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Application of modified Pictet–Spengler reaction for the synthesis of thiazolo- and pyrazolo-quinolines☆

Srinivas Duggineni, Devesh Sawant, Biswajit Saha and Bijoy Kundu*

Medicinal Chemistry Division, Central Drug Research Institute, Lucknow 226 001, India

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Abstract—Two new thiazole and pyrazole-based arylamine substrate have been used for the Pictet–Spengler reaction. This is in contrast to the traditionally used indole/imidazole-based aliphatic amine substrates that has remained in use for the last ~100 years. The condensation of both the substrates with a variety of aldehydes in the presence of 2% TFA–DCM at 0° for 30 min or *p*TsOH in toluene at reflux led to the synthesis of thiazoloquinolines and pyrazoloquinolines, respectively. Unlike aliphatic amine substrates, our substrates readily underwent Pictet–Spengler cyclization even with aldehydes having electron donating group. The studies are based on a new concept proposed by us that arylamines linked to an activated heterocyclic ring can lead to a variety of second-generation substrates for the Pictet–Spengler cyclization. Our studies open up new avenues for the application of Pictet–Spengler reaction beyond syntheses of the tetrahydroisoquinolines and tetrahydro-β-carbolines.

1. Introduction

For the last ~100 years, the Pictet–Spengler reaction[1] has remained as one of the most widely used methods for the syntheses of isoquinolines and β-carbolines via C–C bond formation.[2] In general, it is a two-step method and involves acid catalyzed condensation of an aliphatic amine attached to a sufficiently reactive aromatic nucleus with aldehydes.[3] In the first step an imine is formed, which may be activated by acids and in the second step *endo* cyclization is affected between a carbon nucleophile of a sufficiently reactive aromatic moiety and the activated iminium ion resulting in a *N*-heterocyclic ring via a new C–C bond. Over the years, several groups have studied the detail mechanistic aspects of this reaction and have developed a number of diastereo- and enantio-selective methods for the Pictet–Spengler cyclization.[4] It is interesting to note that the method continues to be a significant focus of research as chemists continue to improve upon the methodology by applying new reaction conditions including asymmetric catalysis of the *N*-acyliminium Pictet–Spengler reaction.[5] However, despite being one of the most powerful method, the strategy has remained unchanged ever since its inception and its use has been limited to only three amine substrates: Trp/tryptamine, His/histamine or dopamine/tyramine, thereby invariably resulting in the formation of heterocycles based on either tetrahydro-β-carbolines/tetrahydroimidazopyridines or tetrahydroisoquinolines.[4] Therefore, the challenge of applying the Pictet–Spengler reaction beyond syntheses of isoquinolines and β-carbolines appears to be associated with the limited availability of amine substrates.

Recently, we described[6] a new strategy for the Pictet–Spengler reaction by using arylamines linked to the *N*-1 of the imidazole (**1** and **2**; Fig. 1) as an alternative substrates instead of traditionally used aliphatic amines linked to the C-3 of the imidazole. We argued that the iminium ion derived from an arylamine would facilitate C–C bond formation better than an aliphatic amine since enhancement of the electrophilic nature of the iminium intermediate is known to be the driving force for the cyclization.[7]

Though the use of substrates **1** and **2** led to the synthesis of *N*-rich heterocycles: imidazoquinoxalines and an unusual seven membered ring triazabenzoazulenes, both of them were derived from the imidazole, an activated aromatic nucleus used traditionally in the Pictet–Spengler reaction. We envisaged that by applying our new concept of 'arylamines linked to an activated heterocyclic ring', a variety of structurally diverse substrates can be designed for the Pictet–Spengler reaction, which in turn may lead to novel benzoannelated heterosystems devoid of any stereochemical issues traditionally associated with a typical

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Keywords: Thiazoloquinoline; Pyrazoloquinoline; Pictet–Spengler reaction; C–C bond formation.
* Corresponding author. Tel.: +91 522 2262411 18x4383; fax: +91 522 2623405; e-mail: bijoy_kundu@yahoo.com

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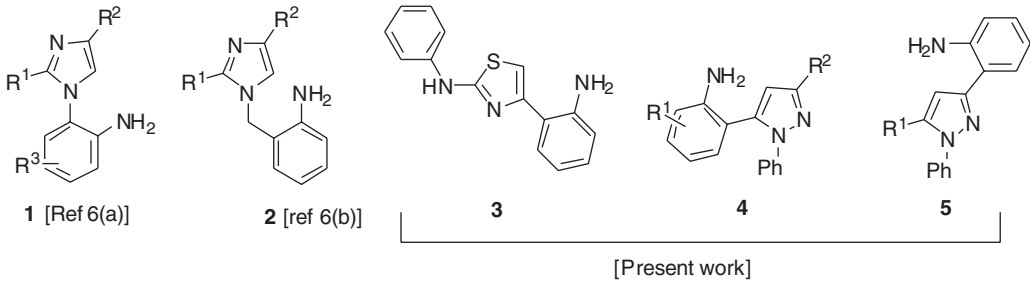


Figure 1. Second generation substrates for the Pictet–Spengler reaction.

