Tetrahedron 65 (2009) 1153–1161

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Application of the Pictet–Spengler reaction to aryl amine-based substrates having pyrimidine as a π-nucleophile: synthesis of pyrimidoquinolines with structural analogy to benzonaphthyridines present in alkaloids☆

Piyush K. Agarwal, Sudhir K. Sharma, Devesh Sawant, Bijoy Kundu *

Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226001, India

ARTICLE INFO

Article history:
Received 22 August 2008
Received in revised form 15 October 2008
Accepted 21 November 2008
Available online 27 November 2008

ABSTRACT

Synthesis of pyrimidine annulated quinolines, structurally analogous to biologically active benzonaphthyridines present in alkaloids, has been described. Our synthetic strategy is based on the modified Pictet–Spengler reaction involving substrates comprising deactivated pyrimidine ring as the nucleophilic partner whereas aryl amine originating from the C-4 of the pyrimidine ring served as the source for electrophilic partner. The resulting substrates **5**–**7** with diversity at 2- and 6-position after condensation with a variety of aldehydes underwent 6-*endo* cyclization to furnish pyrimido[5,4-*c*]quinolines **14** in good yields. However, attempts to further extend this strategy on new structurally analogous substrate involving the pyridine ring as nucleophilic partner failed, thus limiting the scope of the reaction.

1. Introduction

The Pictet–Spengler reaction[1] discovered approximately 100 years ago remains one of the most elegant strategies for C–C bond formation via *endo* cyclization. Traditionally, the substrates (first-generation substrates) used for the Pictet–Spengler reaction such as tryptamine/tryptophan, histidine/histamine, and dimethoxyphenethylamines are based on aliphatic amines that act as a source for iminium/electrophilic partner until the year 2005, when we disclosed a modified strategy[2] for the Pictet–Spengler reaction by demonstrating *endo* cyclization in substrates with aryl amines attached to the activated heterocyclic rings (second-generation substrates). The modified strategy has also been used successfully by others.[3]

During the course of further investigations with modified substrates, recently we reported yet another interesting finding that the Pictet–Spengler reaction could be affected even when aryl amine is linked to a deactivated (poorly nucleophilic) heterocyclic ring.[4] Initially this was demonstrated on a series of deactivated nucleophilic systems categorized under 'third-generation' substrates: quinoxalines, triazoles, and tetrazoles, the substrates had limitation for aldehydes with strong electron-donating group as substituents. In contrast the second-generation substrates[2c] reported earlier underwent π-cyclizations with aldehydes having both electron-donating and electron-withdrawing groups. Thus, in order to expand the repertoire of 'third-generation' substrates with abilities to facilitate *endo* cyclization with all classes of aromatic aldehydes, pyrimidine was identified as yet another class of heterocycle known to be associated with diminished nucleophilicity.

Pyrimidine is one of the nature's most versatile building blocks with established medicinal pedigree and its presence in thymine, cytosine, and uracil, which are the essential building blocks of nucleic acids, DNA and RNA, is one possible reason for their activity. The motif has been given the privileged label[5] as it is found to be present in a variety of therapeutic molecules[6] exhibiting activity ranging from antiinflammatory, antibacterial, anticancer, antiviral, antiHIV, antimalarial, antihypertensive, sedatives, and hypnotics, anticonvulsant to antihistaminic.

A careful survey of the literature for the application of Pictet–Spengler reaction on pyrimidine-based substrates revealed papers by Duncton et al.[3a] and Bai et al.[3b] who by applying the modified Pictet–Spengler concept (substrate **1**; Fig. 1), demonstrated the 6-*endo* cyclization on substrates **2** and **3** (Fig. 1) having 5-aminopyrimidine, as a source for the electrophilic partner, linked either to a phenyl ring via sulfur, nitrogen or oxygen atom or to the N-1 of the indole, respectively. In all the three substrates, the phenyl tethered to NH, imidazole, and the indole served as π-nucleophiles.

As opposed to the precedence of 5-aminopyrimidine being used as a source for electrophile, the present endeavor (proposed substrate **4**; Fig. 1) involves use of the pyrimidine ring (a deactivated ring) as a π-nucleophile after being linked to an aryl amine (source for electrophile) through one of its carbons in a manner to facilitate the π-cyclization. To the best of our knowledge, this is the first

☆ CDRI communication no. 7667.

* Corresponding author. Tel.: +91 522 2612411–18; fax: +91 522 2623405.
E-mail address: bijoy_kundu@yahoo.com (B. Kundu).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.11.067

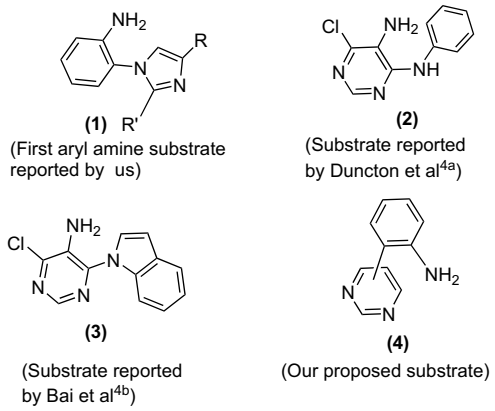


Figure 1. Substrates **2** and **3**: 5-aminopyrimidine acts as a source for electrophile after formation of imine. Substrate **4**: a proposed substrate with pyrimidine as a π-nucleophile.

report involving the use of pyrimidine ring as a π-nucleophile in the Pictet–Spengler reactions.

2. Results and discussion

The studies commenced with the identification of a carbon in the pyrimidine ring for linking an aryl amine by analyzing the electrophilic substitution pattern in pyrimidines. Replacing a CH=CH group in benzene with a heteroatom *N*H as in pyrrole increases the susceptibility of the ring carbon atoms to electrophilic attack very markedly. However, replacement of one CH group in the benzene with nitrogen atom as in pyridine decreases the ease of electrophilic attack at the remaining carbon atoms and replacement of two CH groups with two nitrogen atoms as in pyrimidine decreases it even further (Fig. 2).[7]

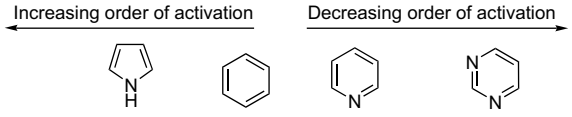


Figure 2. Increasing/decreasing order of activation in five- and six-membered rings with reference to benzene.[8]

Indeed, the influence of heteroatom in the six-membered π-deficient pyrimidine can be predicted based on a general rule that the effect of the heteroatom on the α- and γ-carbons is more pronounced than β-carbon. Thus, the C-4 and C-6 in the pyrimidine are the most deactivated toward electrophilic attack whereas C-5 is the least deactivated and is therefore prone to electrophilic substitutions.[8]

Based on these facts, it was envisaged that an aryl amine originating from the either side of the C-5 in the pyrimidine ring, might act as a novel substrate for the Pictet–Spengler cyclization. Keeping these structural requirements in mind, the synthetic feasibilities for these substrates were analyzed by examining the strategies reported in the literature for the pyrimidine-based compounds.[8] The analysis ultimately led us to the identification of 2-(2,6-di-substituted-pyrimidin-4-yl)phenylamines **5**–**7** as the probable substrates for the application of the Pictet–Spengler reaction (Fig. 3). In the three pyrimidine substrates **5**–**7**, an aryl amine has been allowed to originate from C-4, while the C-2 and C-6 positions have been used for introducing diversity, and C-5, the nucleophilic carbon, has been kept free for π-cyclizations.

Syntheses of substrates **5**–**7** were carried out by the modified procedure reported in the literature[9] and has been depicted in Scheme 1. Substrates **5** and **6** were obtained from the chalcone

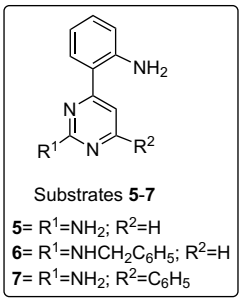
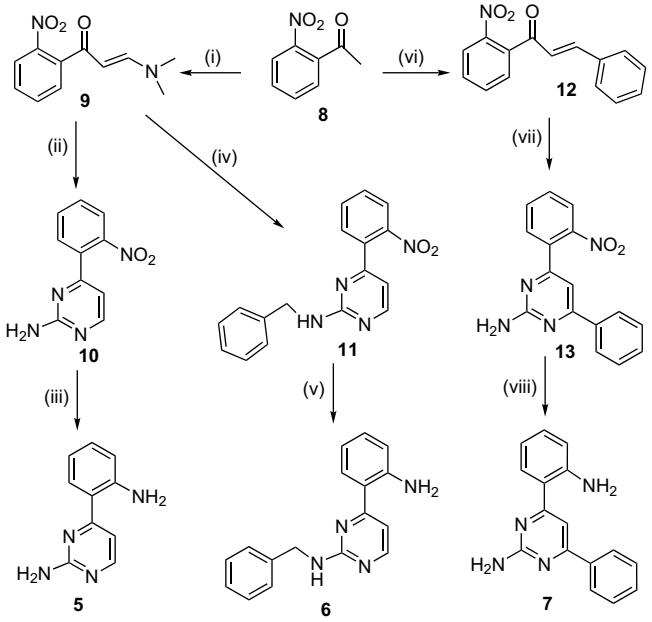


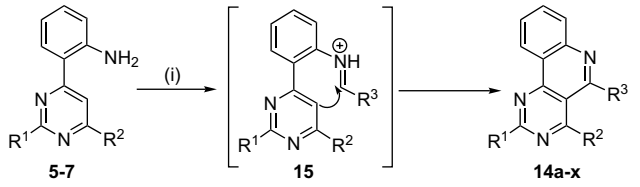
Figure 3. Substrates based on pyrimidine ring as nucleophilic partner for the modified Pictet–Spengler reaction.

