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Application of the Pictet–Spengler reaction to aryl amine substrates linked to deactivated aromatic heterosystems☆

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ABSTRACT

Three new substrates with an aryl amine moiety attached to quinoxalines, triazoles and tetrazoles either via C or N have been used for the Pictet–Spengler reaction. The substrates have been designed by applying the concept of 'aryl amine attached to a deactivated heteroaromatic ring' in a manner to facilitate *endo* cyclization. This is in contrast to the substrates used traditionally and reported earlier by us that are based on either aliphatic or aryl amine, respectively, attached to an activated heterocyclic ring. The Pictet–Spengler condensation of the three substrates with aldehydes led to the synthesis of novel N-rich polyheterocyclic system hitherto not reported. Our modified strategy opens up possibilities to design novel substrates with aryl amines linked via C or N to either deactivated or activated heterocyclic privileged structure, which in turn can be used for the synthesis of novel fused polyheterocyclic skeletons.

1. Introduction

The Pictet–Spengler reaction[1] is one reaction in organic chemistry that has been extensively used for the construction of a variety of natural products and novel heterocycles of biological interest.[2] The method generally involves condensation of an ω-aromatic amine and an aldehyde leading to polycyclic structure of biological significance.[3] The aliphatic amine is generally linked to the electron-rich aromatic/heteroaromatic rings that is involved in π-cyclizations with an electrophilic imine derived from the amine. Traditionally, the π systems employed in these cyclizations are derived from any of the three electron-rich aromatic rings (Fig. 1) as indoles (**1**), activated phenethylamines (**2**) and imidazoles (**3**). Thus, despite being a powerful reaction, it is the activated ring systems (**1**–**3**) that dominated the conventional Pictet–Spengler reaction substrates for the last hundred years and were exclusively used to generate β-carboline, tetrahydroisoquinoline and tetrahydroimidazopyridine ring systems.[4]

The Pictet–Spengler reaction of these substrates with various carbonyl compounds suggests that the use of an aldehyde with electron donating group such as salicylaldehyde generally fails to furnish the desired product due to the poor electrophilic nature of the resulting iminium intermediate. Cook et al. and others have shown that by enhancing the electrophilic nature of the iminium intermediate, 6-*endo* cyclization can be affected.[5] The electrophilicity of the imine has been generally enhanced by two main methods to affect the π-cyclization. In one of the methods stronger acids are used to protonate the imine with the view to produce the iminium ion intermediate with enhanced electrophilicity. But despite its wide application, the strategy is not suitable for acid labile functional groups. The second strategy involves *endo* cyclization via more electrophilic *N*-substituted iminium reactive species such as *N*-acyliminium[6,20]/*N*-alkyliminium[7]/*N*-sulfonyliminium[8] derivatives. Though this elegant strategy has a major impact in the field of Pictet–Spengler reaction, it has a major limitation that the acylating species remains hanged on to the molecule and has to be removed.

Recently, we enhanced the electrophilic nature of the iminium intermediate by replacing aliphatic amine with aryl amine, which was linked to the electron-rich aromatic heterocycles either through C or N.[9] Our observation was based on the fact that imines derived from the aromatic amines are more electrophilic than the aliphatic amines. Using our modified strategy, we extended its application to five new substrates derived from imidazoles (**4** and **5**), thiazoles (**6**), pyrazoles (**7**), benzohistamine (**8**) and bicyclic heterocycles (**9** and **10**). Following our report several groups reported new substrates (Fig. 1) based on our concept derived from dimethoxy arene (**11**), indole (**12**), thiophene (**13**) and benzoquinone (**14**).[10] These aromatic amine-derived substrates represent second-generation substrates[9c] in the line of traditional aliphatic amine-derived first-generation substrates (**1**–**3**; Fig. 1) and led to

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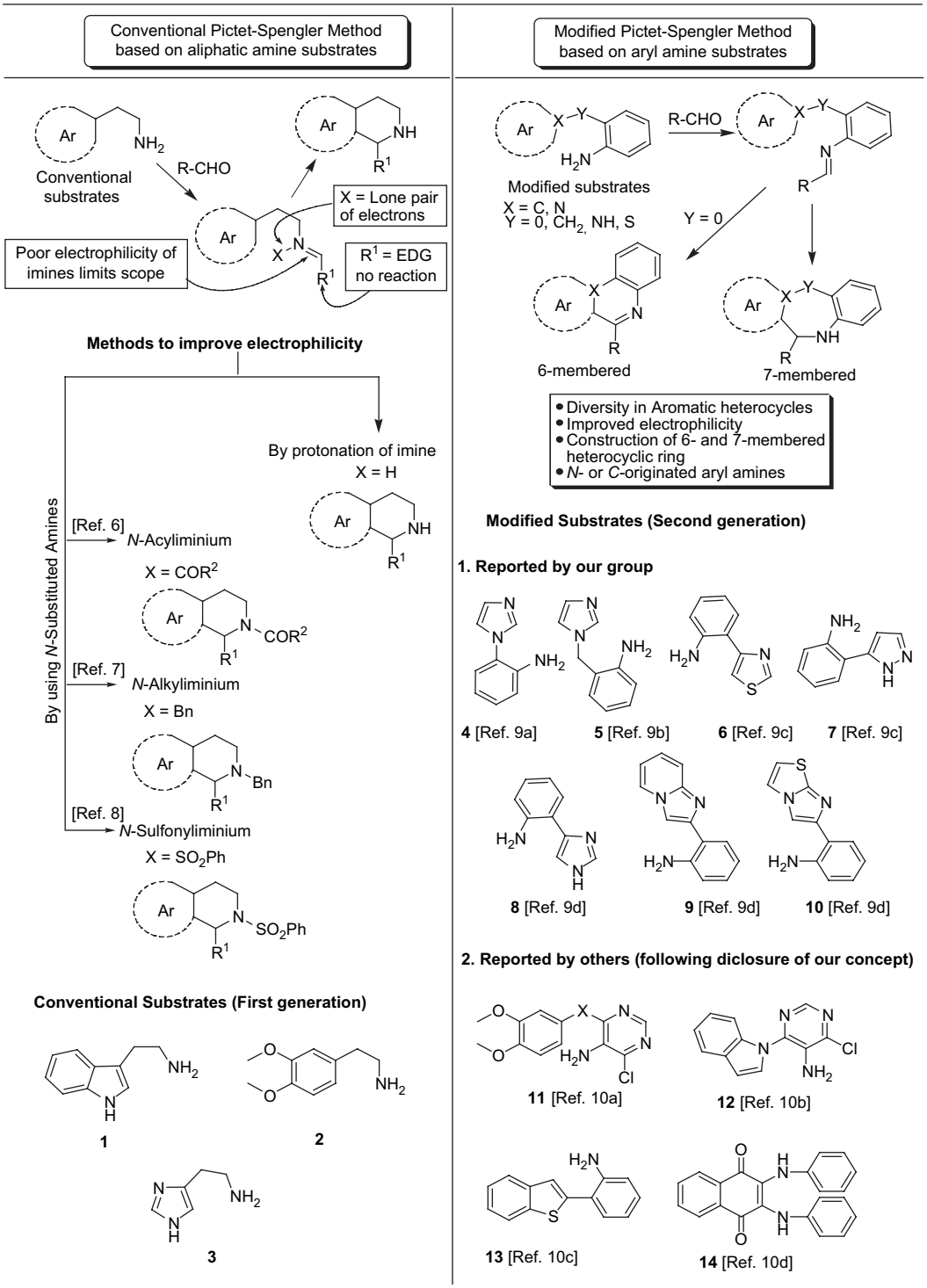