Pictet–Spengler reaction (Fig. 2). While the manuscript was under preparation, Pictet–Spengler reaction was recently demonstrated on heteroaryl amines linked to an activated aromatic ring as substrates, which is also in accordance to our modified strategy.[8] In order to test the viability and generality of our concept, we searched for an entirely new generation of substrates having aryl amines linked to the C of an activated heterocyclic ring other than the traditionally used indoles and imidazoles. In the first instance, we directed our efforts towards the activated heterocycles analogous to imidazole. We envisaged that since imidazole falls under the class of azoles, an arylamine originating from the azoles other than the imidazole could be equally active to facilitate the Pictet–Spengler cyclization. After screening various azoles, our choice ultimately fell for thiazoles and pyrazoles as an activated heterocyclic rings, which are common substructures present in many natural and medicinal compounds. We proposed to link the arylamine through one of the C in the thiazole and pyrazole ring instead of the nitrogen (as in substrates **1** and **2**) in a manner to facilitate the Pictet–Spengler cyclization. In order to select the carbon in both the rings for linking the arylamine, we analyzed the electrophilic substitution patterns in azoles.

The multiply bonded nitrogen atom present in azoles, is generally known to have differential deactivating affects on the carbon atoms in the ring.[9] The α- and γ-positions to the multiply bonded *N*-atom are deactivated towards electrophilic attack whereas the β-carbon is the least deactivated and is therefore prone towards electrophilic substitution. Thus, the C-4 position in the pyrazole while the C-5 position in the thiazole being β to the multiply bonded nitrogen atom are the positions prone to electrophilic substitution (Fig. 3).

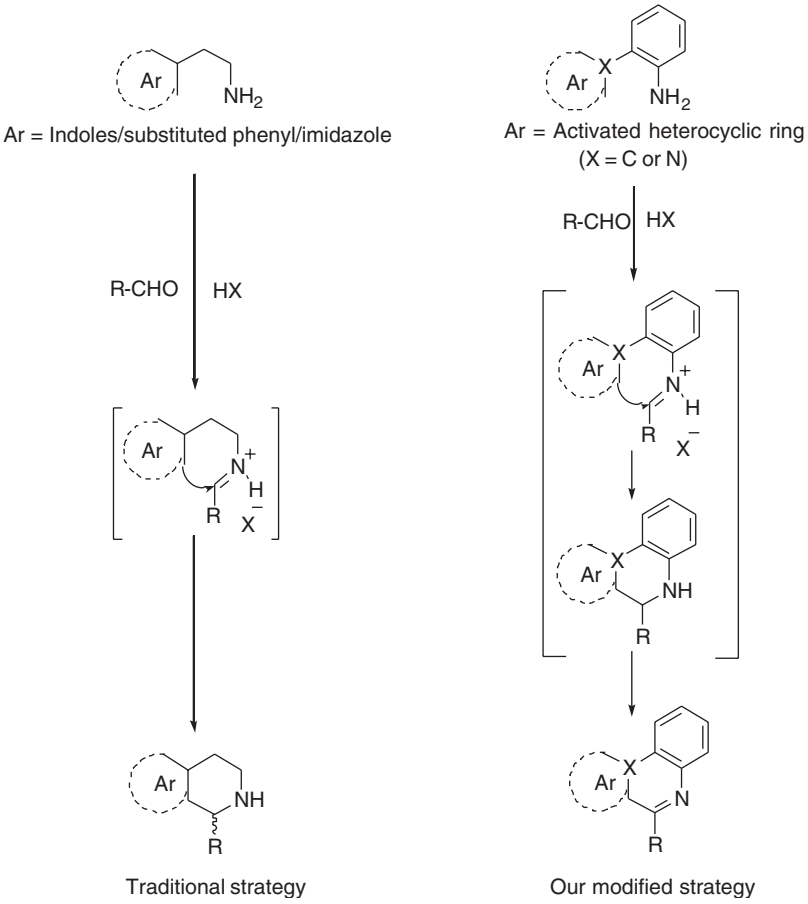


Figure 2. Traditional and modified strategies for the Pictet–Spengler reaction.

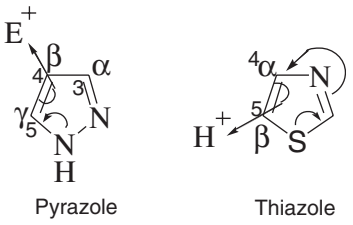


Figure 3. Pattern of electrophilic substitution in pyrazole and thiazole.