3-dimethylamino-1-(2-nitrophenyl)-propenone **9** as a common intermediate, which was obtained by heating 1-(2-nitrophenyl)ethanone **8** with *N*,*N*-dimethylformamide dimethyl acetal. For the synthesis of **5**, chalcone **9** was treated with guanidine hydrochloride to give intermediate **10** followed by reduction of the nitro group with Fe and HCl. For the synthesis of substrate **6**, chalcone **9** was initially treated with 1-benzylguanidine hydrochloride in the presence of potassium carbonate in ethanol under reflux followed by reduction of the nitro group using Fe and HCl. Finally, synthesis of substrate **7** was carried out by treating 2-nitroacetophenone **8** with benzaldehyde in the presence of KOH to give chalcone **12** followed by treatment with guanidine hydrochloride to give pyrimidine intermediate **13**. The nitro group in the resulting intermediate **13** was reduced in the presence of Fe and HCl to give **7**. With the substrates **5**–**7** in hand, their abilities to undergo a Pictet–Spengler cyclization with structurally diverse aldehydes were investigated.



Scheme 1. Synthetic strategy for substrates **5**, **6**, and **7**. *Reagents and conditions*: (i) *N*,*N*-dimethylformamide dimethyl acetal, 100 °C, 3 h; (ii) guanidine hydrochloride, potassium carbonate, EtOH, refluxed, 16 h; (iii) Fe, concd HCl, reflux, 1 h; (iv) 1-benzylguanidine hydrochloride, potassium carbonate, EtOH, reflux, 16 h; (v) Fe, concd HCl, reflux, 1 h; (vi) C_6H_5CHO, EtOH, KOH, H_2O, 3 h 0 °C to rt; (vii) guanidine hydrochloride, sodium ethoxide, *N*,*N*-dimethyl acetamide, 100 °C, 2 h; (viii) Fe, concd HCl, reflux, 1 h.

For the Pictet–Spengler cyclization (Scheme 2), the substrate **5** was treated with 4-nitrobenzaldehyde using a variety of traditional Pictet–Spengler protocols involving *p*TsOH in toluene at reflux, 2% TFA in DCM at 0 °C, AcOH in ethanol at reflux, and neat toluene at



Scheme 2. General strategy for the Pictet–Spengler reaction involving substrates **5**, **6**, and **7**. *Reagents and conditions*: (i) R^3CHO 1% triflic acid in DMF, 120 °C, 8 h.

80 °C. The protocols failed to yield the desired cyclized product **14a** and produced imine as the major product.

Dwelling on the factors affecting π-cyclization, it is well known that the Bronsted acid plays a pivotal role in enhancement of the electrophilicity of the imine, which in turn acts as the driving force for the π-cyclization.[1d] Thus, the use of stronger Bronsted acid may activate the imine leading to the desired cyclized product **14**. Accordingly, the amine **5** was treated with 4-nitrobenzaldehyde using methanesulfonic acid (MSA) and triflic acid as source for proton with the view to obtain maximum yield of **14a**, and the results of the optimization studies are listed in Table 1. During the course of cyclization, no conversion was observed for **5** in the presence of MSA, while presence of 1% triflic acid in DMF cleanly effected complete conversion of **5** and afforded **14a** in >85% purity based on HPLC.

Table 1
Optimization of the reaction conditions for conversion of substrate **5** to **14a**

Entry	Reaction conditions	Temp (°C)	Time (h)	Yield of **14a**[a] (%)
1	2% MSA/CH_3CN	80	48	0
2	2% MSA/DMF	120	48	0
3	2% Triflic acid in ACN	80	24	20
4	2% Triflic acid in DMF	120	8	80
5	1% Triflic acid in DMF	120	8	85
6	0.5% Triflic acid in DMF	120	16	30

[a] Based on HPLC.

The crude product obtained after workup was purified using a series of column chromatography packing materials: silica gel, neutral alumina, and basic alumina but the best recovery of the desired compound occurred only on neutral alumina column chromatography using EtOAc/hexane as an eluent in 63% isolated yield. The low recovery of the compound from column chromatography can be attributed to the basic nature of the compound, which was evident from the fact that after eluting the column with neat EtOAc, the remaining material was recovered in >90% purity. The scope and limitation of the modified strategy with substrate **5** was established by synthesizing nine compounds based on pyrimido[5,4-*c*]quinolines **14b–j** (Table 2), using nine aromatic aldehydes. For the Pictet–Spengler cyclization, 1% triflic acid in DMF at 120 °C protocol was used and in all cases cyclization was found to be complete within 8 h with isolated yields in the range of 56–68%. Pleasingly, aldehydes with either electron-donating or electron-withdrawing group had no adverse effect on the rate of cyclization.

After successfully establishing the strategy on **5**, substrate **6** was then subjected to the Pictet–Spengler reaction with a variety of aldehydes. The crude products obtained after workup was purified on neutral alumina column chromatography furnishing pyrimido[5,4-*c*]quinolines **14k–r** (Table 2) in 50–67% isolated yields. The NH-benzyl substitution present at position 2 in substrate **6** had no affect on the yield and purity of the final *endo* cyclized products (**14k–r**).

Substrate **7**, however, was found to be adamant toward *endo* cyclization when treated with 2-substituted aromatic aldehydes while 4-substituted aldehydes indeed furnished *endo* cyclized products albeit in low yields. This can be attributed to the steric hindrance being conferred by the substitution at position 6 in the substrate **7**, which is next to the position 5, the site involved in the *endo* cyclization. The isolated yields for pyrimido[5,4-*c*]quinolines **14u–x** (Table 2) using 4-substituted aromatic aldehydes remained in the range of 45–53% yields.

A careful survey of the literature revealed that synthesis for such a prototype has not been reported except for the two reports

Table 2
Pyrimido[5,4-*c*]quinolines based on **14**

Entry	Substrates	Aldehyde R^3-CHO	Pictet–Spengler products				Isolated yield (%)	Retention time[a] (t_R, min)
			No.	R^1	R^2	R^3		
1	**5**	4-NO_2-C_6H_4-CHO	**14a**	NH_2	H	4-NO_2-C_6H_4	63	14.07
2	**5**	4-OEt-C_6H_4-CHO	**14b**	NH_2	H	4-OEt-C_6H_4	68	13.04
3	**5**	2-OH-C_6H_4-CHO	**14c**	NH_2	H	2-OH-C_6H_4	56	7.99
4	**5**	4-Cl-C_6H_4-CHO	**14d**	NH_2	H	4-Cl-C_6H_4	59	13.84
5	**5**	4-$(CH_3)_2$N-C_6H_4-CHO	**14e**	NH_2	H	4-$(CH_3)_2$N-C_6H_4	60	13.22
6	**5**	C_6H_5-CHO	**14f**	NH_2	H	C_6H_5	63	14.87
7	**5**	4-Br-C_6H_4-CHO	**14g**	NH_2	H	4-Br-C_6H_4	62	17.91
8	**5**	4-F-C_6H_4-CHO	**14h**	NH_2	H	4-F-C_6H_4	64	15.32
9	**5**	3,4-DiCl-C_6H_4-CHO	**14i**	NH_2	H	3,4-DiCl-C_6H_4	60	19.63
10	**5**	3,4-DiOMe-C_6H_4-CHO	**14j**	NH_2	H	3,4-DiOMe-C_6H_4	65	14.81
11	**6**	4-F-C_6H_4-CHO	**14k**	$NHCH_2C_6H_5$	H	4-F-C_6H_4	60	22.23
12	**6**	4-Br-C_6H_4-CHO	**14l**	$NHCH_2C_6H_5$	H	4-Br-C_6H_4	64	23.06
13	**6**	3,4-DiCl-C_6H_4-CHO	**14m**	$NHCH_2C_6H_5$	H	3,4-DiCl-C_6H_4	62	24.91
14	**6**	2-NO_2-C_6H_4-CHO	**14n**	$NHCH_2C_6H_5$	H	2-NO_2-C_6H_4	52	20.73
15	**6**	4-Cl-C_6H_4-CHO	**14o**	$NHCH_2C_6H_5$	H	4-Cl-C_6H_4	59	22.42
16	**6**	4-NO_2-C_6H_4-CHO	**14p**	$NHCH_2C_6H_5$	H	4-NO_2-C_6H_4	67	21.85
17	**6**	4-$(CH_3)_2$N-C_6H_4-CHO	**14q**	$NHCH_2C_6H_5$	H	4-$(CH_3)_2$N-C_6H_4	50	23.30
18	**6**	4-OEt-C_6H_4-CHO	**14r**	$NHCH_2C_6H_5$	H	4-OEt-C_6H_4	65	21.83
19	**7**	2-NO_2-C_6H_4-CHO	**14s**	NH_2	C_6H_5	2-NO_2-C_6H_4	NR[b]	—
20	**7**	2-OH-C_6H_4-CHO	**14t**	NH_2	C_6H_5	2-OH-C_6H_4	NR[b]	—
21	**7**	4-OEt-C_6H_4-CHO	**14u**	NH_2	C_6H_5	4-OEt-C_6H_4	49	19.45
22	**7**	4-$(CH_3)_2$N-C_6H_4-CHO	**14v**	NH_2	C_6H_5	4-$(CH_3)_2$N-C_6H_4	46	19.84
23	**7**	4-NO_2-C_6H_4-CHO	**14w**	NH_2	C_6H_5	4-NO_2-C_6H_4	53	18.71
24	**7**	4-CN-C_6H_4-CHO	**14x**	NH_2	C_6H_5	4-CN-C_6H_4	45	17.61

[a] Retention time on HPLC (C18 reverse-phase column; 150×4.8 mm; 5 μm) with a linear gradient of 0–100% CH_3CN in water over 30 min, flow rate of 1.0 mL/min, and UV detection at 220/254 nm.

[b] NR=no reaction due to steric hindrance arising from the substitution at position 6.

