, nontoxic for normal cells. Consequently, an adequate decoration of structures 2 has allowed us to describe compounds with nM activities as breakpoint cluster region protein (BCR) kinase inhibitors for B lymphoid malignancies (3),13 discoidin domain-containing receptor 2 (DDR2) inhibitors for treatment of lung cancer (4),14 hepatitis C virus (HCV) inhibitors (5),15 and others (Fig. 1). A drawback of our synthetic methodologies is the fact that a de novo synthesis is needed each time a new pyrido[2,3-d]pyrimidin-7(8H)-one with a different set of substituents in R6 and at the para position of the phenylamino substituent at position C2 is needed.

Consequently, we tried to obtain the dibromo substituted structure 6 (Fig. 1) which should allow the orthogonal decoration of the pyridopyrimidine nucleus. The present paper deals with the unexpected results obtained in such a study.

RESULTS AND DISCUSSION

First, we synthesized the unsubstituted pyridopyrimidine 7 by using the microwave assisted multicomponent reaction protocol previously described by our group.16,17 Thus a 2 : 1 : 1 molar mixture of methyl acrylate (8), malononitrile (9) and guanidine carbonate (10) in MeOH was heated at 140 °C under microwave irradiation in a sealed vial for 10 min to afford 7 in 51% yield (Scheme 1). The structure was confirmed on the basis of the spectral and analytical data (see the ESI†). It should be noted that this is the first time that we obtained a pyrido[2,3-d]pyrimidin-7(8H)-one not substituted in the pyridine ring. All other synthetic protocols developed by our group did not afford such kind of structure due to polymerization of the starting methyl acrylate.

Once compound 7 was obtained, we started to study its bromination by using one equivalent of bromine in AcOH for 3 h at room temperature. The reaction afforded the p-bromo substituted derivative 11 in 97% yield (Scheme 2). The structure was established on the basis of the spectral data, in particular the presence in the 1H-NMR spectrum of two doublets, of relative integral 2H each, at 7.83 and 7.31 ppm with the characteristic splitting pattern of a para substituted phenyl ring, clearly showing that bromination had taken place in such a position of the ring.

Next, we decided to treat 7 with 2 equivalents of bromine to obtain the desired compound 6 (Fig. 1), but in this case a complex mixture was obtained. Then, we increased the amount of Br2/AcOH to 3 equivalents and an orange-red precipitate was abundantly formed for which we proposed structure 12 (Scheme 2) on the basis of a signal at 44.2 ppm in the 13C NMR spectrum assignable to the C4a carbon of the pyridopyrimidine skeleton which undergoes a great upfield shift (from 85.9 ppm in 11) due to the presence of the bromine atom.

The formation of 12 could be rationalized (Scheme 2) by the bromination of the monobromo derivative 11 at position C4a of the 2,4-diaminopyrimidine ring (the most favoured for SEAr in such kind of diamino substituted ring,18 which installs a bromine atom at the bridgehead carbon of the bicyclic system (the first one ever described to the best of our knowledge), to afford the corresponding Wheland intermediate (W1), perfectly referable to the one depicted for the bromination of aniline (W2).

Contrary to W2, in the case of W1 the aromaticity cannot be recovered by losing a proton, so such a Wheland intermediate is captured by the formation of the rare N-bromoimino derivative 12.

A literature search revealed that there is not a single example of the isolation of a Wheland intermediate of the bromination of a pyridopyrimidine or a pyrimidine. In fact, the isolation of Wheland intermediates is unusual and there are only a few examples of it, and only two correspond to halogenations.19–23 Consequently, the theoretical interest of the compound obtained impelled us to try to obtain a single crystal to carry out its structure determination but, as it is described later, such a compound evolved to a different structure, being impossible to obtain a suitable crystal. Thus, we collected the X-ray powder diffraction pattern at the MSPD beamline of the ALBA synchrotron24 and, surprisingly,

the orange solid was not amorphous as expected but presented a microcrystalline structure as shown by the broad peaks obtained (Fig. 2).

Despite the broad peaks and limited d-spacing available, a triclinic unit cell was indexed with DICVOL0625 and the obtained cell parameters were refined using DAjust software.26 A promising structure candidate was obtained with the directspace strategy TALP27 which underwent a final restrained Rietveld refinement with RIBOLS. The final unit cell parameters are: a = 8.757(1), b = 9.668(2), c = 10.106(1) Å, α = 63.6 (4), β = 77.3(7) and γ = 82.0(7)°, V = 747(3) Å3, and space group $P1^{-}$. The crystallographic data for 12, refinement details, additional figures and the Rietveld plot are given in the ESI.†

The solved structure confirmed the N-bromoimino structure 12 (Fig. 2), that is to say, the Wheland intermediate has been stabilized by the subsequent bromination of the imino tautomer of the amino group at C4 of the pyridopyrimidine skeleton.