Based on these facts, we envisaged that an aryl amine originating from the γ-carbon (C-5) in the pyrazole and α-carbon (C-4) in the thiazole, which are adjacent to the β-carbon in both the azoles, might act as novel substrates for the Pictet–Spengler cyclization. Keeping these structural requirements in mind, we next analyzed the structures and synthetic feasibilities of a variety of thiazole and pyrazole based compounds from the literature, which led to the identification of [4-(2-amino-phenyl)-thiazol-2-yl]-phenyl-amine (**3**) and 2-(2,5-diphenyl-2*H*-pyrazol-3-yl)-phenyl-amine (**4**) as probable substrates for the Pictet–Spengler reaction (Fig. 1). In the thiazole-based substrate **3**, an aryl amine has been allowed to originate from the C-4 position; the C-2 position has been derivatized for introducing diversity while the C-5 has been kept devoid of any substitution so as to facilitate *endo* cyclization. Similarly in the pyrazole-based substrate **4**, an aryl amine has been allowed to originate from the C-5 position, the C-3 has been derivatized for introducing diversity while the C-4 has been kept free to facilitate *endo* cyclization. Interestingly, for pyrazoles, we had two options available for the attachment of aryl amine since the C-4 involved in the cyclization is flanked between the C-5 and C-3. The arylamine can be linked to either of these two (Fig. 1) positions resulting in substrates **4** with two-point diversity and **5** with single diversity, respectively. However, in view of the higher chemical diversity, we restricted ourself to the substrate **4** since the synthesis for substrate **5** involves use of *o*-nitroacetophenone for which only a limited commercial diversity is available. In contrast, the synthesis of **4** involves use of *o*-nitrobenzaldehydes for which a plenty of diversity is available commercially. A careful survey of the literature for substrates **3** and **4** revealed, a single reference wherein an unsuccessful attempt[10] was made to synthesize thiazoloquinolines from the thiazole-based substrate **3** using Bischler–Napieralski reaction.

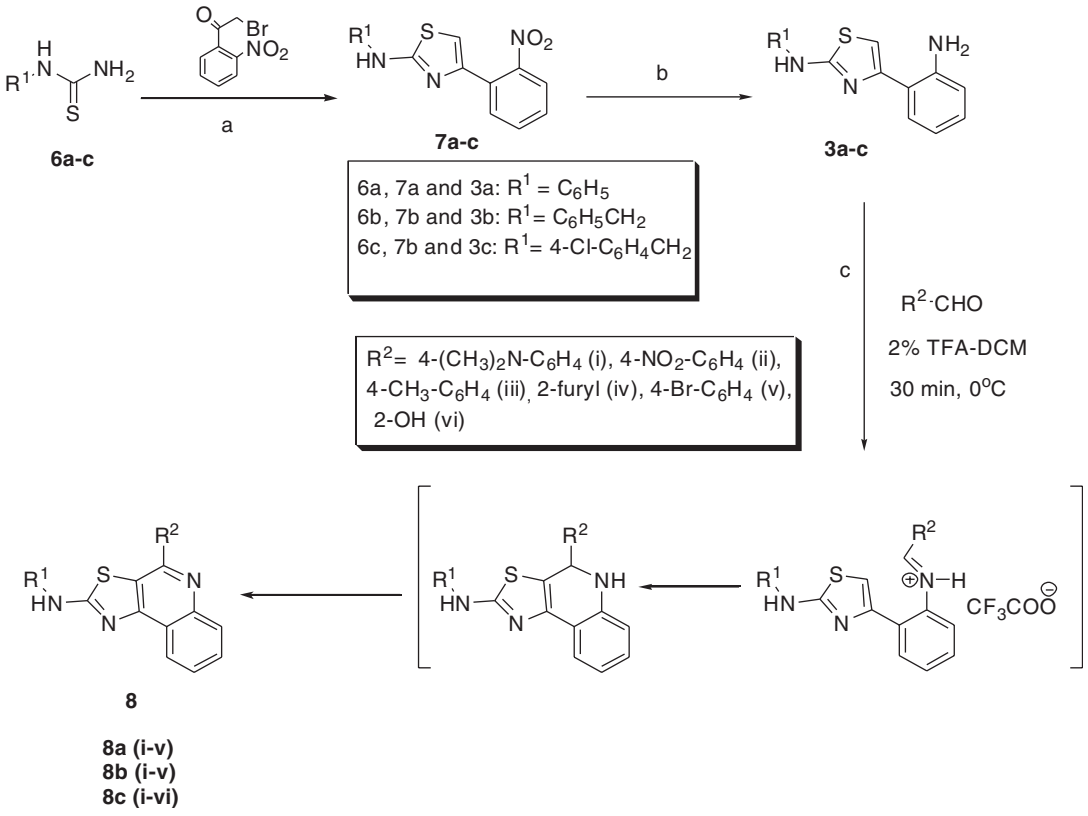
In this communication, we report application of **3** and **4** as novel substrates for the Pictet–Spengler reaction leading to the synthesis of heterocycles beyond isoquinolines and β-carbolines. Though, substrates **3** and **4** with an arylamine originating from the C-4 and C-5, respectively, differs from our previously reported imidazole based substrates **1** and **2** with arylamines originating from the *N*-1, all four of them are based on our new concept wherein arylamines are linked to an activated heterocyclic ring via carbon or nitrogen and therefore can be collectively grouped under second-generation substrates for the Pictet–Spengler reaction (Fig. 1).