Figure 1. Comparison between the traditional and our modified Pictet–Spengler reaction.

the construction of polycyclic frameworks analogous to naturally occurring frameworks. Interestingly, during the course of *endo* cyclization with our aryl amine substrates (**4**–**10**),[9] we observed that (1) unlike traditional substrates, the π-cyclizations occurred with a wide variety of aldehydes having both electron donating and withdrawing substituents and (2) the rate of Pictet–Spengler reaction in substrates (second-generation) with aryl amine was faster than the conventional Pictet–Spengler reaction substrates (first-generation) having aliphatic amine. The faster rate of reaction for aryl amine substrates can be attributed to the enhanced electrophilicity of the resulting imines than the imines derived from aliphatic amine substrates (**1**–**3**). Since enhancement of the electrophilic nature of the iminium intermediate has been documented by several groups[5] as driving force for *endo* cyclization, we envisaged that the π-cyclization could be affected even when aryl amine is linked to a deactivated (poorly nucleophilic) heterocyclic

ring. Accordingly, we decided to explore the application of our aryl amine strategy to deactivated heterocyclic nucleus,[11] with the view to move beyond the age old general concept involving exclusive use of the activated π-nucleophile as substrates for the Pictet–Spengler reaction. Literature search for the Pictet–Spengler reaction involving use of substrate with an amine attached to a heteroaromatic ring with poor π-nucleophilic character led to two papers by Stokker[12] and Zhang et al.[13] In the first paper, it was reported that phenethylamine with or without electron-withdrawing substitution on the phenyl ring, underwent Pictet–Spengler reaction only via *N*-acyliminium strategy and required strong acidic conditions (H_2SO_4). However, major drawback with the strategy was that the reaction could not be extended to other aldehydes except paraformaldehyde. Similarly, the second paper described synthesis of a single compound pyridoindolobenzodiazepine (an antipsychotic agent) by allowing *N*-1-linked aryl amine in the indole to undergo cyclization at the C-7 of the aromatic ring, again only in the presence of paraformaldehyde, and under strong acidic conditions such as neat TFA. In contrast, the traditional and our modified Pictet–Spengler cyclization are generally affected under mild acidic conditions (2% TFA–DCM at 0 °C or *p*TSOH) with a wide variety of aldehydes.

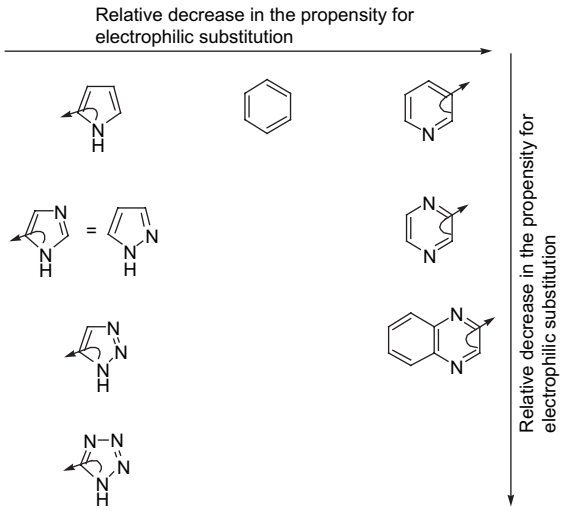


Figure 2. Comparative trends of electrophilic substitutions among five- and six-membered *N*-heterocycles.

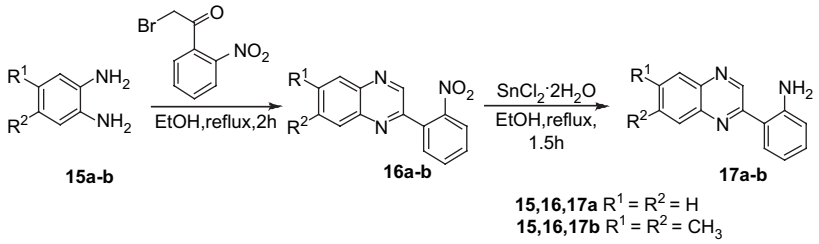
2. Result and discussion

In order to test the viability and generality of our proposed concept, initially we searched for an entirely new generation of substrates having aryl amine linked to either carbon or nitrogen of a deactivated heterocyclic system. In the first instance, we directed our efforts towards five- and six-membered heterocyclic skeletons that behaved as deactivated π-nucleophiles towards the electrophilic substitution. Among five-membered *N*-containing heterocyclic frameworks pyrroles demonstrate superior reactivity towards electrophilic substitution than the six-membered counterpart pyridine.[9] This observation can be attributed to the fact that the electron-sink effect exerted by the multiply bonded nitrogen makes six-membered *N*-containing heterocycles considerably less reactive than the five-membered *N*-containing heterocycles, where nitrogen acts as electron donor thereby activating the ring carbons towards electrophilic substitution. But if a second multiply bonded nitrogen is introduced in the pyrrole (as in azoles), it makes the activated five-membered ring system less reactive towards electrophile and introduces differentiation in the reactivity of heterocyclic carbons towards electrophilic substitution. The carbons at α- and γ-positions to the multiply bonded nitrogen are deactivated, whereas the β-carbon is the least deactivated. However, if more such multiply bonded nitrogen are introduced in the ring system, the π-nucleophilic character is further diminished (Fig. 2). Thus, triazoles and tetrazoles with **3** and **4** nitrogens, respectively, in their rings are the most deactivated heterocycles towards electrophilic substitution. Literature survey also revealed few reports[14] dealing with the electrophilic substitution at the carbon(s) present in triazoles and tetrazoles. Hence, for our studies triazole and tetrazole appeared to be good substrates under five-membered deactivated ring systems to prove our concept.

Among six-membered heterocyclic ring systems, the presence of a doubly bonded nitrogen atom not only deactivates the ring towards electrophilic substitution than benzene (Fig. 2), but also imparts a differentiating effect on the carbons towards electrophilic substitution.[9] The carbons at α- and γ-positions to the multiply bonded nitrogen are more deactivated than β-position, and this is in accordance with the literature reports demonstrating electrophilic substitutions at the β-carbon.[9] However, introduction of one more multiply bonded atom in the ring at C-4, introduces symmetry in the molecule and all the four carbons now behave as α-carbon to either of the nitrogen (pyrazine; Fig. 2). This in turn results in the relative decrease in the overall π-nucleophilic character in such systems. This phenomenon is also evident in the quinoxaline ring system (a benzoannulated derivative of pyrazine), which has been reported to undergo electrophilic substitution exclusively on its benzene ring, thereby suggesting that the heterocyclic counterpart is highly deactivated. Hence, among six-membered deactivated heterocyclic rings we selected quinoxaline as a model to prove our proposed concept. In this communication, we report Pictet–Spengler cyclization on aryl amine substrates **17**, **22** and **27** derived from deactivated heterosystems: quinoxaline, tetrazole and triazole, respectively. In the substrate **17**, an aryl amine has been allowed to originate from one of the α-carbons with the view to facilitate ring closure via 6-*endo* cyclization on the second α-carbon (Fig. 2). In contrast in the substrates **22** and **27**, an aryl amine has been allowed to originate from N-1 with the view to allow ring closure via C–C bond formation at the C-5 (Fig. 2) in both the heterocyclic rings. As depicted in Figure 2, based on electrophilic distribution pattern for triazoles, we had an additional option of allowing the aryl amine to originate from the C-4 followed by ring closure at C-5. However, in view of higher chemical diversity, we restricted our self to the substrate **27** since synthesis of the second substrate with aryl amine originating from C-4 of the triazole involved use of 1-ethynyl-2-nitrobenzene, for which no commercial diversity is available. The Pictet–Spengler reaction on these substrates in the presence of aldehydes led to the formation of new polycyclic skeletons (**18**, **19** and **26**) hitherto not reported in the literature. Polycyclic systems derived from privileged structures (quinoxalines, triazole and tetrazoles) constitute an interesting class of compounds for any drug discovery program.[15]

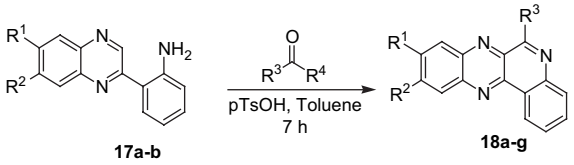
The synthesis of substrate **17** has been depicted in Scheme 1. It can be readily obtained by first treating *o*-nitrophenacyl bromide with *o*-phenylenediamine (**15**) to give nitro derivative of quinoxaline **16**, which was further reduced in the presence of $SnCl_2 \cdot 2H_2O$ to give 2-quinoxalin-2-yl-phenylamine **17**.