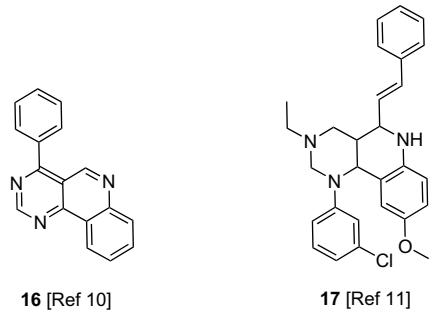


Figure 4. Structural variants of pyrimido[5,4-*c*]quinolines **14** reported in the literature.

dealing with the synthesis of its structural variants: 4-phenyl-pyrimido[5,4-*c*]quinoline[10] **16** and 1-(3-chloro phenyl)-3-ethyl-9-methoxy-5-styryltetrahydro-pyrimido[5,4-*c*]quinoline[11] **17** in which quinoline is fused at positions 5 and 6 of the pyrimidine ring (Fig. 4). On the contrary, in the pyrimido[5,4-*c*]quinolines **14**, the quinoline ring is fused to the positions 4 and 5 of the pyrimidine ring. In addition, the synthetic strategies described for the compounds **16** and **17** were completely different from the synthesis reported for pyrimido[5,4-*c*]quinolines using modified Pictet–Spengler strategy.

Further it is interesting to note that the pyrimidine-based Pictet–Spengler product bored a strong structural analogy to benzo-[*c*][2,7]naphthyridine **18** (Fig. 5), which is a common structural motif present in a wide range of polycyclic alkaloids isolated from marine organisms with diverse biological activity (calcium-releasing, antiviral, antimicrobial, cytotoxic to L1210 murine leukemia cells).[12] The only difference between the two compounds is the presence of extra nitrogen at position 3 in **14**.

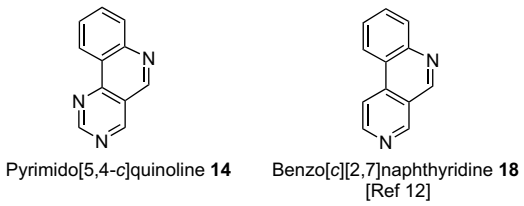
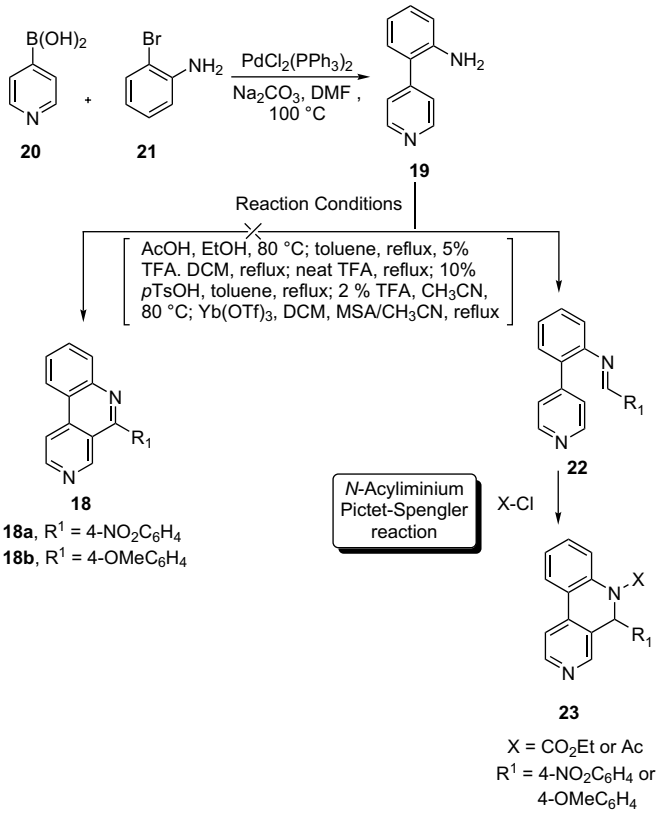


Figure 5. Structural analogy between **14** and benzo[*c*][2,7]-naphthyridine **18** present in natural products.

This prompted us to synthesize benzo[*c*][2,7]naphthyridine **18** using the modified Pictet–Spengler reaction. It was envisaged that **18** could be obtained by subjecting 2-pyridin-4-yl-phenylamine **19** to 6-*endo* cyclization by treating with aromatic aldehydes (Scheme 3). Accordingly, in the first instance synthesis of substrate **19** was carried out by treating pyridine-4-boronic acid **20** with 2-bromoaniline **21** using Suzuki coupling reaction.[13] Finally substrate **19** was subjected to Pictet–Spengler reaction by treating with 4-nitrobenzaldehyde in the presence of 1% triflic acid in DMF in sealed tube at 120 °C. Surprisingly the initial attempts failed to furnish the cyclized product **18a**, instead the corresponding imine **22** remained as the only isolated product. The application of other widely used Pictet–Spengler protocols, acetic acid in ethanol, toluene at reflux, 5% TFA in DCM at reflux, neat TFA at reflux, 10% *p*TsOH in toluene at reflux, 2% TFA in acetonitrile, $Yb(OTf)_3$ in DCM, MSA in CH_3CN at reflux, using both *p*-nitrobenzaldehyde and *p*-methoxybenzaldehyde, also failed to yield the 6-*endo* cyclized product. Most of these conditions either produced the imine **22** as the only product or resulted in the reactants probably due to the degradation of **22**.



Scheme 3. Failure of synthetic attempts for benzo[*c*][2,7]naphthyridines **18** and **23**.

This was followed by application of *N*-acyliminium Pictet–Spengler strategy,[14] a method widely used for facilitating 6-*endo* cyclization. Accordingly, the imine **22** was treated with ethyl chloroformate in pyridine using the methodology reported in the literature to facilitate the 6-*endo* cyclization. However, this failed to furnish the π-cyclized product **23**, even after carrying out the reaction either for the prolonged period or by using different *N*-acyl species reported in the literature.

A close structural examination of the pyrimidine-based substrates **5**–7 and pyridine based substrate **19** revealed that the presence of an additional amino group as electron-releasing substituent at C-2 of the pyrimidine may be facilitating the π-cyclization. Thus, it appears that the failure of pyridine substrate **19** to undergo π-cyclization could be attributed to the lack of electron-releasing substituents in the pyridine ring. Further, no attempts were made to work with 2-substituted pyridines as it would lead to a regioisomeric mixture of cyclized products.

3. Conclusion

In conclusion we have successfully identified 2-amino-pyrimidine, under deactivated class of heterocyclic ring as a nucleophilic partner, which when attached to an aryl amine successfully underwent the Pictet–Spengler reaction with aldehydes having both electron-donating and electron-withdrawing groups. The efficacy of the strategy has been exemplified in a series of pyrimidine rings by introducing diversity at positions 2 and 6. However, explorations of new substrates, involving the pyridine ring as nucleophilic partner, were futile. This example, thus presents a limitation to the aryl amine based third generation substrates, which was otherwise successful when applied in the past to a host of deactivated heterocyclic rings such as triazole, tetrazole, and quinoxaline.

4. Experimental

4.1. General consideration

All solvents were commercially available and used without purification. All products were characterized by ^{1}H NMR, ^{13}C NMR, ESMS, IR, and HPLC. Analytical TLC was performed using 2.5×5 cm plated coated with a 0.25 mm thickness of silica gel 60F_{254} Merck and visualization was accomplished with UV light and iodine. Column chromatography was performed using silica gel 60 Thomas Baker (100–200 mesh). ^{1}H NMR spectra (200/300 MHz) are reported as follows: chemical shifts in parts per million downfield from TMS as internal standard (δ scale), multiplicity [br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, o=overlapped], integration, and coupling constant (Hz). All ^{13}C NMR spectra (50/75 MHz) were recorded at 25 °C with complete proton decoupling and reported in parts per million. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL III microanalyzer in the SAIF division of our institute. Analytical HPLC were performed on C18 reverse-phase column (150 mm×4.8 mm). Mass spectra were recorded on a Merck MS-8000 spectrometer and HR/EI mass spectra were done on JEOL-600H at 70 eV. Melting points reported were uncorrected.

4.2. Procedure for the synthesis of (*E*)-3-(dimethylamino)-1-(2-nitrophenyl)prop-2-en-1-one (9)

A mixture of 1-(2-nitrophenyl)ethan-1-one **8** (1.0 g, 6.05 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (0.72 g, 6.05 mmol) was heated at 100 °C for 3 h. The reaction mixture was then subjected to column chromatography (100–200 silica gel) using ethyl acetate/hexane (80:20, v/v) as eluent.

Yield=1.10 g (85%), red solid, mp 128–129 °C, R_f=0.25 (4:1 EtOAc/hexane); IR (KBr) ν_{max} 3029, 2884, 1640, 1521, 1362 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ=7.92 (1H, d, J=7.7 Hz, ArH), 7.74–7.69 (1H, m, ArH), 7.64–7.48 (3H, m, =CH, ArH), 5.34 (1H, d, J=12.5 Hz, =CH), 3.10 (3H, s, CH_3), 2.86 (3H, s, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ=155.3, 147.9, 137.6, 132.9, 130.1, 128.8, 123.9, 44.6, 37.1; mass (ES$^+$) m/z 221.1 (M$^+$+1). Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.89; H, 5.42; N, 12.62.

4.3. Procedure for the synthesis of 4-(2-nitrophenyl)-pyrimidin-2-ylamine (10)

To a stirred solution of guanidine hydrochloride (1.30 g, 13.62 mmol) and potassium carbonate (2.20 g, 15.89 mmol) in ethanol (20 mL) was added (*E*)-3-(dimethylamino)-1-(2-nitrophenyl)prop-2-en-1-one **9** (1.0 g, 4.54 mmol) and the reaction mixture was refluxed for 16 h. After completion of the reaction as evident by TLC analysis, ethanol was distilled off, water (20 mL) was added, and compound was extracted with ethyl acetate (15 mL×3). The organic layer washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue so obtained was triturated with diethyl ether to furnish pure compound as a light yellow solid.