Pictet–Spengler reaction on substrates **3** and **4** in the presence of aldehydes led to the synthesis of thiazolo[5,4-*c*]-quinolines (**8**) and pyrazolo[4,3-*c*]quinolines (**12**), respectively. Both of them are completely aromatized compounds and devoid of any stereochemical centers. This is in contrast to the traditional Pictet–Spengler reaction involving substrates based on aliphatic amines linked to an activated heterocyclic ring, which invariably furnishes tetrahydro-derivatives with new stereochemical centre. However, prolonged heating at reflux for 48 h under acidic conditions has been reported to produce fully aromatic compounds such as β-carboline.[2c] Literature survey for thiazolo- and pyrazolo-quinolines revealed a single reference for the synthesis of thiazolo[5,4-*c*]quinoline-2-yl-amines analogous to our compounds **8** using disubstituted thioureas and bromine.[11] Indeed, a variety of structural variants such as thiazolo[5,4-*b*]-,[12] thiazolo[4,5-*g*]-, -[5,4-*g*]-, -[4,5-*h*]-, -[5,4-*h*]-, -[4,5-*f*]- and -[5,4-*f*]-quinolines have been reported in the literature with antibacterial,[13] antispasmodics,[14] antiinflammatory[15] and antitumor activities.[16] Similarly a single reference for pyrazolo[4,3-*c*]quinoline (CGS 9896), which is analogous to our compounds **12** have been reported to exhibit nonsedating anxiolytic activity.[17] Synthesis of pyrazolo[4,3-*c*]quinolines have been generally carried out by treating *o*-chloro-derivatives of cyano quinolines with hydrazine hydrate.[18] This is in contrast to our method that involves generation of quinoline ring onto the pyrazole using the Pictet–Spengler reaction. Structural variant in the form of pyrazolo[3,4-*c*]quinoline ring systems has been reported to exhibit significant biological activities such as good affinity and selectivity for adenosine A3 receptors, benzodiazepine receptor activity and NMDA receptor inhibition.[19] Another variant, pyrazolo[3,4-*b*]quinolines has been identified as a potential candidate for the blue light electroluminescent materials.[20]

2. Results and discussion

The synthetic strategy dealing with the application of substrate **3** for the Pictet–Spengler reaction is depicted in Scheme 1. Substrate **3** can be readily obtained using Hantzsch-thiazole synthesis[21] by first treating 2-nitrophenacyl bromide with thioureas **6** followed by the reduction of the resulting [4-(2-nitro-phenyl)-thiazol-2-yl]-phenyl-amine **7** with $SnCl_2 \cdot 2H_2O$. Diversity in thioureas was introduced by derivatizing one of the NH_2' and this has been accomplished by treating aryl isothiocyanates with ammonia. For the Pictet–Spengler cyclization, the substrate **3a** was treated with *p*-*N*,*N*-dimethylbenzaldehyde under 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, neat toluene at 80 °C and with $Yb(OTF)_3$. Interestingly, *endo* cyclization resulting in thiazoloquinoline **8a**(**i**) occurred under all conditions and it took from 30 min (in 2% TFA) to 6 h (toluene) for the completion of the reaction (Table 1). The crude product (>85% based on HPLC) obtained after workup was purified by silica gel column chromatography using EtOAc/hexane as an eluent and characterized by LC–MS and NMR.

It is interesting to note that the Pictet–Spengler reaction on **3** occurred under both protic and nonacidic aprotic media, and, the C–C bond formation was found to be comparatively faster than tryptamine and Trp-OMe (generally used as substrate in the traditional Pictet–Spengler reaction) under



Scheme 1. Pictet–Spengler reaction using (2-amino-phenyl)-thiazolo-phenyl-amine (**3**); conditions: (a) MeOH, rt, 2 h; (b) $SnCl_2 \cdot 2H_2O$, MeOH, reflux, 2 h; (c) 2% TFA in DCM, 0 °C, 15 min.

similar protocols. Indeed, the rate of cyclization was found to be at par with the protocol involving highly reactive cyclic *N*-acyliminium ion strategy.[22] The elegant *N*-acyliminium strategy is known to enhance the reactivity of iminium intermediates; the only limitation is that the acyl group invariably becomes part of the final compound and needs to be removed. Cook et al. attributed electrophilicity of the imine double bond resulting from the condensation of amines with aldehydes as the limiting factor for Pictet–Spengler cyclization and applied pK_a values of amines to compare the electrophilicities of the 'imines'.[23] Thus, comparing the pK_a values of tryptamine 10.2 and Trp-OMe 7.29 with the aniline (in the absence of pK_a value available for **3**, aniline's pK_a value was taken into account) 4.2, clearly suggests that the carbon–nitrogen double bond derived from substrate **3** is highly electrophilic, for the nitrogen carries a less electron density than that found for the imines derived from Trp-OMe and tryptamine, respectively (Fig. 4).

Table 1. Optimization of reaction involving conversion of **3a** to **8a**(**i**) using *p*-*N*,*N*-dimethylbenzaldehyde under different Pictet–Spengler protocols

Entry	Conditions	Time	Product (%)[a]
1	2% TFA, DCM, 0 °C	30 min	98
2	*p*TsOH (0.1 equiv), toluene, reflux	45 min	95
3	5% AcOH in EtOH, reflux	45 min	95
4	$Yb(OTf)_3$, DCM, rt	1 h	92
5	Toluene, reflux	6 h	92

[a] Based on HPLC of crude products.