For the Pictet–Spengler cyclization, substrate **17** was treated with *p*-tolylbenzaldehyde under a variety of traditional Pictet–Spengler protocols involving *p*TsOH in toluene at reflux, 5% TFA in DCM at rt, and neat toluene at 80 °C. The 6-*endo* cyclization resulting in triaza-benzo[*a*]anthracene **18** (Scheme 2) occurred only when *p*TsOH was used as a proton source, other two protocols furnished imines as the only product. The crude product obtained after workup was purified by silica gel column chromatography using EtOAc/hexane as an eluent and characterized by MS and



Scheme 1. Synthesis of the Pictet–Spengler substrate **17** involving deactivated heteroarene quinoxaline.

NMR. The scope and limitation of our strategy were established by synthesizing five compounds based on **18** by using three aldehydes and two phenylenediamines. Purities of the crude products were typically in excess of 85% based on HPLC analysis and substitutions on aldehydes or phenylenediamine had no effect on the isolated yields (62–70%) of the cyclized products. It is interesting to note that aromatic aldehydes with both electron donating (except salicylaldehyde and *N*,*N*-dimethyl benzaldehyde) and withdrawing groups successfully underwent π-cyclizations. No reaction was detected with aliphatic aldehydes and ketones and this may be attributed to the relatively poor electrophilicity of the imines derived from aliphatic aldehydes and ketones coupled with the deactivated π-nucleophile. On the contrary, aromatic aldehydes in general, furnished imine with sufficient electrophilicity that triggered *endo* cyclization even in the presence of a deactivated π-nucleophile.



18a. R^1= R^2= H, R^3 = 4-CH_3-C_6H_4, R^4= H; Yield = 67%
18b. R^1= R^2= H, R^3 = 4-Br-C_6H_4, R^4= H; Yield =68%
18c. R^1= R^2= CH_3, R^3 = 4-CH_3-C_6H_4, R^4= H; Yield =72%
18d. R^1= R^2= CH_3, R^3 = 2-OCH_3-C_6H_4, R^4= H; Yield =62%
18e. R^1= R^2= CH_3, R^3 = 4-Br-C_6H_4, R^4= H; Yield =70%
18f R^1= R^2= H, R^3= 4-$(CH_3)_2$N-C_6H_4, R^4= H; no reaction
18g R^1= R^2= H, R^3 = CH_3CH_2, R^4= H; no reaction
18h R^1= R^2= H, R^3 = C_6H_5, R^4= CH_3; no reaction

Scheme 2. The Pictet–Spengler reaction on substrate **17**.

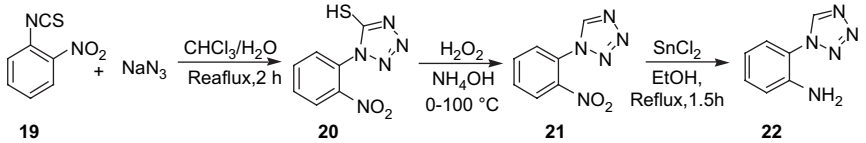
The synthesis of the second substrate based on tetrazole **22** has been depicted in Scheme 3. It commenced with the condensation of sodium azide with *o*-nitro phenylisothiocyanate (**19**) to give intermediate **20** followed by oxidative desulfurization to obtain **21** by the literature procedure.[16] The resulting tetrazole derived nitro derivative **21** was subjected to $SnCl_2$ reduction to give substrate **22**.

For the Pictet–Spengler cyclization, substrate **22** was treated with *p*-tolylbenzaldehyde in toluene at reflux in the presence of *p*TsOH (Scheme 4) to give pentaaza-cyclopenta[*a*]naphthalene **23**. The reaction was monitored on TLC and within 2 h we first observed a spot due to the formation of imine, which slowly disappeared with the appearance of a new spot arising from *endo* cyclization, which was found to be complete after 16 h. The prolonged duration required for the *endo* cyclization of the substrate **22** in comparison to the substrate **17** can be explained by comparing the electrophilicities of the corresponding imines formed as precursors during *endo* cyclization. Cook et al. earlier demonstrated that amines with lower p*K*a value furnished imines with higher electrophilicity thereby facilitating the ease of *endo* cyclization. In our substrate **17**, aryl amine is linked to an already deactivated carbon of the quinoxaline ring, which causes relative decrease in the p*K*a value than the aryl amine in the substrate **22** originating from the N-1, which behaves as an electron donor. Similar observation was made earlier by us during our studies with second-generation substrates comprising C- and N-linked aryl amines.[9] The crude product obtained after workup was purified by silica gel column chromatography using EtOAc/hexane as an eluant and characterized by MS and NMR. The scope and limitation of our strategy were established by synthesizing four compounds based on **23** by treating the substrate **22** with five different aldehydes. Purities of the crude products were typically in excess of 80% based on HPLC analysis with moderate to good isolated yields (47–68%) for the cyclized products **23**. Aliphatic aldehydes and ketones again failed to undergo *endo* cyclization with **22**.

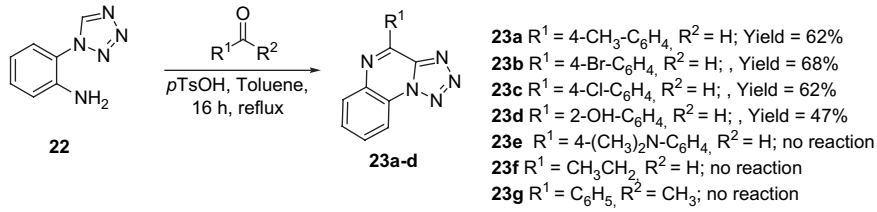
We next examined the efficacy of our strategy on yet another deactivated five-membered ring triazoles. The desired substrate **27** based on triazole was synthesized using a modified Huisgen cycloaddition method as depicted in Scheme 5.[17] Initially the reaction was carried out by subjecting alkyne, *o*-nitroaryl halide and azide to redox coupling in Cu(0)/$CuSO_4$ to get intermediate **26** using the literature procedure.[18] However, the reaction produced the desired intermediate in diminished yield. We then applied our modified strategy reported earlier for the synthesis of *N*-aryltriazoles **26** by replacing $CuSO_4$ by $FeCl_3$ using water as the sole reaction medium.[19] Subsequently, the nitro derivative **26** was reduced in the presence of $SnCl_2$ to furnish **27** in good yield and purity (Scheme 5).

The final *endo* cyclization was performed by reacting **27** with various aryl aldehydes to give triazolo[1,5-*a*]quinoxalines **28** (Scheme 6). The duration required for *endo* cyclization was in par with that observed for substrate **22** as in both the substrates the aryl amine originates from the nitrogen of the deactivated heterocyclic rings.