Yield=0.80 g (82%), yellow solid, mp 209–210 °C, R_f=0.75 (4:1 EtOAc/hexane); IR (KBr) ν_{max} 3329, 3171, 1654, 1524, 1364 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ=8.35 (1H, d, J=5.0 Hz, ArH), 7.98 (1H, d, J=7.7 Hz, ArH), 7.82–7.77 (1H, m, ArH), 7.73–7.67 (2H, m, ArH), 6.80 (1H, d, J=5.0 Hz, ArH), 6.69 (2H, br s, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ=163.4, 163.3, 159.3, 148.7, 133.2, 133.1, 130.8, 130.5, 124.4, 108.3; mass (ES$^+$) m/z 217.1 (M$^+$+1). Anal. Calcd for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.91. Found: C, 55.51; H, 3.63; N, 25.82.

4.4. Procedure for the synthesis of 4-(2-aminophenyl)-pyrimidin-2-ylamine (5)

4-(2-Nitrophenyl)pyrimidin-2-ylamine **10** (2.5 g, 11.6 mmol) was dissolved in a mixture of ethanol (40 mL) and water (10 mL) followed by the addition of iron powder (1.9 g, 34.71 mmol) and concd HCl (10 mL). The reaction mixture was stirred under reflux for 1 h, cooled, and then filtered through a pad of Celite. The filtrate was concentrated in vacuo and compound was extracted in ethyl acetate (15 mL×3). The organic layer washed sequentially with satd $NaHCO_3$ and brine, and after drying over Na_2SO_4 was concentrated in vacuo. The crude product so obtained was purified by recrystallization in EtOH to give 4-(2-aminophenyl)pyrimidin-2-ylamine as a yellow solid.

Yield=1.90 g (90%), yellow solid, mp 171–172 °C, R_f=0.50 (1:1 EtOAc/hexane); IR (KBr) ν_{max} 3428, 3020, 1612, 1216 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ=8.20 (1H, d, J=5.5 Hz, ArH), 7.60 (1H, d, J=7.2 Hz, ArH), 7.13–7.08 (1H, m, ArH), 7.01 (2H, br s, NH_2), 6.96 (1H, d, J=5.5 Hz, ArH), 6.75 (1H, d, J=8.1 Hz, ArH), 6.65 (2H, br s, NH_2), 6.55 (1H, t, J=7.5 Hz, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ=166.4, 162.6, 158.1, 149.3, 131.1, 128.9, 116.9, 116.6, 115.2, 105.9; mass (ES$^+$) m/z 187.2 (M$^+$+1). Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.35; H, 5.37; N, 30.13.

4.5. Procedure for the synthesis of *N*-benzyl-*N*-[4-(2-nitrophenyl)pyrimidin-2-yl]amine (11)

To a stirred solution of 1-benzylguanidine hydrochloride (2.52 g, 13.62 mmol) and potassium carbonate (2.20 g, 15.89 mmol) in ethanol (20 mL) was added (*E*)-3-(dimethylamino)-1-(2-nitrophenyl)prop-2-en-1-one **9** (1.0 g, 4.54 mmol) and reaction mixture was refluxed for 16 h. After completion of the reaction as evident by TLC analysis, ethanol was distilled off, water (20 mL) was added, and the compound was extracted with ethyl acetate (15 mL×3). The organic layer washed with brine, dried over Na_2SO_4, and concentrated. The residue so obtained was triturated with diethyl ether to furnish pure compound as a light yellow solid.

Yield=1.21 g (87%), yellow solid, mp 156 °C, R_f=0.45 (1:1 EtOAc/hexane); IR (KBr) ν_{max} 3230, 2947, 1569, 1525, 1367 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.39 (1H, s, ArH), 7.85 (1H, d, J=7.7 Hz, ArH), 7.68–7.54 (3H, m, ArH), 7.35–7.29 (5H, m, ArH), 6.77–6.74 (1H, m, ArH), 5.58 (1H, br s, NH), 4.62 (2H, d, J=1.7 Hz, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ=163.6, 162.1, 158.9, 149.3, 138.9, 133.5, 132.2, 130.6, 130.0, 128.6, 127.6, 127.2, 124.3, 108.8, 45.4; mass (ES$^+$) m/z 307.1 (M$^+$+1). Anal. Calcd for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.54; H, 4.56; N, 18.36.

4.6. Procedure for the synthesis of *N*-[4-(2-aminophenyl)-pyrimidin-2-yl]-*N*-benzylamine (6)

N-Benzyl-*N*-[4-(2-nitrophenyl)pyrimidin-2-yl]amine **11** (1.0 g, 3.27 mmol) was dissolved in a mixture of ethanol (20 mL) and water (5 mL) followed by the addition of iron powder (0.5 g, 9.80 mmol) and concd HCl (10 mL). The reaction mixture was stirred under reflux for 1 h, cooled, and then filtered through a pad of Celite. The filtrate was concentrated in vacuo and the compound was extracted in ethyl acetate (15 mL×3). The organic layer washed sequentially with satd $NaHCO_3$ and brine, and after drying over Na_2SO_4 was concentrated in vacuo. The crude product so obtained was purified by recrystallization in EtOH to give *N*-[4-(2-aminophenyl)pyrimidin-2-yl]-*N*-benzylamine as a yellow solid.

Yield=0.70 g (80%), yellow solid, mp 159–160 °C, R_f=0.50 (1:1 EtOAc/hexane); IR (KBr) ν_{max} 3232, 3032, 1613, 1587, 1552 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ=8.26 (1H, d, J=5.4 Hz, ArH), 7.83 (1H, t, J=6.1 Hz, NH), 7.60 (1H, d, J=7.3 Hz, ArH), 7.36–7.28 (4H, m, ArH), 7.24–7.19 (1H, m, ArH), 7.10 (1H, t, J=7.1 Hz, ArH), 6.98 (1H, d,

J=5.4 Hz, ArH), 6.73 (1H, d, J=8.0 Hz, ArH), 6.57–6.52 (1H, m, ArH), 4.52 (2H, d, J=6.0 Hz, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ=161.9, 159.5, 148.9, 140.2, 132.7, 130.7, 130.6, 128.6, 128.2, 127.2, 126.6, 124.2, 108.0, 43.9; mass (ES^+) m/z 277.2 (M^++1). Anal. Calcd for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.27. Found: C, 73.72; H, 5.96; N, 20.34.

4.7. Procedure for the synthesis of (*E*)-1-(2-nitrophenyl)-3-phenylprop-2-en-1-one (12)

To a solution of 1-(2-nitrophenyl)ethan-1-one **8** (2.0 g, 12.1 mmol) in 50 mL of ethanol was added potassium hydroxide (1.01 g, 18.1 mmol) in 10 mL of water over a period of 30 min at 0 °C to room temperature. Thereafter, benzaldehyde (1.35 mL, 13.3 mmol) was added slowly to the reaction mixture. The reaction mixture was stirred at room temperature for 3 h. The solvent was removed from the reaction mixture under reduced pressure. Water was added and the aqueous phase was extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (90:10) as eluent to furnish the title compound as yellow solid.

Yield=2.5 g (83%), white solid, mp 126–127 °C, R_f=0.40 (1:9, EtOAc/hexane); IR (KBr) ν_{max} 3044, 1657, 1526, 1341 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.21–8.18 (1H, dd, J=0.1, 8.2 Hz, ArH), 7.81–7.75 (1H, m, ArH), 7.70–7.64 (1H, m, ArH), 7.54–7.50 (3H, m, ArH), 7.41–7.36 (3H, m, ArH), 7.26 (1H, d, J=16.3 Hz, =CH), 7.02 (1H, d, J=16.3 Hz, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=192.9, 146.7, 146.3, 136.3, 134.1, 133.9, 131.1, 130.6, 129.0, 128.8, 128.6, 126.3, 124.6; mass (ES^+) m/z 254.2 (M^++1). Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.26; H, 4.45; N, 5.65.

4.8. Procedure for the synthesis of 4-(2-nitrophenyl)-6-phenylpyrimidin-2-ylamine (13)

To a solution of guanidine hydrochloride (2.26 g, 23.71 mmol) in *N*,*N*-dimethyl acetamide (20 mL), sodium ethoxide (1.88 g, 27.65 mmol) was added. The reaction mixture was heated at 100 °C for 30 min and 1-(2-nitrophenyl)-3-phenylprop-2-en-1-one **12** (2 g, 7.90 mmol) was added and refluxed for 2 h. The solvent was removed from the reaction mixture under reduced pressure. Water was added and the aqueous phase was extracted with ethyl acetate (15 mL×3). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate 60:40).

Yield=1.65 g (72%), yellow solid, mp 191–192 °C, R_f=0.45 (1:3 EtOAc/hexane); IR (KBr) ν_{max} 3021, 1634, 1573, 1362 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.06–8.02 (2H, m, ArH), 7.95 (1H, d, J=7.9 Hz, ArH), 7.73–7.58 (3H, m, ArH), 7.51–7.49 (3H, m, ArH), 7.20 (1H, s, ArH), 5.21 (2H, br s, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ=166.5, 164.9, 163.1, 148.9, 137.1, 134.0, 132.7, 130.8, 130.7, 130.1, 128.8, 127.2, 124.5, 106.2; mass (ES^+) m/z 293.2 (M^++1). Anal. Calcd for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.64; H, 4.08; N, 19.24.

4.9. Procedure for the synthesis of 4-(2-aminophenyl)-6-phenylpyrimidin-2-ylamine (7)

4-(2-Nitrophenyl)-6-phenylpyrimidin-2-amine **13** (0.5 g, 1.71 mmol) was dissolved in a mixture of ethanol (10 mL) and water (2 mL). Iron powder (0.29 g, 5.13 mmol) and concd HCl (2 mL) were added, the mixture was stirred under reflux for 1 h, cooled, and filtered through a pad of Celite. The filtrate was concentrated in vacuo. The residue was extracted with EtOAc (15 mL×3). The organic layer washed sequentially with satd $NaHCO_3$ and brine, and after drying over Na_2SO_4 was concentrated in vacuo. The crude product so obtained was purified by recrystallization in EtOH to give a yellow solid.