This structure was fully compatible with all the spectral data obtained for such an orange solid, particularly with the elemental analysis and HRMS spectrum (ESI-TOF) that presented a peak at m/z 489.8497 [M + H]+ (calculated for C13H11Br3N5O, 489.8514).

It is remarkable in the crystal structure of 12 that the formation of a stereocenter due to the introduction of the bromine atom at the C4a bridgehead carbon is reflected in the internal structure by the presence of the two enantiomers of 12 associated in a self-complementary ADAD-DADA quadruple hydrogen-bonding centrosymmetric motif, which is in turn associated with a second pair of enantiomers through a π–π interaction of the p-bromophenyl rings, thus forming a ribbon of pairs of enantiomers (see Fig. S4 in the ESI†).

The N-bromoimino feature present in 12 is very rare; in fact the CvN–Br motif is present in 11 crystalline structures included in the Cambridge Crystallographic Database, and only four of them are heterocyclic compounds.28–31 The one reported by Samadi et al.31 is the most referable to compound 12 because it also contains an axial bromine atom. In any case, 12 is the first structure presenting the N-bromimino feature on a pyrimidine ring system.

During the characterization of compound 12, we realized that such a molecule evolves spontaneously to a new compound during the recording of its NMR spectrum in DMSO-d6. To accomplish a complete transformation, we heated 12 at 80 °C in DMSO under vacuum (50 mbar) to afford 6-bromo substituted pyrido[2,3-d]pyrimidine 13 in an almost quantitative yield (Fig. 3). The use of reduced pressure helps to complete the reaction by removing the HBr formed. The structure of 13 was confirmed by single-crystal X-ray diffraction of a 1 : 1 solvate with acetone, very slowly formed during the assays carried out to achieve a single crystal of 12 (see the ESI†).

Our initial objective was to obtain the dibromo substituted structure 6 (Fig. 1) which should allow the orthogonal decoration of the pyridopyrimidine nucleus. The synthesis of 13 double accomplishes such an objective: the bromine atom is placed at position C6 of the pyridopyrimidine skeleton and, additionally,

a double bond is introduced between C5 and C6, a step that normally is carried out by dehydrogenation of the C6 aryl substituted compound to achieve the required biological activity.10

Once we had unequivocally established the structures of 12 and 13, we decided to test if such a behaviour was extensible to other 4-aminopyrido[2,3-d]pyrimidines (Fig. 3). Therefore, we synthesized compounds 14 (R2 = H), 15 (R2 = 4-fluorophenyl) and 16 (R2 = 4-chlorophenyl) by using the same protocol used for the synthesis of 7 starting from methyl acrylate 8, malononitrile 9 and the corresponding guanidine (guanidine carbonate for 14, N-fluorophenylguanidine nitrate for 15, and N-chlorophenylguanidine carbonate for 16). The treatment of 14, 15 and 16 with, in these cases, 2 equiv. of bromine in acetic acid afforded the corresponding captured room temperature stable Wheland intermediates 17 (R2 = H), 18 (R2 = 4-fluorophenyl), and 19 (R2 = 4-chlorophenyl) which were transformed upon heating in DMSO to the corresponding 6-bromopyridopyrimidines 20 (R2 = H), 21 (R2 = 4-fluorophenyl) and 22 (R2 = 4-chlorophenyl) in good yields. Consequently, this bromination and transposition protocol seems to be general for 2,4-diaminopyrido[2,3-d]pyrimidin-7 (8H)-ones, provided that the substituent R2 does not further react with bromine.

A way to rationalize the formation of 13 is to consider 12 as a reagent capable of transferring two bromonium ions or bromine radicals to the α-carbonyl position, either intra- or intermolecularly, to afford an α,α-dibromo intermediate.

The subsequent elimination of HBr, probably mediated by DMSO,32 would afford the 6-bromo substituted pyridopyrimidine 13. Such transformation would be similar to the protocol described by Zhang et al.33 for the preparation of 3-bromo-5,6-dihydropyridin-2(1H)-one starting from piperidin-2-one, in which they dibrominate the α-carbonyl position to subsequently eliminate HBr.