These findings suggest that the aryl amine derived substrates are likely to undergo the Pictet–Spengler reaction relatively faster than the substrate derived from aliphatic amines. The scope and limitation of our strategy was established by synthesizing 15 compounds based on thiazoloquinolines **8** by using three thiazole substrates based on **3** and five aromatic aldehydes. For the Pictet–Spengler cyclization 2% TFA–DCM protocol was used. Purities of the crude products were typically in the excess of 85% based on HPLC analysis and substitutions on either **3** or aldehydes had no affect on the rate and yield of the *endo* cyclized product. We were especially pleased to see that aldehydes with electron-donating group had no adverse effect on the rate of cyclization. This is in contrast to the typical Pictet–Spengler reaction where aldehydes with electron withdrawing group had favorable affects on *endo* cyclization while aldehydes with electron donating substituent such as salicylaldehyde produced imine as the only product when treated with Trp-OMe. Cook et al. circumvented this problem by using N_b-benzyl Trp-OMe that furnished an iminium ion intermediate with enhanced electrophilicity than the imine obtained from the Trp-OMe and in turn facilitated *endo* cyclization. Condensation of substrate **3c** with salicylaldehyde furnished thiazoloquinoline **8c**(**vi**) in 78% isolated yield. We believe that in the substrate **3**, the imine intermediate derived from the aldehydes with electron donating group is relatively more electrophilic than the imine derived from the Trp-OMe using the same aldehyde since the pK_a value of aryl amine (4.2 for aniline) is significantly less than that of Trp-OMe (7.29).

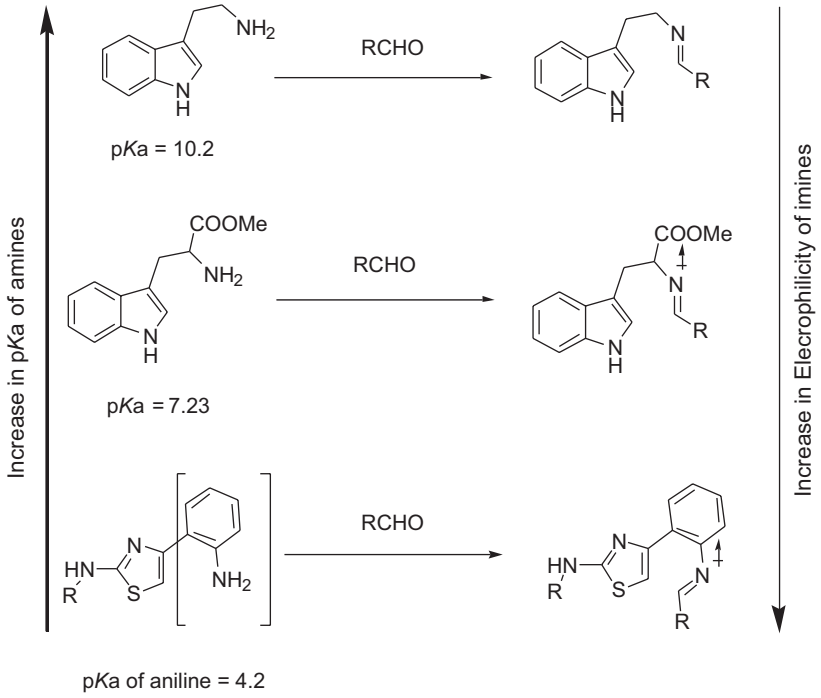


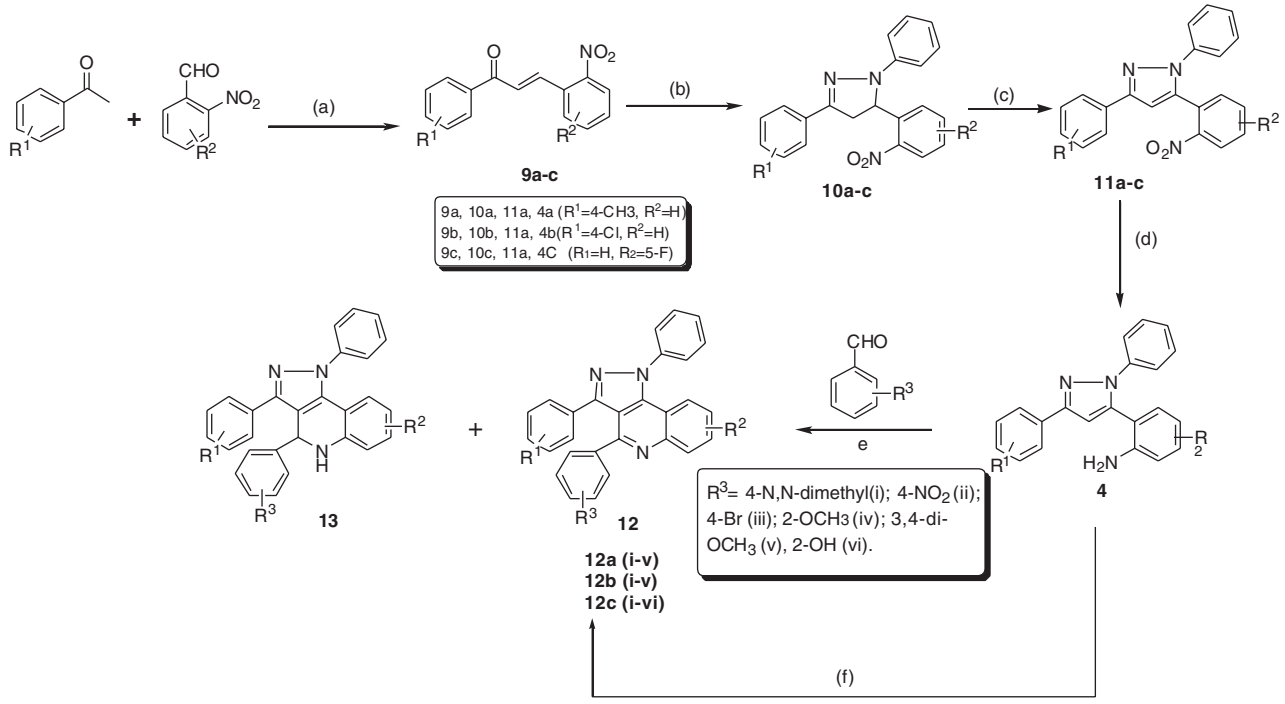
Figure 4. pK_a of amines versus electrophilicity of imines.