Yield=0.35 g (78%), yellow solid, mp 151–152 °C, R_f=0.50 (1:3 EtOAc/hexane); IR (KBr) ν_{max} 3507, 3395, 1601, 1530 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.07–8.03 (2H, m, ArH), 7.67–7.64 (1H, dd, J=1.2, 7.9 Hz, ArH), 7.50 (3H, t, J=3.3 Hz, ArH), 7.41 (1H, s, ArH), 7.26–7.21 (1H, m, ArH), 6.83–6.75 (2H, m, ArH), 5.78 (2H, br s, NH_2), 5.16 (2H, br s, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ=168.1, 166.0, 162.5, 147.3, 137.8, 131.3, 130.4, 129.5, 128.8, 127.1, 120.0, 117.5, 117.4, 105.6; mass (ES^+) m/z 263.3 (M^++1). Anal. Calcd for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36. Found: C, 73.18; H, 5.26; N, 21.17.

4.10. General procedure for the synthesis of pyrimido-[5,4-*c*]quinolines via the Pictet–Spengler reaction from substrates 5, 6, and 7

A mixture of **5** or **6** or **7** (1.34 mmol) and aldehyde (1.47 mmol) in DMF (2 mL) was treated with 1% triflic acid (1 mL) at 120 °C for 8 h. The completion of Pictet–Spengler cyclization was monitored by TLC. After that the solvent was evaporated and the residue so obtained was triturated with aq $NaHCO_3$ (10 mL). It was then extracted with EtOAc (20 mL), washed with brine (10 mL), and dried over Na_2SO_4. EtOAC was evaporated to dryness under reduced pressure and the crude product was purified on a neutral alumina column using hexane/ethyl acetate (1:4, v/v) as eluent.

*4.10.1. 5-(4-Nitrophenyl)pyrimido[5,4-c]quinolin-2-ylamine (**14a**)*

Yield=0.29 g (68%), yellow solid, mp >250 °C, R_f=0.58 (1:1 EtOAc/hexane); IR (KBr) ν_{max} 3315, 3205, 1646, 1513, 1347 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ=8.99 (1H, s, ArH), 8.82–8.79 (1H, dd, J=1.0, 8.1 Hz, ArH), 8.43 (2H, d, J=8.8 Hz, ArH), 8.07 (3H, d, J=8.9 Hz, ArH), 7.94–7.89 (1H, m, ArH), 7.76–7.71 (3H, m, NH and ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ=162.9, 161.2, 157.3, 155.5, 147.9, 147.2, 143.9, 132.2, 131.3, 129.32, 127.1, 123.6, 123.5, 122.9, 110.2; mass (ES^+) m/z 318.3 (M^++1). Anal. Calcd for $C_{17}H_{11}N_5O_2$: C, 64.35; H, 3.49; N, 22.07. Found: C, 64.25; H, 3.54; N, 22.16.

*4.10.2. 5-(4-Ethoxyphenyl)pyrimido[5,4-c]quinolin-2-ylamine (**14b**)*

Yield=0.27 g (63%), white solid, mp 236 °C, R_f=0.43 (1:1 EtOAc/hexane); IR (KBr) ν_{max} 3294, 3162, 2976, 1639, 1346, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=9.19 (1H, s, ArH), 8.89 (1H, d, J=8.1 Hz, ArH), 8.15 (1H, d, J=8.2 Hz, ArH), 7.88–7.83 (1H, m, ArH), 7.72 (2H, d, J=8.6 Hz, ArH), 7.64 (1H, t, J=7.5 Hz, ArH), 7.09 (2H, d, J=8.6 Hz, ArH), 5.63 (2H, br s, NH_2), 4.16 (2H, q, J=6.9 Hz, CH_2), 1.49 (3H, t, J=6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$+TFA) δ=164.9, 159.4, 157.3, 138.1, 137.8, 132.5, 131.1, 126.3, 121.2, 120.9, 118.3, 116.6, 109.1, 64.7, 13.9; mass (ES^+) m/z 317.3 (M^++1). Anal. Calcd for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.10; N, 17.71. Found: C, 72.23; H, 5.18; N, 17.64.

*4.10.3. 2-(2-Aminopyrimido[5,4-c]quinolin-5-yl)phenol (**14c**)*

Yield=0.22 g (56%), white solid, mp 228–229 °C, R_f=0.45 (1:1 EtOAc/hexane); IR (KBr) ν_{max} 3303, 3138, 1642, 1597, 1344 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=12.53 (1H, s, OH), 9.43 (1H, s, ArH), 8.89 (1H, d, J=8.0 Hz, ArH), 8.03 (1H, d, J=8.3 Hz, ArH), 7.89–7.84 (1H, m, ArH), 7.70–7.63 (2H, m, ArH), 7.47–7.42 (1H, m, ArH), 7.22 (1H, d, J=8.2 Hz, ArH), 7.06 (1H, t, J=7.5 Hz, ArH), 5.68 (2H, br s, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ=162.9, 162.2, 158.1, 155.0, 154.7, 147.6, 131.8, 131.2, 130.6, 128.9, 126.4, 124.7, 123.3, 122.9, 119.4, 115.9, 110.8; mass (ES^+) m/z 289.4; (M^++1); MS (HREI) m/z calcd for [M^+] 288.1011, found 288.1013. Anal. Calcd for $C_{17}H_{12}N_4O$: C, 70.82; H, 4.20; N, 19.43. Found: C, 70.62; H, 4.35; N, 19.28.

*4.10.4. 5-(4-Chlorophenyl)pyrimido[5,4-c]quinolin-2-ylamine (**14d**)*

Yield=0.24 g (59%), white solid, mp >250 °C, R_f=0.45 (1:1 EtOAc/hexane); IR (KBr) ν_{max} 3315, 3308, 1646, 1593 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ=8.99 (1H, s, ArH), 8.80–8.77 (1H, dd, J=1.0,

8.0 Hz, ArH), 8.02 (1H, d, J=8.0 Hz, ArH), 7.91–7.86 (1H, m, ArH), 7.80 (2H, d, J=8.4 Hz, ArH), 7.70–7.64 (5H, m, NH_2, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ=162.8, 161.2, 157.9, 155.5, 147.3, 136.5, 134.1, 132.00, 131.7, 129.1, 128.5, 126.6, 123.4, 122.7, 110.2; mass (ES^+) m/z 307.4 (M^++1). Anal. Calcd for $C_{17}H_{11}ClN_4$: C, 66.56; H, 3.61; N, 18.26. Found: C, 66.45; H, 3.49; N, 18.14.

4.10.5. 5-[4-(Dimethylamino)phenyl]pyrimido[5,4-c]quinolin-2-amine (**14e**)

Yield=0.24 g (60%), yellow solid, mp >250 °C, R_f=0.45 (1:1 EtOAc/hexane); IR (KBr) ν_{max} 3295, 3130, 2922, 1639, 1346 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ=9.09 (1H, s, ArH), 8.74 (1H, d, J=8.0 Hz, ArH), 7.96 (1H, d, J=8.2 Hz, ArH), 7.86–7.81 (1H, m, ArH), 7.64 (3H, t, J=8.4 Hz, ArH), 7.57 (2H, br s, NH_2), 6.88 (2H, d, J=8.7 Hz, ArH), 3.01 (6H, s, 2×CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ=162.6, 161.5, 159.1, 155.7, 150.9, 147.7, 131.7, 131.0, 128.8, 125.7, 124.9, 123.3, 122.2, 111.6, 110.3; DEPT 135 (75 MHz, DMSO-d_6) δ=161.9, 132.2, 131.5, 129.3, 126.2, 123.8, 112.1, 40.3; mass (ES^+) m/z 316.4 (M^++1). Anal. Calcd for $C_{19}H_{17}N_5$: C, 72.36; H, 5.43; N, 22.21. Found: C, 72.25; H, 5.33; N, 22.15.

4.10.6. 5-Phenylpyrimido[5,4-c]quinolin-2-ylamine (**14f**)

Yield=0.29 g (63%), yellow solid, mp 229–230 °C, R_f=0.43 (1:1 EtOAc/hexane); IR (KBr) ν_{max} 3301, 3132, 1643, 1591 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=9.13 (1H, s, ArH), 8.89 (1H, dd, J=1.2, 8.1 Hz, ArH), 8.15 (1H, d, J=8.2 Hz, ArH), 7.88–7.83 (1H, m, ArH), 7.76–7.72 (2H, m, ArH), 7.68–7.63 (1H, m, ArH), 7.58–7.55 (3H, m, ArH), 5.64 (2H, br s, NH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ=163.2, 161.8, 159.6, 155.9, 147.8, 138.1, 132.4, 130.3, 129.6, 129.5, 128.9, 126.9, 123.8, 123.1, 110.7; mass (ES^+) m/z 273.4 (M^++1). Anal. Calcd for $C_{17}H_{12}N_4$: C, 74.98; H, 4.44; N, 20.58. Found: C, 74.93; H, 4.34; N, 20.65.

4.10.7. 5-(4-Bromophenyl)pyrimido[5,4-c]quinolin-2-ylamine (**14g**)

Yield=0.29 g (62%), yellow solid, mp >250 °C, R_f=0.44 (1:1 EtOAc/hexane); IR (KBr) ν_{max} 3306, 3189, 1636, 1593 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ=8.99 (1H, s, ArH), 8.78 (1H, dd, J=0.9, 7.9 Hz, ArH), 8.02 (1H, d, J=7.9 Hz, ArH), 7.92–7.87 (1H, m, ArH), 7.81–7.70 (5H, m, ArH), 7.68 (2H, br s, NH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ=163.3, 161.7, 158.4, 155.9, 147.7, 137.3, 132.4, 132.3, 131.8, 129.5, 127.0, 123.8, 123.3, 123.1, 100.6; mass (ES^+) m/z 351.3 (M^++1). Anal. Calcd for $C_{17}H_{11}BrN_4$: C, 58.14; H, 3.16; N, 15.95. Found: C, 58.07; H, 3.25; N, 15.89.