Taking into account that, in our hands, 4-amino-pyrido[2,3-d]pyrimidin-7(8H)-ones have shown very promising anticancer activities when methylated at the N8 nitrogen, we prepared 24 (R2 = Ph), the 8-methyl derivative of 7, in a high yield using MeI in NaH/DMSO (Fig. 3). The subsequent treatment of 24 with 1 equiv. of NBS in DMSO afforded compound 25 (R2 = 4-bromophenyl), which upon treatment with 2 equiv. of NIS/DMSO yielded the orthogonally substituted 2-(p-bromophenyl) amino-6-iodo substituted compound 26 in 83% yield.

The formation of 6-halopyridopyrimidines such as 20 (X = Br) or 23 (X = I) using NBS or NIS, which includes the introduction of C5–C6 unsaturation, can be explained considering two possible itineraries: (a) dihalogenation in α-carbonyl followed by loss of HX (a path already described in the case of NBS33) (Scheme 3, path A) or (b) monohalogenation in α-carbonyl followed by loss of HX and the subsequent halogenation in position C6 as described for similar cases with NBS34 or NIS35 (Scheme 3, path B).

Path B in Scheme 3 is also supported by the bromination in our hands with NBS/DMSO in 70% yield of the C5–C6 unsaturated compound included in such a path, directly obtained by the dehydrogenation of compound 14 (Fig. 3) by heating at 175 °C for 3 days in the presence of 10% Pd(C) and decalin in around 40% yield (see the ESI†). In fact, there are other examples of multistep procedures

(starting from pyrimidine aldehydes) that first construct a structure with a C5–C6 double bond that later is brominated or iodinated with bromine (or NBS) or iodine.36

Finally, once the two dihalo substituted compounds 13 and 26 (Fig. 3) were obtained, we carried out a proof of concept of the orthogonality of the halogens present in both compounds using the Suzuki reaction protocol.

In the case of the dibromo substituted compound 13, we were only able to find a set of reaction conditions using 1.4 equiv. of 3,4,5-trimethoxyphenyl boronic acid (2.5 equiv. of K2CO3, 13 mol% of Pd(PPh3)4, 80 °C, 19 h) which allowed a total consumption of the starting 13 and a selectivity of 78% of the C6-aryl monosubstituted product (Ar = 3,4,5-triMeOC6H2).

The low solubility of the reaction product in the common solvents did not allow adequate purification of such a compound. In contrast, the use of the 8-methyl protected 6-iodo derivative 26 allowed the regiospecific Suzuki coupling at position C6 with a wide range of arylboronic acids (Table 1).

The iodine and bromine atoms present in compound 26 can be sequentially substituted using Suzuki, Ullman and other protocols, as we have previously shown,13 to achieve potentially active tyrosine kinase inhibitors. As a proof of concept, we performed a cross coupling Suzuki reaction on compound 27e using p-tolylboronic acid to afford compound 28 (Fig. 4).

Such orthogonal decoration of compound 26 allows a rapid and convenient approach to pyrido[2,3-d]pyrimidin-7(8H)-ones such as 3 without needing de novo synthesis (6 to 7 steps long) from an α,β-unsaturated ester bearing the aryl substituent for each combination of substituents.13

CONCLUSIONS

As a privileged scaffold, pyrido[2,3-d]pyrimidin-7(8H)-ones (2) are linked to a wide range of biological activities that have attracted the interest of the scientific community, as shown by an almost exponential increase in the number of references included in SciFinder in the last 10 years (more than 300 and a large number of them being patents).37 The reported synthetic methodologies are multistep protocols that need de novo synthesis when a new substituent is needed at position C6, the one particularly linked with the biological activity.37

In the present paper, we have shown (Scheme 2) that in the bromination of compound 7 (easily accessible in one step by a multicomponent reaction, see Scheme 1), after the formation of the monobromo derivative 11, the second bromination occurs at C4a (the first bromine atom installed at a bridgehead carbon to the best of our knowledge) affording the corresponding Wheland intermediate (W1), which is captured by the formation of a rare N-bromoimino derivative 12. The precipitation of 12 as a microcrystalline powder led to such a compound with enough stability to determine its structure from the X-ray powder registered at the ALBA synchrotron; however, the treatment of 12 with DMSO converted such a compound to the dibromo substituted pyridopyrimidine 13.