Results of the analytical data of thiazoloquinoline derivatives **8** are summarized in Table 2.

The synthetic strategy for pyrazoloquinolines from substrate **4** is depicted in Scheme 2. Out of the variety of regioselective methods reported for dihydropyrazoles (pyrazolines) or pyrazoles, we decided to synthesize dihydropyrazoles from enones in the first instance followed by oxidation to give the desired pyrazole substrate **4**. Surprisingly, our initial attempts to prepare chalcones from *o*-nitrobenzaldehyde and acetophenones using KOH/EtOH as general procedure were not successful. Though, $BF_3\cdot$ AcOH has been reported for the synthesis of chalcones from *o*-nitrobenzaldehyde by stirring it with acetophenone for 5 days,[24] we decided to use ammonium acetate instead and were pleased to see the formation of chalcones in 60% yield after being refluxed in toluene for only 7 h. For the synthesis of regioselective dihydropyrazoles, we treated chalcones (enones) with *N*-phenylhydrazine as described earlier by Powers et al.[25] The authors established the regioselectivity by X-ray analysis of the dihydropyrazoles. Chalcones (enones) **9** derived from acetophenone and *o*-nitrobenzaldehydes were reacted with *N*-phenylhydrazine to give dihydropyrazoles **10**. As expected, the reaction furnished a single pyrazolines regiomer; no product of the alternative regiochemistry of addition was detected. The structure was confirmed by ^{1}H NMR, which showed the presence of three alkyl protons with appropriate geminal and vicinal constants. Next, dihydropyrazoles **10**, which are quite stable and do not suffer from aerial oxidation upon storage, were oxidized to pyrazoles **11** using DDQ. The resulting C-5 linked aryl nitro in **11** was then reduced to NH_2 functionality via catalytic hydrogenation to give substrate **4**. Finally, **4** was subjected to Pictet–Spengler reaction by treating it with *2*-methoxybenzaldehyde in the presence *p*TsOH in toluene at reflux for 18–20 h. As evident by both

Table 2. Syntheses of thiazoloquinolines **8**

Product	R^1	R^2	Isolated yield (%)
8a(i)	C_6H_5	4-$(CH_3)_2NC_6H_4$	83
8a(ii)	C_6H_5	4-$NO_2C_6H_4$	80
8a(iii)	C_6H_5	4-$CH_3C_6H_4$	82
8a(iv)	C_6H_5	2-C_4H_3O	85
8a(v)	C_6H_5	4-BrC_6H_4	76
8b(i)	C_6H_5–CH_2	4-$(CH_3)_2NC_6H_4$	81
8b(ii)	C_6H_5–CH_2	4-$NO_2C_6H_4$	79
8b(iii)	C_6H_5–CH_2	4-$CH_3C_6H_4$	85
8b(iv)	C_6H_5–CH_2	2-C_4H_3O	83
8b(v)	C_6H_5–CH_2	4-BrC_6H_4	78
8c(i)	4-Cl–$C_6H_4CH_2$	4-$(CH_3)_2NC_6H_4$	80
8c(ii)	4-Cl–$C_6H_4CH_2$	4-$NO_2C_6H_4$	77
8c(iii)	4-Cl–$C_6H_4CH_2$	4-$CH_3C_6H_4$	81
8c(iv)	4-Cl–$C_6H_4CH_2$	2-C_4H_3O	83
8c(v)	4-Cl–$C_6H_4CH_2$	4-BrC_6H_4	75
8c(vi)	4-Cl–$C_6H_4CH_2$	2-OH	78



Scheme 2. Pictet–Spengler reaction using 2-(2,5-diphenyl-2*H*-pyrazol-3-yl)-phenylamine (**4**); conditions: (a) NH_4OAc, toluene, reflux, 7 h; (b) phenyl hydrazine, EtOH, reflux 7 h; (c) DDQ, DCM–THF (1/1), rt, 4 h; (d) $SnCl_2 \cdot 2H_2O$, EtOH, reflux, 1.5 h; (e) *p*-TsOH, toluene, reflux, 4 h; (f) *p*-TsOH, toluene reflux 4 h and DDQ, DCM–THF (1/1), rt, 2 h.