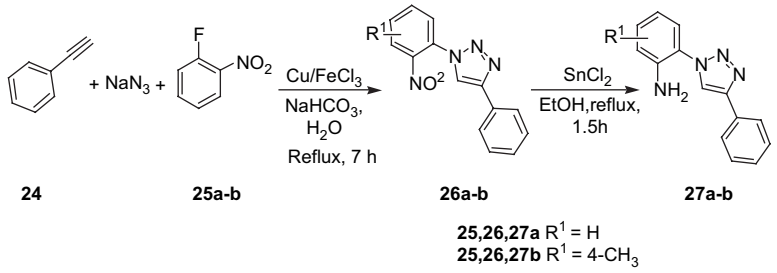
Thus, using substrates **17**, **22** and **27**, we have successfully demonstrated that the Pictet–Spengler cyclization could be carried out even with deactivated π-nucleophile systems by introducing an aryl amine. The incorporation of aryl amine instead of aliphatic amine compensates for the loss in the availability of activated



Scheme 3. Synthesis of the Pictet–Spengler substrate **22** involving deactivated heteroarene tetrazole.



Scheme 4. The Pictet–Spengler reaction on substrate **22**.



Scheme 5. Synthesis of the Pictet–Spengler substrate **27** involving deactivated heteroarene triazole.

π-nucleophile by furnishing imines with enhanced electrophilic character than imines derived from aliphatic amines. However, we did observe few exceptions with respect to the generality of our strategy. Aldehydes with strong electron donating groups such as *N*,*N*-dimethylbenzaldehyde failed to undergo π-cyclizations with substrates **17**, **22** and **27**. This may be attributed to the deactivated π-nucleophile systems that in turn failed to facilitate C–C bond formation. This is in contrast to our observation on the second-generation substrates (**4**–**12**; Fig. 2) where *N*,*N*-dimethylbenzaldehyde successfully underwent π-cyclizations, probably due to the presence of electron-rich π-systems. However, studies with the first-generation substrates **1**, **2** and **3** have shown that despite the presence of electron-rich π-systems, they failed to undergo *endo* cyclization with *N*,*N*-dimethylbenzaldehyde due to the comparatively poor electrophilic character of imines derived from aliphatic amines than aryl amines. Indeed, increasing the electrophilic character of imines derived from **1**, **2** and **3** either via *N*-acyliminium[20] or via N_a-benzylation strategy[6e,g–k,21] eventually furnished the *endo* cyclized product. It is thus evident that substrates with an aryl amine furnished imine with relative increase in its electrophilic character to the extent that even when linked to the deactivated π-systems, 6-*endo* cyclization is favoured albeit with limitations for aldehydes with strong electron donating group. Since our present substrates with deactivated heterosystems differ from the second-generation substrates having activated heterosystems reported earlier by us, substrates **17**, **22** and **27** could be grouped under 'third-generation' substrates for the Pictet–Spengler cyclization.

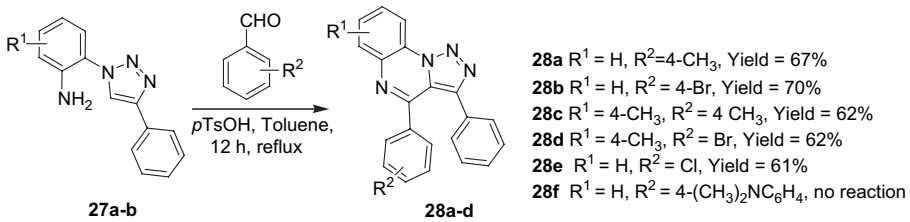
3. Conclusion

In summary, we have identified new substrates for the Pictet–Spengler reaction, based on the concept of 'aryl amine attached to a deactivated heterocyclic ring'. Our modified strategy opens up possibilities to design novel substrates with aryl amines linked via C or N to heterocyclic privileged structures, which in turn can be used for the synthesis of novel fused polyheterocyclic skeletons. *N*-Substituted fused polyheterocyclic systems due to their strong structural analogy to natural products are widely known to be associated with a wide range of biological activities.[22] Currently work is in progress in our lab with several second- and third-generation substrates designed on the basis of our new concept for the Pictet–Spengler reaction and will be reported soon.

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 except for compounds **18b**, **23b**, **23c** and **23d**, which were insoluble at higher concentration. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL III microanalyzer. Analytical HPLC was performed on C-18 reverse-phase column



Scheme 6. The Pictet–Spengler reaction on substrate **27**.

(250×4.6 mm). The micro-analyses were performed at Sophisticated Analytical Instrument Facility Division, of our institute. Mass spectra were recorded on a Merck MS-8000 spectrometer. Melting points reported were uncorrected.

4.2. General procedure for the synthesis of 2-(2-nitrophenyl)-quinoxaline (16)

A mixture of phenylenediamine **15a** (1.06 g, 8.3 mmol), and 2-bromo-2′-nitro acetophenone (2.00 g, 8.19 mmol) was refluxed in ethanol (20 mL) for 2 h. Ethanol was evaporated in vacuo and EtOAC (2×50 mL) was added to the reaction mixture. The organic layer was washed with saturated $NaHCO_3$ solution (30 mL), water and brine (30 mL) and dried over Na_2SO_4 and evaporated to obtain a residue. The residue so obtained was purified on a silica gel column using hexane/ethyl acetate (80:20, v/v) as eluent to afford **16a** as a solid.

*4.2.1. 2-(2-Nitrophenyl)-quinoxaline (**16a**)*

Yield 78%; yellow solid; mp 116–118 °C; R_f=0.52 (1:9 EtOAc/hexane); IR ν_{max} (KBr) 1610, 1533, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.96 (s, 1H, ArH), 8.20–8.09 (m, 3H, ArH), 7.85–7.68 (m, 5H, ArH). Mass (FAB) *m*/*z* 252 (M^++1). Anal. Calcd for $C_{14}H_9N_3O_2$: C, 66.93; H, 3.61; N, 16.73. Found: C, 66.73; H, 3.53; N, 16.80.

*4.2.2. 6,7-Dimethyl-2-(2-nitro-phenyl)-quinoxaline (**16b**)*

Yield 72%; brown solid; mp 154–157 °C; R_f=0.61 (1:9 EtOAc/hexane); IR ν_{max} (KBr) 2939, 2849, 1604, 1522, 1338 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=8.87 (s, 1H, ArH), 8.07 (d, *J*=8.0 Hz, 1H, ArH), 7.93–7.61 (overlapped, 5H, ArH), 2.53 (s, 3H, CH_3), 2.51 (s, 3H, CH_3). ^{13}C (50 MHz, $CDCl_3$): δ=150.28, 149.36, 143.56, 141.68, 141.60, 141.19, 140.95, 133.42, 132.14, 131.31, 130.42, 128.96, 128.63, 125.25, 20.77. Mass (FAB) *m*/*z* 280 (M^++1). Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.69; H, 4.83; N, 15.25.

4.3. General procedure of reduction of 2-(2-nitro-phenyl)-quinoxaline (16a) to 2-quinoxalin-2-yl-phenylamine (17a)

To the solution of compound **16a** (2.0 g, 7.93 mmol) in ethanol (20 mL) was added $SnCl_2 \cdot 2H_2O$ (5.34 g, 23.8 mmol) and the reaction mixture was heated at reflux with stirring for 1.5 h under nitrogen atmosphere. After this ethanol was evaporated and the residue was made alkaline with saturated $NaHCO_3$ (30 mL) and then EtOAc (100 mL) was added. The organic layer was separated, dried (Na_2SO_4) and concentrated to afford a residue, which was purified by silica gel chromatography using hexane/EtOAc (20:80, v/v) as eluent to afford **17a**.