Although 13 already presented a certain degree of orthogonal reactivity between both bromo substituents, its low solubility forced us to use the 8-methyl protected monobromo substituted compound 25 (cleavable protections can be also used) which allows the synthesis of the fully orthogonal 2-(p-bromophenylamino)-6-iodo substituted compound 26 upon treatment with NIS. Such orthogonality has been tested by using different boronic acids and this protocol is currently being used in different projects in the field of tyrosine kinase inhibitors aimed at the synthesis of anticancer drugs.

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Legends to figures

Figure. 1 Biologically active pyrido[2,3-d]pyrimidin-7(8H)-ones 1–5 and dibromo substituted structure 6**.**

Scheme 1 Multicomponent synthesis of pyrido[2,3-d]pyrimidin-7(8H)-one 7.

Scheme 2 Monobrominated compound 11 and capture of the Wheland intermediate W1 as the corresponding N-bromoimino derivative 12 and comparison of W1 with the Wheland intermediate of the aniline bromination W2.

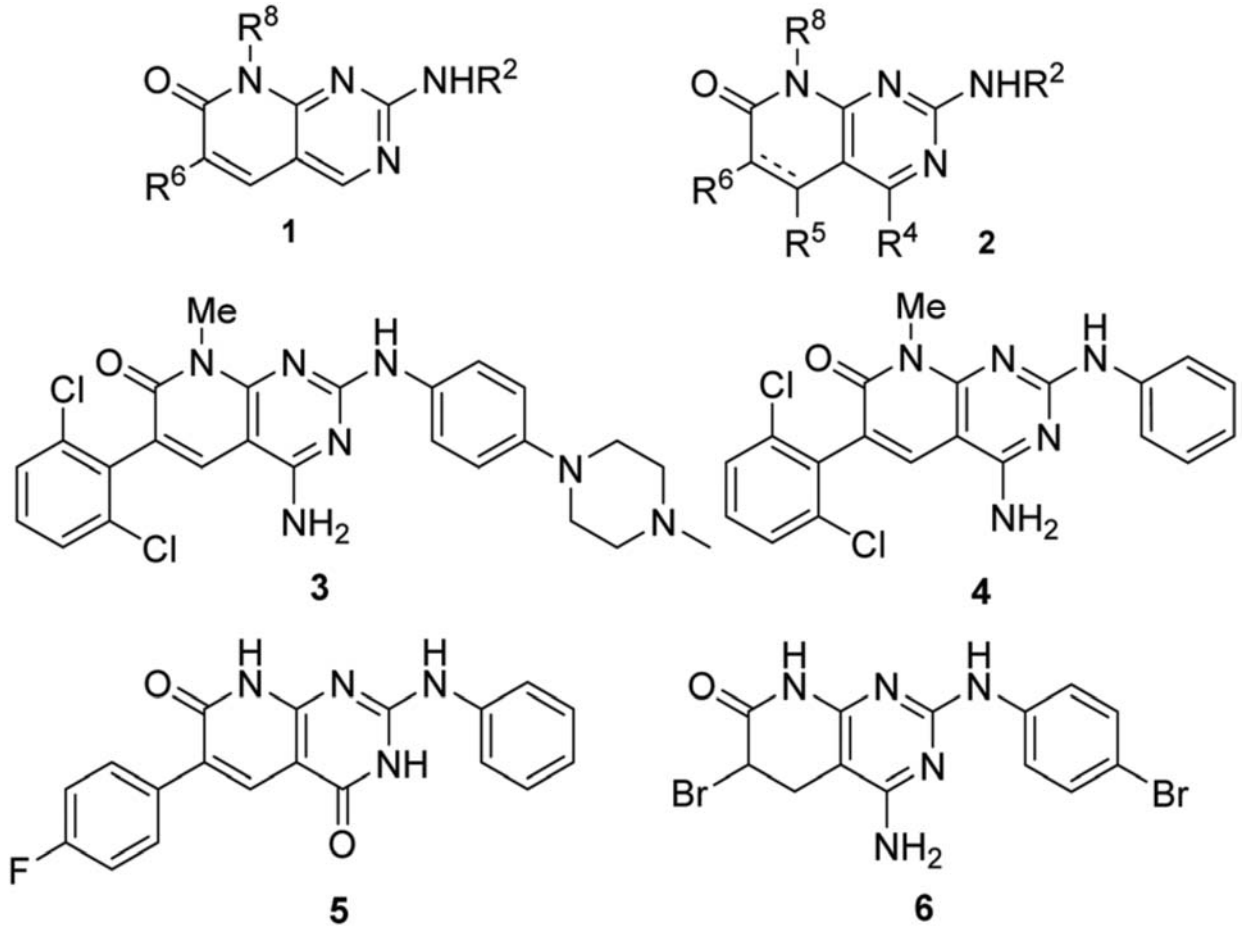
Figure 2. a) Powder diffraction pattern of 12 (0.95250 Å wavelength) and (b) crystal structure of 12 showing the bromine atom at the C4a bridgehead carbon atom and the intermolecular hydrogen bonding in the selfassembled dimer.