HPLC and TLC, the crude product was found to be a mixture of two components with a major spot ~85% and minor <10%. The two spots were separated by column chromatography using 10–30% EtOAc–hexane as mobile phase and characterized by ESMS and NMR. One of the components with lower R_f on TLC was found to be the dihydropyrazoloquinolines **13** and the second component with higher R_f was pyrazoloquinolines **12**, an oxidized product of the first component. The former had a moderate stability, as even after purification it had a tendency to undergo slow oxidation to **12**. Such an oxidation for dihydroimidazoquinoxaline to imine has been reported earlier by us and TenBrink et al.[26]

In order to synthesize **12** as the only product, we treated **4a** with 2-methoxybenzaldehyde by applying other traditionally used Pictet–Spengler protocols involving 2% TFA in DCM at 0 °C, AcOH in ethanol at reflux, and toluene at 80 °C (Table 3). All protocols except toluene at 80 °C, where schiff base was the only isolated product (Table 3), were accompanied with the formation of the **13**. This led us to add an oxidizing agent after the Pictet–Spengler reaction so as to convert the remaining **13** into **12**. Thus, after the Pictet–Spengler reaction of the substrate **4** with an aldehyde, the resulting crude product was treated with DDQ to give **12** as the only product. The scope and limitation of our strategy was examined by utilizing three 3,5 disubstituted pyrazoles and five aldehydes. In all cases, the title compounds were obtained in excellent yields (75–82%) and aldehydes with electron-donating group had no adverse effect on the rate of cyclization. Condensation of salicylaldehyde having electron donating substituent with **4c** furnished pyrazoloquinoline **12c**(**vi**) (Table 5) in 75% yield. A comparative profile of the Pictet–Spengler reaction of aliphatic and aryl amine based substrates with salicylaldehyde has been depicted in Table 4. It is thus clear that substrates with aryl amine attached directly to either C or N of the heterocyclic ring readily underwent Pictet–Spengler cyclization with aldehydes bearing electron donating groups whereas substrates derived either from aliphatic amine (Trp-OMe) or even from aryl amine not directly linked to the heterocycle (**2**) failed to undergo cyclization. The structure of 16 compounds based on **12** has been summarized in Table 5.

Table 3. Ratio of pyrazoloquinoline **12** and its dihydro-derivative **13** formed during the Pictet–Spengler reaction of **4a** with *2*-methoxybenzaldehyde

Entry	Conditions	**12** (%)[a]	**13** (%)[a]	Time
1	2% TFA, DCM, 0°	20	80	2 h
2	*p*TsOH (0.1 equiv), toluene, reflux	80	8	5 h
3	5% AcOH in EtOH, reflux	40	60	8 h
4	Toluene, reflux[b]	—	—	20 h
5	(i) *p*TsOH (0.1 equiv), toluene, reflux, (ii) DDQ	89	—	4 and 2 h

[a] Based on HPLC of crude reaction product.
[b] Schiff base was isolated as the only product.

Though both the substrates **3** and **4** successfully underwent Pictet–Spengler cyclization, however, when compared with the *N*-linked aryl amine substrates **1** and **2** described earlier, we observed that C-linked aryl amine substrates **3** and **4** underwent Pictet–Spengler cyclization faster than **1** and **2**. This may be attributed to the relative decrease in the pK_a value of the aryl amine linked to the C-4 and C-5 in **3** and **4**, respectively, which are the already deactivated positions due to the multiply bonded *N*-atom than the pK_a value of aryl amine linked to the nitrogen, which behaves as an electron donor.

Table 4. Comparative profile of substrates undergoing Pictet–Spengler cyclization with salicylaldehyde

Substrate	Reaction condition	Cyclized product	Yield (%)	Ref.
1	Toluene, 80 °C, 48 h	Imidazoquinoxalines	73	6a
2	*p*-TsOH, toluene, 125 °C, 18 h	No product[a]	—	6b
3	2% TFA–DCM	Thiazoloquinoline	78	—
4	*p*-TsOH, toluene, reflux, 5 h	Pyrazoloquinoline	75	—
Trp-OMe	*p*-TsOH, toluene, reflux	Tetrahydro-β-carboline	5	22
Trp-OMe	Toluene, reflux	No product[a]	—	22

[a] Imine was isolated as the only product.