4.10.8. 5-(4-Fluorophenyl)pyrimido[5,4-c]quinolin-2-ylamine (**14h**)

Yield=0.25 g (64%), yellow solid, mp 243–244 °C, R_f=0.40 (1:1 EtOAc/hexane); IR (KBr) ν_{max} 3306, 3186, 1636, 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=9.09 (1H, s, ArH), 8.89 (1H, dd, J=1.0, 8.1 Hz, ArH), 8.14 (1H, d, J=8.2 Hz, ArH), 7.89–7.83 (1H, m, ArH), 7.76–7.71 (2H, m, ArH), 7.69–7.63 (1H, m, ArH), 7.29–7.24 (2H, m, ArH), 5.64 (2H, br s, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$+TFA) δ=167.3, 164.7, 164.2, 158.9, 158.6, 137.8, 136.2, 132.9, 132.8, 130.4, 125.5, 123.9, 123.1, 121.6, 117.4, 113.7, 110.8; mass (ES^+) m/z 291.4 (M^++1). Anal. Calcd for $C_{17}H_{11}FN_4$: C, 70.34; H, 3.82; N, 19.30. Found: C, 70.29; H, 3.85; N, 19.35.

4.10.9. 5-(3,4-Dichlorophenyl)pyrimido[5,4-c]quinolin-2-ylamine (**14i**)

Yield=0.27 g (60%), yellow solid, mp >250 °C, R_f=0.43 (1:1 EtOAc/hexane); IR (KBr) ν_{max} 3306, 3180, 1641, 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=9.09 (1H, s, ArH), 8.90 (1H, d, J=7.9 Hz, ArH), 8.13 (1H, d, J=8.2 Hz, ArH), 7.90–7.86 (2H, m, ArH), 7.71–7.64 (2H, m, ArH), 7.59–7.57 (1H, m, ArH), 5.62 (2H, br s, NH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ=163.3, 161.7, 157.1, 155.9, 147.6, 138.7, 132.5, 132.5, 131.9, 131.8, 131.1, 130.5, 129.6, 127.3, 123.8, 123.2, 110.6; mass (ES^+) m/z 341.4 (M^++1). Anal. Calcd for $C_{17}H_{10}Cl_2N_4$: C, 59.84; H, 2.95; N, 16.42. Found: C, 59.75; H, 2.90; N, 16.37.

4.10.10. 5-(3,4-Dimethoxyphenyl)pyrimido[5,4-c]quinolin-2-ylamine (**14j**)

Yield=0.29 g (65%), yellow solid, mp 212–213 °C, R_f=0.40 (1:1 EtOAc/hexane); IR (KBr) ν_{max} 3321, 3182, 1649, 1591 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=9.20 (1H, s, ArH), 8.88 (1H, dd, J=1.1, 8.1 Hz, ArH), 8.15 (1H, d, J=7.8 Hz, ArH), 7.88–7.82 (1H, m, ArH), 7.67–7.62 (1H, m, ArH), 7.36 (1H, d, J=1.9 Hz, ArH), 7.28 (1H, d, J=1.9 Hz, ArH), 7.05 (1H, d, J=8.2 Hz, ArH), 5.63 (2H, s, NH_2), 3.98 (6H, s, 2×OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ=163.2, 161.9, 159.3, 156.0, 150.2, 149.0, 147.8, 132.3, 130.6, 129.4, 126.6, 123.8, 123.3, 122.9, 113.7, 111.8, 110.9; mass (ES^+) m/z 333.3 (M^++1). Anal. Calcd for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.86. Found: C, 68.55; H, 4.92; N, 16.78.

4.10.11. N-Benzyl-N-[5-(4-fluorophenyl)pyrimido[5,4-c]quinolin-2-yl]amine (**14k**)

Yield=0.30 g (60%), white solid, mp 198–199 °C, R_f=0.40 (2:3 EtOAc/hexane); IR (KBr) ν_{max} 3250, 3091, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.96 (2H, d, J=8.2 Hz, ArH), 8.12 (1H, d, J=8.2 Hz, ArH), 7.87–7.81 (1H, m, ArH), 7.75–7.70 (2H, m, ArH), 7.64 (1H, t, J=7.60 Hz, ArH), 7.44 (2H, s, ArH), 7.34 (2H, t, J=7.2 Hz, ArH), 7.29–7.22 (3H, m, ArH), 6.18 (1H, s, NH), 4.91 (2H, s, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ=165.6, 158.3, 157.3, 144.3, 137.8, 133.6, 132.4, 132.3, 130.2, 128.9, 127.9, 127.2, 126.3, 124.5, 123.4, 110.7, 46.1; mass (ES^+) m/z 381.4 (M^++1). Anal. Calcd for $C_{24}H_{17}FN_4$: C, 75.77; H, 4.50; N, 14.73. Found: C, 75.65; H, 4.43; N, 14.67.

4.10.12. N-Benzyl-N-[5-(4-bromophenyl)pyrimido[5,4-c]-quinolin-2-yl]amine (**14l**)

Yield=0.37 g (64%), white solid, mp 192–193 °C, R_f=0.42 (2:3 EtOAc/hexane); IR (KBr) ν_{max} 3248, 2924, 1596, 1549 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.96 (2H, s, ArH), 8.12 (1H, d, J=8.13 Hz, ArH), 7.87–7.81 (1H, m, ArH), 7.72–7.67 (2H, m, ArH), 7.64–7.60 (3H, m, ArH), 7.74 (2H, s, ArH), 7.37–7.28 (3H, m, ArH), 6.17 (1H, s, NH), 4.91 (2H, s, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ=161.26, 158.6, 156.3, 148.0, 138.6, 136.9, 132.3, 131.9, 131.8, 131.5, 129.5, 128.7, 127.9, 127.6, 126.8, 124.1, 123.9, 123.5, 111.3; mass (ES^+) m/z 441.2 (M^++1). Anal. Calcd for $C_{24}H_{17}BrN_4$: C, 65.32; H, 3.88; N, 12.70. Found: C, 65.25; H, 3.75; N, 12.76.

4.10.13. N-Benzyl-N-[5-(3,4-dichlorophenyl)pyrimido[5,4-c]-quinolin-2-yl]amine (**14m**)

Yield=0.35 g (62%), white solid, mp 199–200 °C, R_f=0.42 (2:3 EtOAc/hexane); IR (KBr) ν_{max} 3083, 2925, 1599, 1560 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.96 (2H, s, ArH), 8.11 (1H, d, J=6.1 Hz, ArH), 7.87–7.83 (2H, m, ArH), 7.68–7.61 (2H, m, ArH), 7.56 (1H, dd, J=1.0, 6.1 Hz, ArH), 7.45 (2H, s, ArH), 7.36–7.33 (2H, m, ArH), 7.30 (1H, d, J=6.2 Hz, ArH), 6.25 (1H, br s, NH), 4.92 (2H, s, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$+TFA) δ=164.7, 158.4, 155.9, 139.3, 137.6, 136.5, 135.3, 134.2, 131.8, 131.4, 129.6, 129.3, 128.9, 128.2, 127.8, 127.7, 124.9, 109.5, 109.5, 46.2; mass (ES^+) m/z 431.3 (M^++1). Anal. Calcd for $C_{24}H_{16}Cl_2N_4$: C, 66.83; H, 3.74; N, 12.99. Found: C, 66.75; H, 3.82; N, 12.93.

4.10.14. N-Benzyl-N-[5-(2-nitrophenyl)pyrimido[5,4-c]quinolin-2-yl]-amine (**14n**)

Yield=0.28 g (52%), yellow solid, mp 238–239 °C, R_f=0.45 (2:3 EtOAc/hexane); IR (KBr) ν_{max} 3022, 1643, 1347, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.97 (1H, s, ArH), 8.63 (1H, s, ArH), 8.24 (1H, dd, J=1.1, 8.1 Hz, ArH), 8.06 (1H, d, J=8.2 Hz, ArH), 7.89–7.82 (2H, m, ArH), 7.75–7.61 (3H, m, ArH), 7.47 (2H, s, ArH), 7.40–7.28 (3H, m, ArH), 6.18 (1H, s, NH), 4.93 (2H, s, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$+TFA) δ=158.1, 156.3, 147.5, 139.8, 136.7, 135.3, 134.7, 133.1,

132.1, 129.7, 128.0, 128.3, 127.8, 125.9, 125.2, 125.1, 123.8, 123.3, 46.3; mass (ES^+) m/z 408.2 (M^++1). Anal. Calcd for $C_{24}H_{17}N_5O_2$: C, 70.75; H, 4.21; N, 17.19. Found: C, 70.75; H, 4.35; N, 17.24.

4.10.15. *N-Benzyl-N-[5-(4-chlorophenyl)pyrimido[5,4-c]quinolin-2-yl]amine (**14o**)*

Yield=0.31 g (59%), white solid, mp 208 °C, R_f=0.45 (1:1 EtOAc/hexane); IR (KBr) ν_{max} 3248, 3085, 1597 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ=9.00 (1H, s, ArH), 8.83 (2H, d, J=7.9 Hz, ArH), 8.01 (1H, d, J=8.1 Hz, ArH), 7.88 (1H, t, J=7.6 Hz, ArH), 7.80 (2H, d, J=8.4 Hz, ArH), 7.71 (1H, d, J=7.9 Hz, ArH), 7.65 (2H, d, J=8.4 Hz, ArH), 7.49 (1H, d, J=7.3 Hz, ArH), 7.33 (2H, t, J=7.4 Hz, ArH), 7.23 (1H, d, J=7.2 Hz, ArH), 4.78 (2H, d, J=6.2 Hz, CH_2); ^{13}C NMR (75 MHz, DMSO-d_6+TFA) δ=164.5, 162.8, 157.9, 157.5, 139.1, 138.9, 137.9, 135.2, 133.1, 129.8, 129.6, 129.0, 128.4, 127.9, 127.8, 125.0, 123.8, 122.2, 110.0, 45.4; mass (ES^+) m/z 397.3 (M^++1). Anal. Calcd for $C_{24}H_{17}ClN_4$: C, 72.63; H, 4.32; N, 14.12. Found: C, 72.56; H, 4.27; N, 14.08.