Figure 3. 6-Halo (X = Br and I) obtained using Br2 in AcOH or NBS/NIS in DMSO.

Scheme 3 Rationalization of the formation of 20 and 23 using NBS or NIS in DMSO.

Figure 4. Example of orthogonal decoration of compound 26.

FIGURE 1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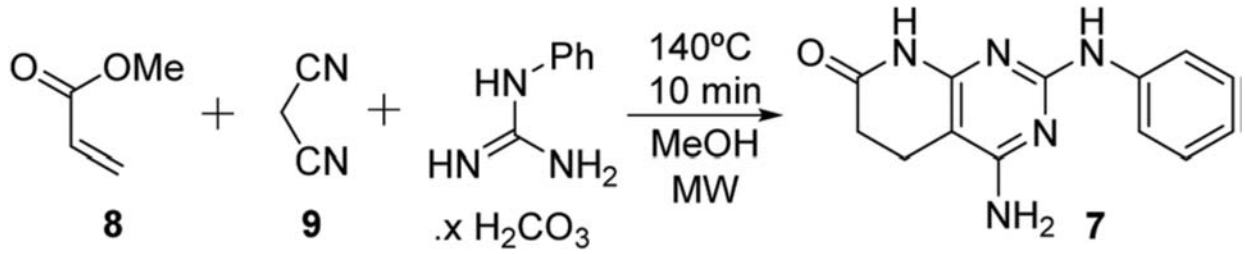
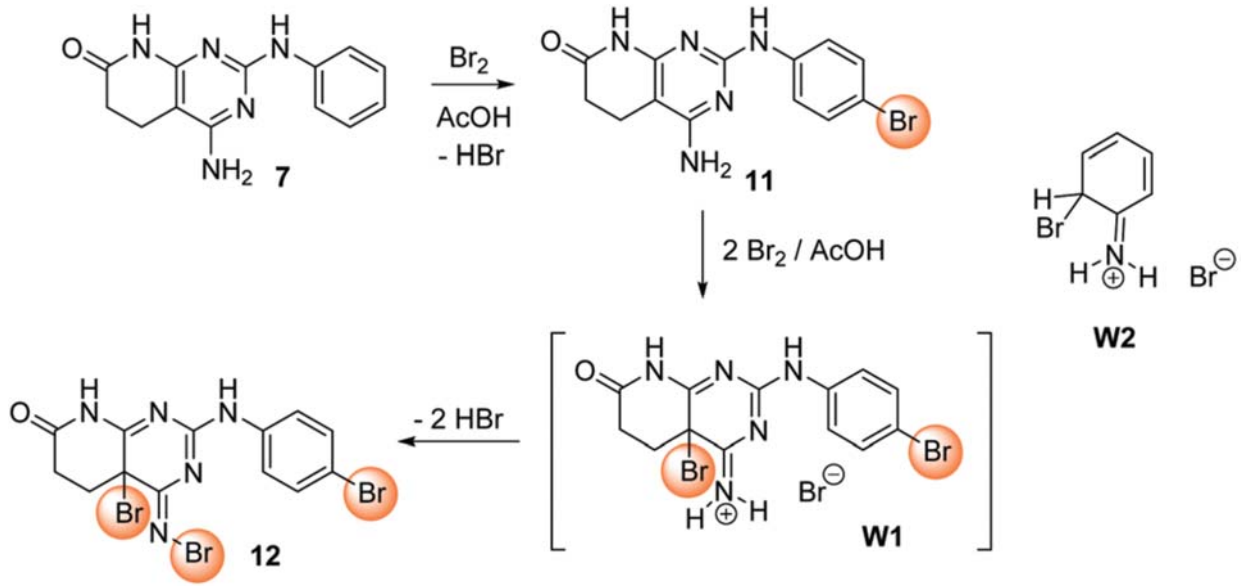
SCHEME 1.



8 **9** **10** **7**

SCHEME 2.