*4.3.1. 2-Quinoxalin-2-yl-phenylamine (**17a**)*

Yield 68%; yellow solid; mp 146–148 °C; R_f=0.45 (1:4 EtOAc/hexane); IR ν_{max} (KBr) 3426, 1595 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=9.32 (s, 1H, ArH), 8.12–8.02 (m, 2H, ArH), 7.85–7.65 (m, 3H, ArH), 7.32–7.23 (overlapped, 1H, ArH), 6.86–6.81 (m, 2H, ArH). ^{13}C (50 MHz, $CDCl_3$): δ=150.28, 149.36, 143.56, 141.68, 141.60, 140.95, 133.42, 132.14, 131.31, 130.42, 128.96, 128.63, 125.25, 20.77. Mass (FAB) *m*/*z* 222 (M^++1). Anal. Calcd for $C_{14}H_{11}N_3$: C, 76.00; H, 5.01; N, 18.99. Found: C, 76.30; H, 5.21; N, 18.75.

*4.3.2. 2-(6,7-Dimethyl-quinoxalin-2-yl)-phenylamine (**17b**)*

Yield 63%; yellow solid; mp 160–164 °C; R_f=0.51 (1:4 EtOAc/hexane); IR ν_{max} (KBr) 3373, 2921, 2859, 1603, 1349 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=9.19 (s, 1H, ArH), 7.82–7.78 (m, 3H, ArH), 7.26–7.24 (m, 1H, ArH), 6.84 (t, *J*=8.2 Hz, 2H, ArH), 7.10 (br s, 2H, NH_2), 2.45 (s, 6H, 2×CH_3). ^{13}C (50.2 MHz, $CDCl_3$): δ=153.04, 148.32, 144.07, 140.96, 139.92, 139.71, 139.48, 131.30, 129.55, 128.55, 128.16, 119.01, 117.90, 117.80, 20.65. Mass (FAB) *m*/*z* 250 (M^++1). Anal. Calcd for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.85. Found: C, 77.24; H, 6.20; N, 16.51.

4.4. General procedure for the Pictet–Spengler reaction on substrate 17

A mixture of 2-quinoxalin-2-yl-phenylamine (**17a**) (0.10 g, 0.45 mmol), *p*-tolylbenzaldehyde (54 μL, 0.49 mmol) and *p*-tolylsulphonic acid (6.08 mg, 0.032 mmol) was refluxed in toluene (5 mL) for 7 h. Toluene was evaporated in vacuo and residue so obtained was dissolved in ethyl acetate (50 mL). The organic layer was washed with 5% aqueous sodium bicarbonate, water (2×10 mL) and brine solution (1×10 mL). The organic layers were combined and dried over anhydrous Na_2SO_4 and evaporated to obtain a residue. The residue so obtained was purified on column chromatography on silica gel with hexane/ethyl acetate (80:20, v/v) as eluent to afford **18a** as a yellow solid.

*4.4.1. 6-p-Tolyl-5,7,12-triaza-benzo[a]anthracene (**18a**)*

Yield 67%; yellow solid; mp 230–232 °C; R_f=0.56 (1:19 EtOAc/hexane); –IR ν_{max} (KBr) 3023, 2973, 2843 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=9.27 (d, *J*=8.1 Hz, 1H, ArH), 8.39–8.22 (m, 5H, ArH), 7.99–7.87 (m, 3H, ArH), 7.89 (t, *J*=7.2 Hz, 1H, ArH), 7.42 (d, *J*=7.5 Hz, 2H, ArH), 2.51 (s, 3H, CH_3). ^{13}C (50.2 MHz, $CDCl_3$): δ=161.17, 145.49, 143.94, 140.10, 136.89, 135.52, 132.49, 131.76, 131.04, 130.65, 130.32, 129.75, 129.20, 128.07, 127.61, 124.78, 21.95. Mass (FAB) *m*/*z* 322 (M^++1). Anal. Calcd for $C_{22}H_{15}N_3$: C, 82.22; H, 4.70; N, 13.08. Found: C, 82.34; H, 4.82; N, 13.30.

*4.4.2. 6-(4-Bromo-phenyl)-5,7,12-triaza-benzo[a]anthracene (**18b**)*

Yield 68%; brown solid; mp 214–216 °C; R_f=0.62 (1:19 EtOAc/hexane); IR ν_{max} (KBr) 3033 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=9.28 (d, *J*=7.8 Hz, 1H, ArH), 8.37–8.22 (m, 5H, ArH), 7.97–7.91 (m, 4H, ArH), 7.74 (d, *J*=8.5 Hz, 2H, ArH). Mass (ES^+) *m*/*z* 386.1 (M^++1). DART-HRMS Calcd for $C_{21}H_{13}BrN_3$: 386.02928, found 386.02671. Anal. Calcd for $C_{21}H_{12}BrN_3$: C, 65.30; H, 3.13; N, 10.88. Found: C, 65.13; H, 3.32; N, 103.67.

*4.4.3. 9,10-Dimethyl-6-p-tolyl-5,7,12-triaza-benzo[a]-262#anthracene (**18c**)*

Yield 72%; yellow solid; mp 210–212 °C; R_f=0.65 (1:19 EtOAc/hexane); IR ν_{max} (KBr) 3061, 2981, 2830 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=9.23 (d, *J*=8.6 Hz, 1H, ArH), 8.27–8.19 (m, 3H, ArH), 8.05 (d, *J*=7.8 Hz, 2H, ArH), 7.90–7.76 (m, 3H, ArH), 7.41 (d, *J*=8.2 Hz, 1H, ArH), 2.57 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.45 (s, 3H, CH_3). ^{13}C (50.2 MHz, $CDCl_3$): δ=161.13, 143.99, 142.16, 139.68, 135.76, 131.77, 130.76, 130.21, 129.80, 129.41, 128.82, 128.25, 127.78, 125.12, 124.52, 122.74, 121.19, 112.42, 110.38, 21.95, 21.10, 20.8. Mass (FAB) *m*/*z* 350 (M^++1). Anal. Calcd for $C_{24}H_{19}N_3$: C, 82.49; H, 5.48; N, 12.03. Found: C, 82.72; H, 5.32; N, 12.34.

*4.4.4. 6-(2-Methoxy-phenyl)-9,10-dimethyl-5,7,12-triaza-benzo[a]-anthracene (**18d**)*

Yield 62%; brown solid; mp >250 °C; R_f=0.53 (1:19 EtOAc/hexane); IR ν_{max} (KBr) 1341, 2923, 2844 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=8.46 (d, *J*=8.4 Hz, 1H, ArH), 8.06 (s, 1H, ArH), 7.88 (s, 1H, ArH), 7.57 (t, *J*=7.6 Hz, 1H, ArH), 7.34 (t, *J*=7.6 Hz, 2H, ArH), 7.30–7.17 (overlapped, 1H, ArH), 6.92 (d, *J*=8.2 Hz, 2H, ArH), 6.75 (t, *J*=8.4 Hz, 1H, ArH), 3.94 (s, 3H, OCH_3), 2.52 (s, 6H, 2×CH_3). ^{13}C (50.2 MHz, $CDCl_3$): δ=157.41, 146.25, 144.59, 139.88, 139.51, 138.76, 136.38, 130.77, 128.94, 128.84, 128.42, 127.57, 125.14, 122.63, 121.11, 121.03, 120.17, 110.63, 55.79, 20.76, 20.51. Mass (FAB) *m*/*z* 366 (M^++1). Anal. Calcd for $C_{24}H_{19}N_3O$: C, 78.88; H, 5.24; N, 11.50. Found: C, 78.78; H, 5.36; N, 11.34.