4.10.16. *N-Benzyl-N-[5-(4-nitrophenyl)pyrimido[5,4-c]quinolin-2-yl]amine (**14p**)*

Yield=0.36 g (67%), yellow solid, mp 204 °C, R_f=0.40 (2:3 EtOAc/hexane); IR (KBr) ν_{max} 3020, 1593, 1528, 1349 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.96 (2H, s, ArH), 8.45 (2H, d, J=8.7 Hz, ArH), 8.15 (1H, d, J=8.2 Hz, ArH), 7.95 (2H, d, J=8.6 Hz, ArH), 7.89 (1H, d, J=7.0 Hz, ArH), 7.71 (1H, t, J=7.4 Hz, ArH), 7.40 (2H, br s, NH_2), 7.40–7.29 (3H, m, ArH), 6.24 (1H, br s, NH), 4.95 (2H, s, CH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ=161.2, 160.8, 157.0, 155.0, 147.7, 147.2, 143.9, 139.6, 132.2, 131.2, 129.1, 128.3, 127.6, 127.1, 126.8, 123.5, 122.9, 110.2, 44.4; mass (ES^+) m/z 408.3 (M^++1). Anal. Calcd for $C_{24}H_{17}N_5O_2$: C, 70.75; H, 4.21; N, 17.19. Found: C, 70.67; H, 4.34; N, 17.25.

4.10.17. *N-Benzyl-N-[5-(4-dimethylamino)pyrimido[5,4-c]-quinolin-2-yl]amine (**14q**)*

Yield=0.27 g (50%), yellow solid, mp 228 °C, R_f=0.50 (2:3 EtOAc/hexane); IR (KBr) ν_{max} 3241, 3081, 1590, 1349 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=9.21 (1H, s, ArH), 8.91 (1H, s, ArH), 8.12 (1H, d, J=8.1 Hz, ArH), 7.85–7.79 (1H, m, ArH), 7.68 (2H, d, J=8.8 Hz, ArH), 7.60 (1H, t, J=7.8 Hz, ArH), 7.47 (2H, s, ArH), 7.39–7.28 (3H, m, ArH), 6.89 (2H, d, J=8.8 Hz, ArH), 6.07 (1H, t, J=5.5 Hz, NH), 4.92 (2H, s, CH_2), 3.08 (6H, s, 2×CH_3); ^{13}C NMR (75 MHz, DMSO-d_6+TFA) δ=164.1, 162.1, 153.1, 138.6, 137.9, 134.5, 132.8, 128.5, 128.2, 127.8, 127.4, 127.2, 124.4, 122.4, 114.9, 111.8, 44.7; mass (ES^+) m/z 406.4 (M^++1). Anal. Calcd for $C_{26}H_{23}N_5$: C, 77.01; H, 5.72; N, 17.27. Found: C, 77.15; H, 5.62; N, 17.35.

4.10.18. *N-Benzyl-[5-(4-ethoxyphenyl)-pyrimido[5,4-c]quinolin-2-yl]amine (**14r**)*

Yield=0.35 g (65%), white solid, mp 203 °C, R_f=0.46 (2:3 EtOAc/hexane); IR (KBr) ν_{max} 3020, 1643, 1535, 1216 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ=9.04 (1H, s, ArH), 8.81 (1H, d, J=7.9 Hz, ArH), 8.72 (1H, t, J=6.2 Hz, NH), 8.0 (1H, d, J=8.2 Hz, ArH), 7.86 (1H, t, J=7.5 Hz, ArH), 7.72 (2H, d, J=8.6 Hz, ArH), 7.66 (1H, t, J=7.7 Hz, ArH), 7.49 (1H, d, J=7.3 Hz, ArH), 7.33 (2H, t, J=7.4 Hz, ArH), 7.22 (1H, t, J=7.2 Hz, ArH), 7.12 (2H, d, J=8.5 Hz, ArH), 4.78 (2H, d, J=5.91 Hz, ArH), 4.14 (2H, q, J=6.9 Hz, CH_2), 1.39 (3H, t, J=6.9 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ=161.4, 161.2, 159.6, 158.6, 155.8, 155.3, 147.2, 139.8, 132.1, 131.5, 129.5, 128.6, 128.3, 127.6, 127.2, 126.9, 126.4, 123.6, 122.6, 114.4, 110.4, 63.3, 44.5, 14.4; mass (ES^+) m/z 407.3 (M^++1). Anal. Calcd for $C_{26}H_{22}N_4O$: C, 76.83; H, 5.46; N, 13.78. Found: C, 76.65; H, 5.34; N, 13.67.

4.10.19. *5-(4-Ethoxyphenyl)-4-phenylpyrimido[5,4-c]quinolin-2-amine (**14u**)*

Yield=0.26 g (49%), white solid, mp 208 °C, R_f=0.55 (1:3 EtOAc/hexane); IR (KBr) ν_{max} 3275, 3116, 1631, 1543 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ=8.84 (1H, d, J=7.3 Hz, ArH), 7.98 (1H, d, J=8.0 Hz, ArH), 7.89–7.83 (1H, m, ArH), 7.68–7.63 (1H, m, ArH), 7.59 (2H, s, NH_2), 7.26 (4H, t, J=7.2 Hz, ArH), 7.17–7.05 (3H, m, ArH), 6.56 (2H, d, J=8.7 Hz, ArH), 3.90 (2H, q, J=6.9 Hz, CH_2), 1.25 (3H, t, J=6.9 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ=169.8, 161.2, 158.9, 158.1, 157.7, 146.8, 139.2, 133.4, 131.7, 131.1, 129.8, 128.7, 128.6, 127.2, 125.9, 123.7, 122.3, 113.3, 108.8, 62.9, 14.5; mass (ES^+) m/z 393.3 (M^++1). Anal. Calcd for $C_{25}H_{20}N_4O$: C, 76.51; H, 5.14; N, 14.28. Found: C, 76.46; H, 5.07; N, 14.15.

4.10.20. *5-(4-(Dimethylamino)phenyl)-4-phenylpyrimido[5,4-c]-quinolin-2-amine (**14v**)*

Yield=0.24 g (46%), yellow solid, mp >250 °C, R_f=0.40 (1:3 EtOAc/hexane); IR (KBr) ν_{max} 3297, 3165, 1630, 1538 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ=8.80 (1H, d, J=8.2 Hz, ArH), 7.95 (1H, d, J=7.9 Hz, ArH), 7.86–7.81 (1H, m, ArH), 7.64–7.58 (1H, m, ArH), 7.54 (2H, s, NH_2), 7.30 (2H, d, J=6.5 Hz, ArH), 7.20 (2H, d, J=8.7 Hz, ArH), 7.13–7.05 (3H, m, ArH), 6.36 (2H, d, J=8.8 Hz, ArH), 2.79 (6H, s, 2×CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ=169.8, 161.1, 159.2, 157.8, 150.1, 146.9, 139.3, 131.6, 130.8, 129.8, 128.7, 128.6, 128.3, 127.2, 126.7, 125.4, 123.7, 122.0, 110.9, 108.6; mass (ES^+) m/z 392.4 (M^++1). Anal. Calcd for $C_{25}H_{21}N_5$: C, 76.70; H, 5.41; N, 17.89. Found: C, 76.59; H, 5.34; N, 17.72.

4.10.21. *5-(4-Nitrophenyl)-4-phenylpyrimido[5,4-c]quinolin-2-amine (**14w**)*

Yield=0.28 g (53%), yellow solid, mp 210 °C, R_f=0.45 (1:3 EtOAc/hexane); IR (KBr) ν_{max} 3021, 1631, 1541, 1345 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ=8.89 (1H, d, J=7.2 Hz, ArH), 8.05 (1H, d, J=7.9 Hz, ArH), 7.95–7.89 (1H, m, ArH), 7.85 (2H, d, J=8.7 Hz, ArH), 7.85 (2H, d, J=8.7 Hz, ArH), 7.77–7.72 (3H, m, ArH, NH_2), 7.27 (2H, d, J=8.1 Hz, ArH), 7.15–7.03 (3H, m, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ=169.6, 161.5, 157.6, 157.3, 147.5, 146.4, 146.2, 138.9, 132.0, 130.9, 129.9, 128.9, 127.4, 127.0, 123.8, 122.8, 122.6, 122.1, 109.0; mass (ES^+) m/z 394.3 (M^++1). Anal. Calcd for $C_{23}H_{15}N_5O_2$: C, 70.22; H, 3.84; N, 17.80. Found: C, 70.10; H, 3.65; N, 17.76.

4.10.22. *4-(2-Amino-4-phenylpyrimido[5,4-c]quinolin-5-yl)benzonitrile (**14x**)*

Yield=0.22 g (45%), yellow solid, mp 216–217 °C, R_f=0.50 (1:3 EtOAc/hexane); IR (KBr) ν_{max} 3387, 3294, 2339, 1632, 1540 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ=8.89 (1H, d, J=7.4 Hz, ArH), 8.03 (1H, d, J=8.0 Hz, ArH), 7.94–7.88 (1H, m, ArH), 7.75–7.71 (3H, m, ArH, NH_2), 7.51–7.44 (4H, m, ArH), 7.26 (2H, d, J=7.0 Hz, ArH), 7.18 (1H, t, J=7.3 Hz, ArH), 7.08 (2H, t, J=7.6 Hz, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ=169.6, 161.4, 157.7, 157.6, 146.4, 145.5, 138.9, 131.9, 130.9, 130.4, 129.9, 128.9, 128.8, 127.4, 126.8, 123.8, 122.7, 118.7, 109.9, 108.9; mass (ES^+) m/z 374.4 (M^++1). Anal. Calcd for $C_{24}H_{15}N_5$: C, 77.20; H, 4.05; N, 18.76. Found: C, 77.12; H, 4.15; N, 18.61.