345
346 **FIGURE** 2

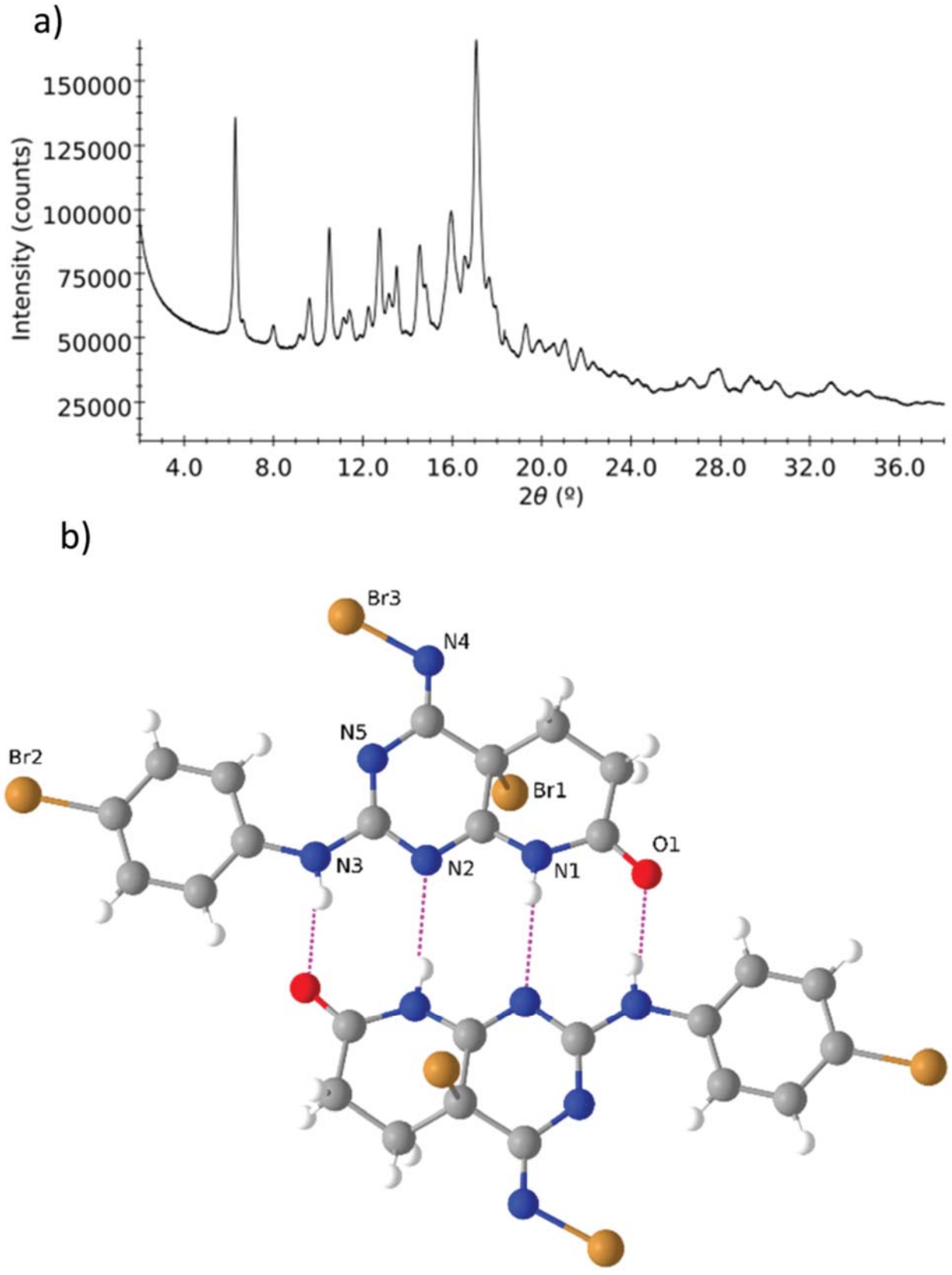


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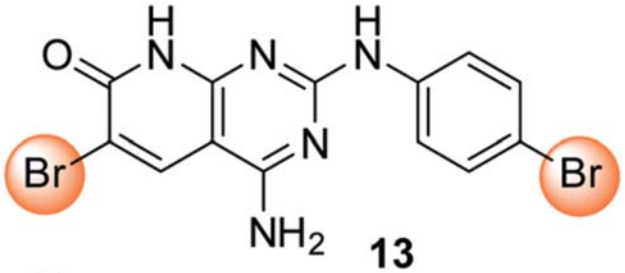
FIGURE 3