*4.4.5. 6-(4-Bromo-phenyl)-9,10-dimethyl-5,7,12-triaza-benzo[a]-anthracene (**18e**)*

Yield 70%; yellow solid; mp 198–200 °C; R_f=0.59 (1:19 EtOAc/hexane); IR ν_{max} (KBr) 3021, 2931, 2853 cm^{-1}; ^1H NMR (200 MHz,

$CDCl_3$): δ=9.23 (dd, J=7.8, 1.4 Hz, 1H, ArH), 8.27–8.20 (m, 3H, ArH), 8.10 (s, 1H, ArH), 8.02 (s, 1H, ArH), 7.92–7.71 (m, 4H, ArH), 2.59 (s, 3H, CH_3), 2.55 (s, 3H, CH_3). ^{13}C (75 MHz, $CDCl_3$): δ=158.2, 157.9, 144.2, 142.1, 133.2, 132.1, 131.3, 130.7, 130.1, 129.1, 128.1, 124.3, 121.3, 117.5, 21.0, 20.7. Mass (ES^+) m/z 414.1 (M^++1). DART-HRMS Calcd for $C_{23}H_{17}BrN_3$: 414.06058, found 414.05659. Anal. Calcd for $C_{23}H_{16}BrN_3$: C, 66.68; H, 3.89; N, 10.14. Found: C, 66.60; H, 3.66; N, 10.24.

4.5. Preparation of 1-(*o*-nitrophenyl)-5-mercapto-tetrazole (20)

A solution of *o*-nitro phenylisothiocyanate **19** (2.00 g, 11.11 mmol) in 5 mL of chloroform was placed in a round-bottom flask equipped with a magnetic stirrer and reflux condenser. Sodium azide (1.08 g, 16.55 mmol) dissolved in 10 mL of water was added dropwise at rt to the reaction mixture. After the initial exothermic reaction subsided, the stirred solution was heated to reflux for 3 h. Then the solution was cooled and filtered. The aqueous layer was separated and acidified with 10 mL of 37% hydrochloric acid. The precipitate of crude yellow thiol containing some *o*-nitrophenylcyanamide was separated by suction filtration, washed with distilled water and air dried. The crude solid was slurried with 20 mL of benzene and allowed to stand for 1–3 days. The mixture was filtered and the pure 1-(*o*-nitrophenyl)-5-mercaptotetrazole **20** was washed with benzene and was air dried.

*4.5.1. 1-(2-Nitro-phenyl)-1H-tetrazole-5-thiol (**20**)*

Yield 75%; yellow solid; mp 118–120 °C; IR ν_{max} (KBr) 1607, 1529, 1348, 1292 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.25 (d, J=8.0 Hz, 1H, ArH), 7.93–7.71 (m, 3H, ArH). ^{13}C (50.2 MHz, $CDCl_3$): 164.78, 144.75, 135.72, 132.94, 130.64, 126.56, 126.40. Mass (ES^+) m/z 224 (M^++1). Anal. Calcd for $C_7H_5N_5O_2S$: C, 37.67; H, 2.26; N, 31.38. Found: C, 37.71; H, 2.31; N, 31.10.

4.6. Oxidation of 1-(2-nitro-phenyl)-1*H*-tetrazole-5-thiol (20) to 1-(2-nitro-phenyl)-1*H*-tetrazole (21)

To a stirred solution of 1-(2-nitro-phenyl)-1*H*-tetrazole-5-thiol **20** (1.8 g, 8.07 mmol) in NH_4OH (1 N, 10 mL) at 0 °C was added dropwise 30% H_2O_2 (7 mL) and stirring was continued for 4 h at 0 °C. The solution was boiled for 10 min and cooled. The solid product was collected by suction filtration, washed and dried to give white crystals **21**.

*4.6.1. 1-(2-Nitro-phenyl)-1H-tetrazole (**21**)*

Yield 82%; yellow solid; mp 65–66 °C; R_f=0.55 (1:9 EtOAc/hexane); IR ν_{max} (KBr) 1606, 1533, 1353 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=9.04 (s, 1H, ArH), 8.25 (dd, J=8.0, 1.8 Hz, 1H, ArH), 7.96–7.81 (m, 2H, ArH), 7.65 (dd, J=7.6, 1.8 Hz, 1H, ArH). ^{13}C (50.2 MHz, $CDCl_3$): δ=144.38, 143.97, 135.16, 132.70, 129.15, 127.31, 126.64. Mass (ES^+) m/z 192.3 (M^++1). Anal. Calcd for $C_7H_5N_5O_2$: C, 43.98; H, 2.64; N, 36.64. Found: C, 43.76; H, 2.73; N, 36.79.

4.7. Reduction of 1-(2-nitro-phenyl)-1*H*-tetrazole (21) to 2-tetrazol-1-yl-phenylamine (22)

To the solution of compound **21** (1.4 g, 7.32 mmol) in ethanol (20 mL) was added $SnCl_2 \cdot 2H_2O$ (4.95 g, 21.98 mmol) and the reaction mixture was heated at reflux with stirring for 1.5 h under nitrogen atmosphere. After this ethanol was evaporated and the residue was made alkaline with saturated $NaHCO_3$ (30 mL) and then EtOAc (100 mL) was added. The suspension was passed through a bed of Celite and the filtrate was partitioned in a separating funnel. The organic layer was separated, dried (Na_2SO_4) and concentrated to afford a residue, which was purified by silica gel chromatography using hexane/EtOAc (60:40, v/v) as eluent to afford **22** as off white solid.

*4.7.1. 2-Tetrazol-1-yl-phenylamine (**22**)*

Yield 84%; off white solid; mp 98–99 °C; R_f=0.64 (2:3 EtOAc/hexane); IR ν_{max} (KBr) 3440, 3355, 1602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.98 (s, 1H, ArH), 7.37–7.19 (overlapped, 2H, ArH), 6.98–6.85 (m, 2H, ArH), 4.45 (s, 2H, NH_2). ^{13}C (50.2 MHz, $CDCl_3$): δ=143.39, 141.86, 131.57, 125.33, 119.55, 118.32, 118.10. Mass (FAB) m/z 162 (M^++1). Anal. Calcd for $C_7H_7N_5$: C, 52.17; H, 4.38; N, 43.45. Found: C, 52.27; H, 4.67; N, 43.67.

4.8. General procedure for the Pictet–Spengler reaction on substrate 22

A mixture of 2-tetrazol-1-yl-phenylamine **22** (0.10 g, 0.62 mmol), *p*-tolylbenzaldehyde (74 μL, 0.62 mmol) and *p*-tolylsulphonic acid (12 mg, 0.064 mmol) was refluxed in toluene (5 mL) for 12 h. Toluene was evaporated in vacuo and residue so obtained was dissolved in ethyl acetate (50 mL). The organic layer was washed with 5% aqueous sodium bicarbonate, water (2×10 mL) and brine solution (1×10 mL). The organic layers were combined and dried over anhydrous Na_2SO_4 and evaporated to obtain a residue. The residue so obtained was purified by column chromatography on silica gel with hexane/ethyl acetate (70:30, v/v) as eluent to afford **23a** as off white solid.