4.11. Procedure for the synthesis of 2-pyridin-4-yl-phenylamine 19

The solution of 2-bromoaniline **21** (1 g, 5.8 mmol) in DMF (15 mL) was degassed with nitrogen for 15 min followed by addition of satd Na_2CO_3 solution (10 mL, 2 M) under continuous flow of nitrogen. After 10 min, pyridine-4-boronic acid **20** (0.85 g, 6.97 mmol) and $PdCl_2(PPh_3)_2$ (0.29 g, 0.4 mmol) were added to the reaction mixture under a nitrogen atmosphere. The reaction mixture was stirred at 100 °C for 3 h. The solution was diluted with H_2O (5 mL), and then the product was extracted three times with EtOAc (20 mL). The combined organic layer was dried over MgSO4 and the solvent was removed in vacuo. The crude product was purified on a silica gel column using hexane/ethyl acetate (7:3, v/v) as eluent to afford 2-pyridin-4-yl-phenylamine **19**.

Yield=0.84 g (85%), brown solid, mp 85–86 °C, R_f=0.40 (1:1 EtOAc/hexane); IR (KBr) ν_{max} 3398, 3020, 1602 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ=8.65 (2H, d, J=5.0 Hz, ArH), 7.41 (2H, d, J=5.2 Hz, ArH), 7.22–7.17 (1H, m, ArH), 7.12 (1H, d, J=7.6 Hz, ArH), 6.84 (1H, t, J=7.4 Hz, ArH), 6.76 (1H, d, J=8.0 Hz, ArH), 3.82 (2H, br s, NH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ=150.0, 147.8, 143.3, 130.0, 129.8, 128.5, 128.4, 124.3, 123.9, 118.9, 116.1; mass (ES^+) m/z 171.4 (M^++1). Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.58; H, 5.93; N, 16.49.

4.12. Protocols for the attempted Pictet–Spengler reaction on 19

Substrate **19** was subjected to the various Pictet–Spengler reaction conditions as described in the Table 1. The reaction mixture was then quenched with satd $NaHCO_3$ solution and then extracted with EtOAc. The organic layer was washed with brine, dried, and concentrated in vacuo. The crude product so obtained was purified using neutral alumina column chromatography with hexane/ethyl acetate (7:3, v/v) as eluent to afford 4-nitro-*N*-[(*E*)-(2-pyridin-4-ylphenyl)methylidene]aniline **22** as the only product.

Yield=0.36 g (90%), yellow solid, mp 185–186 °C, R_f=0.35 (1:1 EtOAc/hexane); IR (KBr) ν_{max} 3021, 1597, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.62 (2H, dd, J=1.6, 4.5 Hz, ArH), 8.50 (1H, s, ArH), 8.30 (2H, d, J=8.8 Hz, ArH), 7.96 (2H, d, J=8.8 Hz, ArH), 7.52–7.46 (2H, m, ArH), 7.43–7.38 (3H, m, ArH), 7.18–7.15 (1H, m, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ=157.9, 149.4, 149.2, 148.5, 147.1, 141.3, 133.4, 130.2, 129.9, 129.5, 127.4, 124.9, 124.1, 118.5; mass (ES^+) m/z 304.3 (M^++1). Anal. Calcd for $C_{18}H_{13}N_3O_2$: C, 71.28; H, 4.32; N, 13.85. Found: C, 71.23; H, 4.29; N, 13.89.

Acknowledgements

P.K.A., S.K.S., and D.S. are thankful to CSIR, New Delhi, India for fellowships.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.11.067.

References and notes

1. For the seminal work in the Pictet–Spengler reaction: (a) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030–2036. For reviews on the Pictet–Spengler reaction see: (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352; (c) Nielsen, T. E.; Diness, F.; Meldal, M. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 801–814; (d) Cox, E. D.; Cook, J. *Chem. Rev.* **1995**, *95*, 1797–1842; (e) Larghi, E. L.; Amongero, M.; Bracca, A. B. J.; Kauffman, T. S. *ARKIVOC* **2005**, *xii*, 98–153.
2. (a) Kundu, B.; Sawant, D.; Chhabra, R. *J. Comb. Chem.* **2005**, *7*, 317–321; (b) Kundu, B.; Sawant, D.; Partani, P.; Kesarwani, A. P. *J. Org. Chem.* **2005**, *70*, 4889–4892; (c) Duggineni, S.; Sawant, D.; Kundu, B. *Tetrahedron* **2006**, *62*, 3228–3241; (d) Sharma, S.; Saha, B.; Sawant, D.; Kundu, B. *J. Comb. Chem.* **2007**, *9*, 783–792.
3. (a) Duncton, M. A. J.; Smith, L. M.; Burdzovic-Wizeman, S.; Burns, A.; Liu, H.; Mao, Y.; Wong, W. C.; Kiselyov, A. S. *J. Org. Chem.* **2005**, *70*, 9629–9631; (b) Zheng, L.; Xiang, J.; Daang, Q. D.; Bai, X. *J. Comb. Chem.* **2005**, *7*, 813–815; (c) David, E.; Pellet-Rostaing, S.; Lemaire, M. *Tetrahedron* **2007**, *63*, 8999–9006; (d) Wang, X. L.; Zheng, X. F.; Liu, R. H.; Reiner, J.; Chang, J. B. *Tetrahedron* **2007**, *63*, 3389–3394; (e) Gracia, S.; Schulz, J.; Pellet-Rostaing, S. *Synlett* **2008**, 1852–1856; (f) Che, X.; Zheng, L.; Dang, Q.; Bai, X. *J. Org. Chem.* **2008**, *73*, 1147–1149.
4. Saha, B.; Sharma, S.; Sawant, D.; Kundu, B. *Tetrahedron* **2008**, *64*, 8676–8684.
5. (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930; (b) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235–2246; (c) Smith, R. G.; Van der Ploeg, L. H. T.; Howard, A. D.; Feighner, S. D.; Cheng, K.; Hickey, G. J.; Wyvratt, M. J., Jr.; Fisher, M. H.; Nargund, R. P.; Patchett, A. A. *Endocr. Rev.* **1997**, *18*, 621–645; (d) Mason, J. S.; Morize, I.; Menard, P. R.; Cheney, D. L.; Hulme, C.; Labaudiniere, R. F. *J. Med. Chem.* **1999**, *42*, 3251–3264; (e) Patchett, A. A.; Nargund, R. P. *Annu. Rep. Med. Chem.* **2000**, *35*, 289–298; (f) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939–9953; (g) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *J. Comput.-Aided Mol. Des.* **2002**, *16*, 415–430; (h) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Mol. Divers.* **2002**, *5*, 289–304; (i) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930; (j) Guo, T.; Hobbs, D. W. *Assay Drug Dev. Technol.* **2003**, *1*, 579–592; (k) Müller, G. *Drug Discov. Today* **2003**, *8*, 681–691; (l) DeSimone, R. W.; Currie, K. S.; Mitchell, S. A.; Darrow, J. W.; Pippin, D. A. *Comb. Chem. High Throughput Screen.* **2004**, *7*, 473–493; (m) Bondensgaard, K.; Ankersen, M.; Thogersen, H.; Hansen, B. S.; Wulff, B. S.; Bywater, R. P. *J. Med. Chem.* **2004**, *47*, 888–899; (n) Mills, J. S.; Showell, G. A. *Expert Opin. Investig. Drugs* **2004**, *13*, 1149–1157.
6. (a) Wishart, D. S.; Knox, C.; Guo, A. C.; Shrivastava, S.; Hassanali, M.; Stothard, P.; Chang, Z.; Woolsey, J. *Nucleic Acids Res.* **2006**, D668–D672 (Database issue); (b) Vorcaonazole: Herbrecht, R. *Expert Rev. Anti Infect. Ther.* **2004**, 485–497; (c) Pyrimidine as antiinflammatory agent: a review Amir, M.; Javed, S. A.; Kumar, H. *Indian J. Pharm. Sci.* **2007**, *69*, 337–343.
7. (a) Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry*; Katritzky, R., Ed.; 1984; Vol. 5, pp 41–410; (b) Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry*; Katritzky, R., Ed.; 1984; Vol. 3, pp 68–71; (c) Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry*; Katritzky, R., Ed.; 1984; Vol. 2, pp 29–31.
8. For a recent review see: Hill M. D.; Movassaghi, M. *Chem.—Eur J.* **2008**, *14*, 6836–6844.
9. (a) Katritzky, A. R.; Serdyuk, L.; Chassaing, C.; Toader, D.; Wang, X.; Forood, B.; Flatt, B.; Sun, C.; Vo, K. *J. Comb. Chem.* **2000**, *2*, 182–185; (b) Zimmermann, J.; Buchdunger, E.; Mett, H.; Meyer, T.; Lydon, N. B. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 187–192; (c) Kantevari, S.; Chary, M. V.; Vuppalapati, S. V. N. *Tetrahedron* **2007**, *63*, 13024–13031; (d) Li, Y.; Luo, Y.; Huang, W.; Wang, J.; Lu, W. *Tetrahedron Lett.* **2006**, *47*, 4153–4155; (e) Ono, M.; Hori, M.; Haratake, M.; Tomiyama, T.; Mori, H.; Nakayama, M. *Bioorg. Med. Chem. Lett.* **2007**, *15*, 6388–6396.
10. Mamaev, V. P.; Kim, A. M. *Chem. Heterocycl. Compd.* **1967**, *2*, 189–193.
11. Nasr, M.; Nabih, I.; Burckhalter, J. H. *J. Med. Chem.* **1978**, *21*, 295–298.
12. (a) Molinski, T. F. *Chem. Rev.* **1993**, *93*, 1825–1838; (b) Görlitzer, K.; Enge, C. H.; Jones, P. G.; Jomaa, H.; Wiesner, J. *Pharmazie* **2006**, *61*, 975–980.
13. Thompson, A. E.; Batsanov, A. S.; Bryce, M. R.; Saygili, N.; Parry, P. R.; Tarbit, B. *Tetrahedron* **2005**, *61*, 5131–5135.
14. (a) Yamanaka, E.; Shibata, N.; Sakai, S.-I. *Heterocycles* **1984**, *22*, 371–374; (b) Jackson, A. H.; Smith, A. E. *Tetrahedron* **1981**, *22*, 2501–2504.