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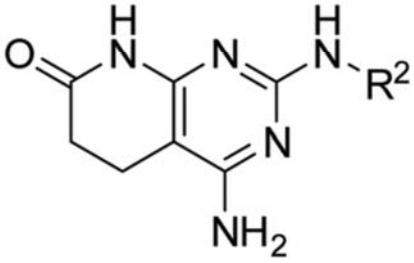
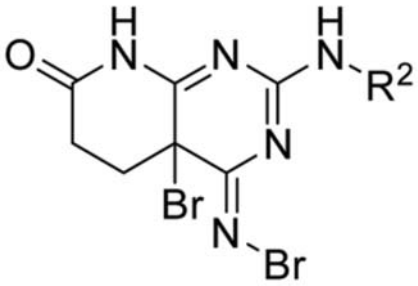
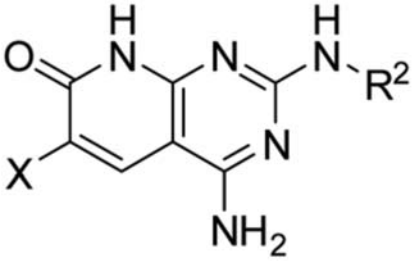


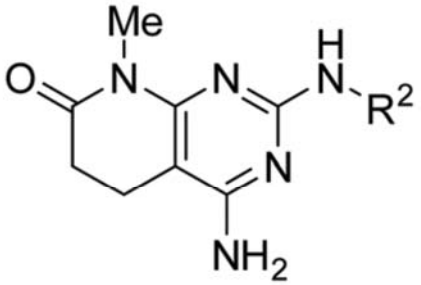
14: R^2 = H
15: R^2 = *p*-FC_6H_4
16: R^2 = *p*-ClC_6H_4



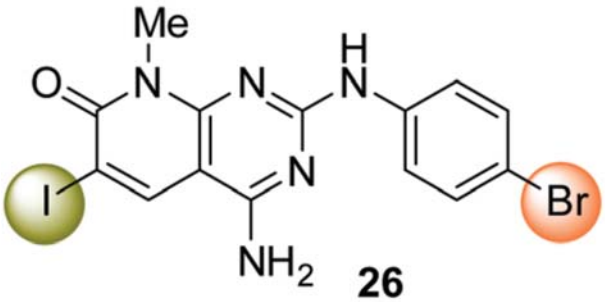
17: R^2 = H
18: R^2 = *p*-FC_6H_4
19: R^2 = *p*-ClC_6H_4



20: X = Br, R^2 = H
21: X = Br, R^2 = *p*-FC_6H_4
22: X = Br, R^2 = *p*-ClC_6H_4
23: X = I, R^2 = H



24: R^2= Ph
25: R^2 = *p*-BrC_6H_4



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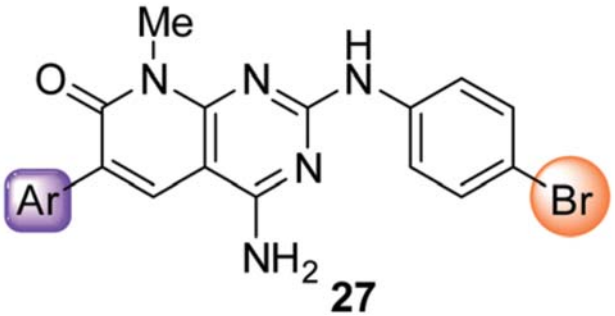