*4.8.1. 4-p-Tolyl-tetrazolo[1,5-a]quinoxaline (**23a**)*

Yield 62%; off white solid; mp 170–172 °C; R_f=0.46 (3:7 EtOAc/hexane); IR ν_{max} (KBr) 3042, 2928, 2849, 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.85 (d, J=8.1 Hz, 2H, ArH), 8.63 (dd, J=8.1, 3.0 Hz, 1H, ArH), 8.31 (dd, J=8.1, 1.8 Hz, 1H, ArH), 7.87–7.82 (m, 2H, ArH), 7.44 (d, J=8.1 Hz, 2H, ArH), 2.49 (s, 3H, CH_3). ^{13}C (50.2 MHz, $CDCl_3$): δ=148.15, 143.17, 142.41, 137.15, 131.70, 130.75, 130.61, 130.15, 129.97, 129.81, 129.36, 123.98, 116.46, 22.02. Mass (FAB) m/z 262 (M^++1). Anal. Calcd for $C_{15}H_{11}N_5$: C, 68.95; H, 4.24; N, 26.80. Found: C, 68.88; H, 4.39; N, 26.98.

*4.8.2. 4-(4-Bromo-phenyl)-tetrazolo[1,5-a]quinoxaline (**23b**)*

Yield 68%; white solid; mp 181–182 °C; R_f=0.54 (3:7 EtOAc/hexane); IR ν_{max} (KBr) 3028, 1611 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.85 (d, J=8.6 Hz, 2H, ArH), 8.64–8.61 (m, 1H, ArH), 8.33–8.29 (m, 1H, ArH), 7.88–7.86 (m, 2H, ArH), 7.75 (d, J=8.6 Hz, 2H, ArH). Mass (FAB) m/z 326 (M^++1). Anal. Calcd for $C_{14}H_8BrN_5$: C, 51.56; H, 2.47; N, 21.47. Found: C, 51.45; H, 2.86; N, 21.68.

*4.8.3. 4-(4-Chloro-phenyl)-tetrazolo[1,5-a]quinoxaline (**23c**)*

Yield 62%; white solid; mp 165–167 °C; R_f=0.62 (3:7 EtOAc/hexane); IR ν_{max} (KBr) 3031, 1608, 1593 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.95 (d, J=8.4 Hz, 2H, ArH), 8.67–8.64 (m, 1H, ArH), 8.36–8.32 (m, 2H, ArH), 7.91–7.87 (m, 2H, ArH), 7.44 (d, J=8.4 Hz, 1H, ArH). Mass (ES^+) m/z 298.2 (M^++1). Anal. Calcd for $C_{14}H_8ClN_5$: C, 59.69; H, 2.86; N, 24.86. Found: C, 59.78; H, 2.76; N, 24.76.

*4.8.4. 4-(2-Hydroxyphenyl)-tetrazolo[1,5-a]quinoxaline (**23d**)*

Yield 47%; yellow solid; mp 230–231 °C; R_f=0.41 (3:7 EtOAc/hexane); IR ν_{max} (KBr) 3404, 1605, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=9.68 (d, J=7.6 Hz, 1H, ArH), 8.68–8.63 (m, 1H, ArH), 8.23–8.18 (m, 1H, ArH), 7.90–7.85 (m, 2H, ArH), 7.53 (t, J=7.2 Hz, 1H, ArH), 7.18–7.11 (overlapped, 3H, ArH). Mass (FAB) m/z 264 (M^++1). Anal. Calcd for $C_{14}H_9N_5O$: C, 63.87; H, 3.45; N, 26.60. Found: C, 63.58; H, 3.53; N, 26.87.

4.9. General procedure for the preparation of 1-(2-nitro-phenyl)-4-phenyl-1*H*-[1,2,3]triazole (26a)

1-Fluoro-2-nitrobenzene **25a** (2.0 mmol), phenylacetylene (2.2 mmol), sodium azide (2.2 mmol) and $NaHCO_3$ (2.2 mmol) were suspended in water (10 mL) in a 50 mL round-bottom flask equipped with a small magnetic stirring bar. To this was added copper powder (100 mg) and ferric chloride (100 mg). The mixture was then heated to reflux for 7 h. After cooling the reaction mixture, EtOAc (50 mL) was added. The suspension was passed through a bed of Celite and the filtrate was partitioned in a separating funnel. The organic layer was separated, dried (Na_2SO_4) and concentrated to afford a residue, which was purified by silica gel chromatography using hexane/EtOAc (70:30, v/v) as eluent to afford **26a** as yellow solid.

*4.9.1. 1-(2-Nitro-phenyl)-4-phenyl-1H-[1,2,3]triazole (**26a**)*

Yield 65%; yellow solid; mp 144–145 °C; R_f=0.63 (3:7 EtOAc/hexane); IR ν_{max} (KBr) 1604, 1534, 1351 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.12 (dd, J=7.9, 1.3 Hz, 1H, ArH), 8.09 (s, 1H, ArH), 7.94–7.91 (m, 2H, ArH), 7.84–7.81 (m, 1H, ArH), 7.76–7.70 (m, 2H, ArH), 7.51–7.46 (m, 2H, ArH), 7.43–7.40 (m, 1H, ArH). Mass (ES^+) m/z 267.1 (M^++1). Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.26; H, 3.57; N, 21.25.

*4.9.2. 1-(4-Methyl-2-nitrophenyl)-4-phenyl-1H-1,2,3-triazole (**26b**)*

Yield 71%; yellow solid; mp 162–165 °C; R_f=0.77 (3:7 EtOAc/hexane); IR ν_{max} (KBr) 1604, 1529, 1356 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.036–8.03 (overlapped, 2H, ArH), 7.93–7.89 (m, 2H, ArH), 7.51–7.45 (m, 4H, ArH), 7.42–7.37 (m, 1H, ArH), 2.57 (s, 3H, CH_3). Mass (ES^+) m/z 281.1 (M^++1). Anal. Calcd for $C_{15}H_{12}N_4O_2$: C, 64.28; H, 4.32; N, 19.99. Found: C, 64.39; H, 4.53; N, 19.76.

4.10. Reduction of 1-(2-nitro-phenyl)-4-phenyl-1*H*-[1,2,3]triazole (26a) to 2-(4-phenyl-[1,2,3]triazol-1-yl)-phenylamine (27a)

To the solution of compound **26a** (1.2 g, 4.51 mmol) in ethanol (10 mL) was added $SnCl_2\cdot 2H_2O$ (3.05 g, 13.53 mmol) and the reaction mixture was heated at reflux with stirring for 1.5 h under nitrogen atmosphere. After this ethanol was evaporated and the residue was made alkaline with saturated $NaHCO_3$ (30 mL) and then EtOAc (100 mL) was added. The suspension was passed through a bed of Celite and the filtrate was partitioned in a separating funnel. The organic layer was separated, dried (Na_2SO_4) and concentrated to afford a residue, which was purified by silica gel chromatography using hexane/EtOAc (80:20, v/v) as eluent to afford **27a** as brown oil.

*4.10.1. 2-(4-Phenyl-[1,2,3]triazol-1-yl)-phenylamine (**27a**)*

Yield 82%; brown oil; R_f=0.32 (1:4 EtOAc/hexane); IR ν_{max} (neat) 3322, 1631, 1530 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.06 (s, 1H, ArH), 7.92 (d, J=8.1 Hz, 2H, ArH), 7.50–7.45 (m, 2H, ArH), 7.41–7.38 (m, 1H, ArH), 7.29–7.24 (overlapped, 2H, ArH), 6.93–6.83 (m, 2H, ArH), 4.60 (br s, 2H, NH_2). Mass (ES^+) m/z 237.2 (M^++1). Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.32; H, 5.18; N, 23.88.

*4.10.2. 5-Methyl-2-(4-phenyl-[1,2,3]triazol-1-yl)-phenylamine (**27b**)*

Yield 84%; brown oil; R_f=0.25 (1:4 EtOAc/hexane); IR ν_{max} (neat) 3458, 3363, 1630, 1518 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.07 (s, 1H, ArH), 7.93 (d, J=8.10 Hz, 2H, ArH), 7.51–7.46 (m, 2H, ArH), 7.42–7.39 (m, 1H, ArH), 7.11–7.08 (overlapped, 2H, ArH), 6.83 (d, J=8.1 Hz, 1H, ArH), 4.43 (br s, 2H, NH_2), 2.33 (s, 3H, CH_3). Mass (ES^+) m/z 251.1 (M^++1). Anal. Calcd for $C_{15}H_{14}N_4$: C, 71.98; H, 5.64; N, 22.38. Found: C, 71.88; H, 5.72; N, 22.61.

4.11. General procedure for the Pictet–Spengler reaction on substrate 27

A mixture of 2-(4-phenyl-[1,2,3]triazol-1-yl)-phenylamine (**27a**) (0.10 g, 0.42 mmol), *p*-tolylbenzaldehyde (46 μL, 0.42 mmol) and *p*-tolylsulphonic acid (8 mg, 0.042 mmol) was refluxed in toluene for 12 h. Toluene was evaporated in vacuo and residue so obtained was dissolved in ethyl acetate (50 mL). The organic layer was washed with 5% aqueous sodium bicarbonate (30 mL), water (2×10 mL) and brine solution (1×10 mL). The organic layers were combined and dried over anhydrous Na_2SO_4 and evaporated to obtain a residue. The residue so obtained was purified by column chromatography on silica gel with hexane/ethyl acetate (70:30, v/v) as eluent to afford **28a** as a white solid.

*4.11.1. 3-Phenyl-4-p-tolyl-[1,2,3]triazolo[1,5-a]quinoxaline (**28a**)*

Yield 67%; off white solid; mp 160–171 °C; R_f=0.39 (3:7 EtOAc/hexane); IR ν_{max} (KBr) 3038, 2938, 2852 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.81 (d, J=7.2 Hz, 1H, ArH), 8.24 (dd, J=8.1, 1.8 Hz, 1H, ArH), 7.81–7.77 (m, 2H, ArH), 7.37 (d, J=8.1 Hz, 2H, ArH), 7.32–7.25 (overlapped, 3H, ArH), 7.25–7.17 (m, 2H, ArH), 7.03 (d, J=7.90 Hz, 2H, ArH), 2.36 (s, 3H, CH_3). ^{13}C (75 MHz, $CDCl_3$): δ=152.76, 142.02, 139.05, 135.42, 132.13, 129.26, 128.76, 128.64, 126.96, 126.47, 123.97, 121.41, 114.34, 20.06. Mass (FAB) m/z 337 (M^++1). Anal. Calcd for $C_{22}H_{16}N_4$: C, 78.55; H, 4.79; N, 16.66. Found: C, 78.44; H, 4.53; N, 16.73.

*4.11.2. 4-(4-Bromo-phenyl)-3-phenyl-[1,2,3]triazolo[1,5-a]-quinoxaline (**28b**)*

Yield 70%; off white solid; mp 184–186 °C; R_f=0.46 (3:7 EtOAc/hexane); IR ν_{max} (KBr) 3032, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.82 (dd, J=7.6, 1.4 Hz, 1H, ArH), 8.25 (dd, J=8.2, 1.8 Hz, 1H, ArH), 8.06 (d, J=8.2 Hz, 1H, ArH), 7.94–7.91 (m, 2H, ArH), 7.85–7.79 (m, 2H, ArH), 7.36–7.23 (overlapped, 6H, ArH). ^{13}C (75 MHz, $CDCl_3$): δ=151.45, 146, 40, 133.67, 130.52, 130.00, 129.37, 129.09, 128.86, 127.74, 127.69, 127.41, 126.73, 124.53, 124.02, 123.43, 122.86, 115.63. Mass (FAB) m/z 401 (M^++1). Anal. Calcd for $C_{21}H_{13}BrN_4$: C, 62.86; H, 3.27; N, 13.96. Found: C, 62.72; H, 3.32; N, 13.84.

*4.11.3. 7-Methyl-3-phenyl-4-p-tolyl-[1,2,3]triazolo[1,5-a]-quinoxaline (**28c**)*

Yield 62%; off white solid; mp 220–221 °C; R_f=0.38 (3:7 EtOAc/hexane); IR ν_{max} (KBr) 3048, 2922, 2867, 1601, 1352 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.63 (d, J=8.3 Hz, 1H, ArH), 8.12 (d, J=8.3 Hz, 1H, ArH), 7.58 (dd, J=8.3, 1.6 Hz, 1H, ArH), 7.35 (d, J=8.1 Hz, 2H, ArH), 7.30–7.26 (overlapped, 3H, ArH), 7.23–7.20 (m, 2H, ArH), 7.02 (d, J=8.1 Hz, 2H, ArH), 2.69 (s, 3H, CH_3), 2.35 (s, 3H, CH_3). ^{13}C (75 MHz, $CDCl_3$): δ=151.64, 142.43, 139.48, 138.86, 133.53, 132.19, 129.29, 129.08, 128.74, 128.27, 128.06, 127.70, 127.45, 126.91, 123.69, 121.43, 114.03, 20.71, 20.09. Mass (ES^+) m/z 351 (M^++1). Anal. Calcd for $C_{23}H_{18}N_4$: C, 78.83; H, 5.18; N, 15.99. Found: C, 78.52; H, 5.37; N, 16.02.

*4.11.4. 4-(4-Bromo-phenyl)-7-methyl-3-phenyl-[1,2,3]triazolo-[1,5-a]quinoxaline (**28d**)*

Yield 62%; white solid; mp 183–185 °C; R_f=0.52 (3:7 EtOAc/hexane); IR ν_{max} (KBr) 2926, 2872, 1595, 1351 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.63 (s, 1H, ArH), 8.11 (d, J=8.40 Hz, 1H, ArH), 7.61 (d, J=8.4 Hz, 1H, ArH), 7.37–7.32 (overlapped, 4H, ArH), 7.28–7.24 (m, 5H, ArH), 2.70 (s, 3H, CH_3). ^{13}C (75 MHz, $CDCl_3$): δ=150.29, 142.27, 140.05, 133.82, 133.41, 129.95, 129.35, 129.22, 128.72, 128.37, 127.31, 126.67, 123.78, 123.20, 121.18, 114.08, 20.72. Mass (ES^+) m/z

415 (M^+). Anal. Calcd for $C_{22}H_{15}BrN_4$: C, 63.63; H, 3.64; N, 13.49. Found: C, 63.81; H, 3.53; N, 13.50.

*4.11.5. 4-(4-Chloro-phenyl)-3-phenyl-[1,2,3]triazolo[1,5-a]-quinoxaline (**28e**)*

Yield 61%; brown solid; mp 227–230 °C; R_f=0.50 (3:7 EtOAc/hexane); IR ν_{max} (KBr) 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.80 (dd, J=7.6, 1.9 Hz, 1H, ArH), 8.21 (dd, J=7.5, 1.9 Hz, 1H, ArH), 7.90 (dd, J=7.1, 1.7 Hz, 1H, ArH), 7.83–7.77 (m, 2H, ArH), 7.47–7.34 (m, 2H, ArH), 7.30–7.18 (m, 6H, ArH). ^{13}C (75 MHz, $CDCl_3$): δ=151.38, 142.50, 135.22, 135.42, 133.19, 129.18, 129.10, 128.87, 128.74, 127.70, 127.42, 127.24, 126.73, 124.51, 123.98, 119.20, 115.60. Mass (FAB) m/z 357 (M^++1). Anal. Calcd for $C_{21}H_{13}ClN_4$: C, 70.69; H, 3.67; N, 15.70. Found: C, 70.44; H, 3.51; N, 15.73.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.07.003.

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