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SCHEME 3

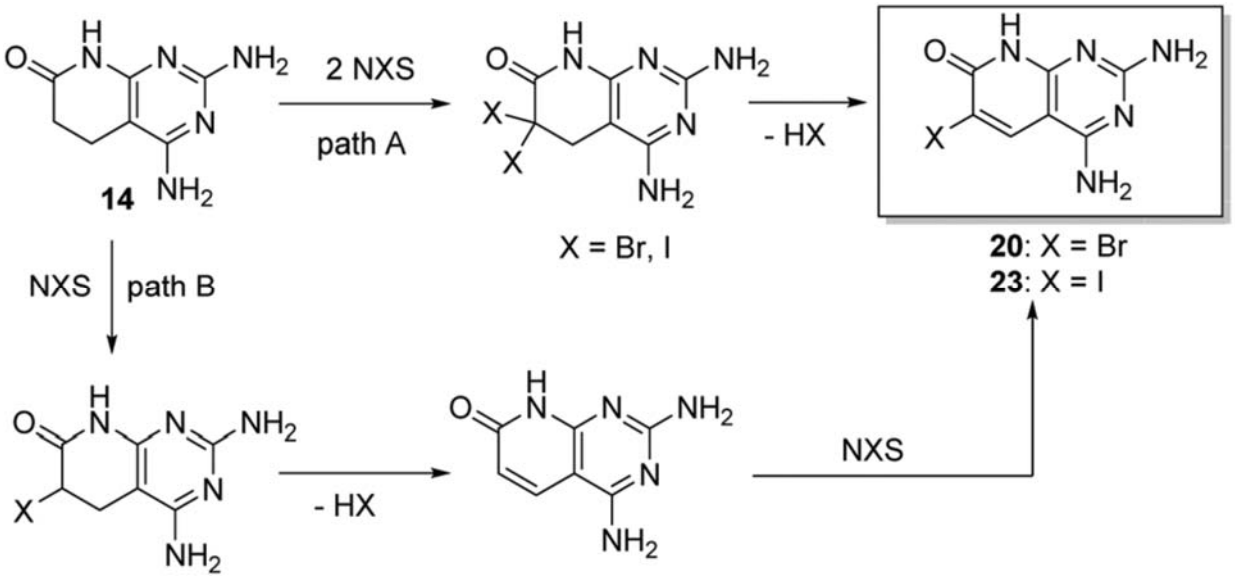
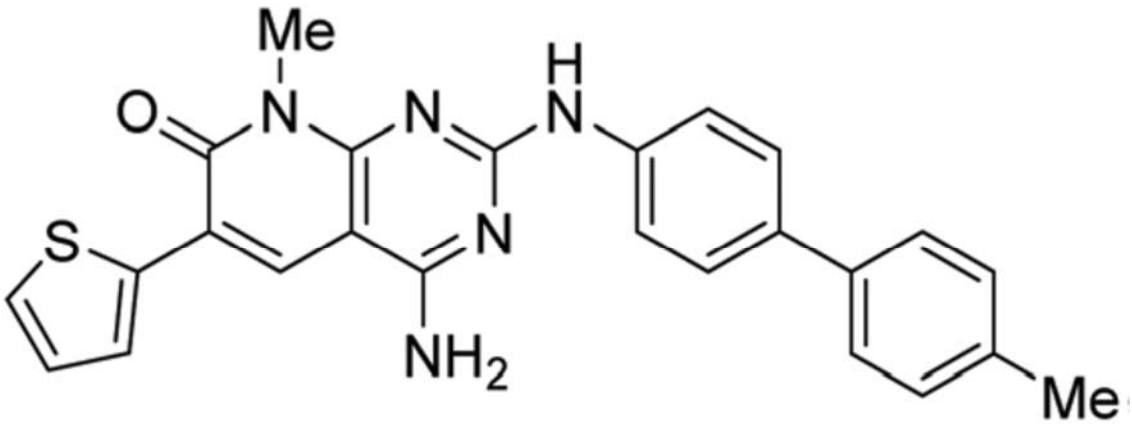


FIGURE 4



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367 **Table 1** Synthesis of 6-aryl substituted pyridopyrimidines 27a–f

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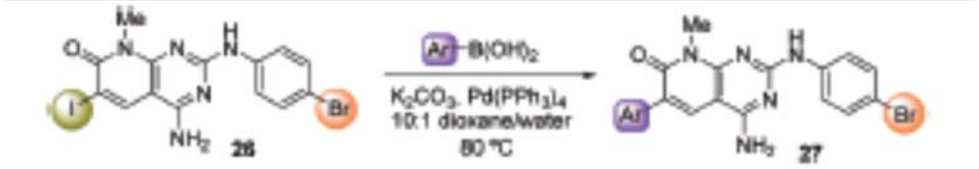
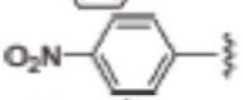


Ar	Product	Yield [%]
	**27a**	75
	**27b**[a]	36
	**27c**	63
	**27d**	61
	**27e**	73
	**27f**	52

Reaction conditions: boronic acid (1.4 equiv.), $Pd(PPh_3)_4$ (2 mol%), K_2CO_3 (2.5 equiv.), 10 : 1 dioxane/water, 80 °C. [a] $Pd(PPh_3)_4$ (15 mol%).

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