Table 5. Synthesis of pyrazoloquinolines **12**

Product	R^1	R^2	R^3	Isolated yield (%)
12a(i)	4-CH_3	H	4-$(CH_3)_2N$	79
12a(ii)	4-CH_3	H	4-NO_2	75
12a(iii)	4-CH_3	H	4-Br	76
12a(iv)	4-CH_3	H	2-OCH_3	82
12a(v)	4-CH_3	H	3,4-Di-OCH_3	80
12b(i)	4-Cl	H	4-$(CH_3)_2N$	82
12b(ii)	4-Cl	H	4-NO_2	80
12b(iii)	4-Cl	H	4-Br	76
12b(iv)	4-Cl	H	2-OCH_3	79
12b(v)	4-Cl	H	3,4-Di-OCH_3	82
12c(i)	H	5-F	4-$(CH_3)_2N$	80
12c(ii)	H	5-F	4-NO_2	75
12c(iii)	H	5-F	4-Br	77
12c(iv)	H	5-F	2-OCH_3	79
12c(v)	H	5-F	3,4-Di-OCH_3	80
12c(vi)	4-CH_3	H	2-OH	75

3. Conclusion

In summary, we have identified new thiazole and pyrazole derived substrates for the Pictet–Spengler reaction, which is based on our concept of 'arylamine attached to an activated heterocyclic ring'. This in turn will set the stage for a wide application of this powerful reaction and can be used for the synthesis of novel polyheterocyclic skeletons based on privileged structures. Currently work is in progress in our lab with several second-generation substrates designed on the basis of our new concept for the Pictet–Spengler reaction and will be reported soon.

4. Experimental

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 (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) are determined with complete proton decoupling and reported in ppm. All spectra were recorded at 25 °C Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL III microanalyzer. Analytical HPLC were performed on C-18 reverse-phase column (250 mm×4.6 mm). Mass spectra were recorded on a Merck MS-8000 spectrometer. Phenylisothiocyanates, aldehydes, and *o*-nitrophenacylbromide, tin chloride dihydrate etc were purchased from Aldrich and Lancaster. The LC–Ms profile of selected compounds were generated using High Throughput LC–MS (Lachrom MS- 8000) using a 5 μ, 10×50 mm C-18 Reverse Phase Column with a Linear gradient 10–100% methanol–water v/v with 0.1% formic acid over 12 min with a flow rate of 6 mL/min. Melting points reported were uncorrected.

4.1. General method for the preparation of (2-nitro-phenyl)-thiazolo-phenyl-amine (7)

2-Nitro phenacyl bromide (0.50 g, 2.05 mmol) was added to a solution of **6a** (0.31 g, 2.05 mmol) in methanol (5 mL). The reaction mixture was stirred for 2 h. The reaction mixture was evaporated and digested with water and then extracted with ethyl acetate. The organic phase was washed with a saturated solution of sodium bicarbonate (100 mL) followed by brine (50 mL), dried over sodium sulfate and evaporated to dryness under reduced pressure to obtained a crude solid, which was further purified by recrystallization in ethanol to afford **7a** as a yellow solid.

4.1.1. [4-(2-Nitro-phenyl)-thiazol-2-yl]-phenyl-amine (7a). Yield 95%; yellow solid; mp 162–164 °C; IR (KBr) ν_{max} 1599, 1528, 1334, ^{1}H NMR (300 MHz, DMSO) δ=10.27 (s, 1H, NH), 7.86 (t, 2H, ArH), 7.76 (t, 1H, ArH), 7.56 (t, 3H, ArH), 7.34 (s, 1H, thiazole H), 7.28 (t, 2H, J=8.1 Hz, ArH), 6.95 (t, 1H, J=7.2 Hz, ArH); ^{13}C NMR (50 MHz, DMSO) δ=170.6, 163.4, 149.2, 146.1, 141.2, 132.3, 130.2, 129.2, 128.1, 124.7, 123.9, 122.3, 121.7, 117.1, 107.3; mass (ES^+) m/z 298 (M^++1). Anal. Calcd for $C_{15}H_{11}N_3O_2S$: C, 60.59; H, 3.73; N, 14.13. Found: C, 60.69; H, 3.53; N, 14.50.

4.1.2. Benzyl-[4-(2-nitro-phenyl)-thiazol-2-yl]-amine (7b). Yield 98%; solid, mp 152–154 °C; IR (KBr) ν_{max} 3382, 2832, 2719, 1589, 1366; ^{1}H NMR (300 MHz, DMSO) δ=8.18 (t, 1H, J=5.7 Hz, NH), 7.76 (d, 2H, J=8.1 Hz, ArH), 7.64 (t, 1H, J=7.65 Hz, ArH), 7.52 (t, 1H, J=7.8 Hz, ArH), 7.29 (m, 5H, ArH), 7.01 (s, 1H, thiazole H), 4.38 (d, 2H, J=5.7 Hz, CH_2); ^{13}C NMR (75 MHz, DMSO) δ=168.2, 148.8, 145.6, 139.1, 131.9, 129.9, 128.6, 128.3, 128.2, 127.7, 127.0, 123.5, 105.0, 47.7; mass (ES^+) m/z 312 (M^++1). Anal. Calcd for $C_{16}H_{13}N_3O_2S$: C, 61.72; H, 4.21; N, 13.50. Found: C, 61.68; H, 4.35; N, 13.45.

4.1.3. (4-Chloro-benzyl)-[4-(2-nitro-phenyl)-thiazol-2-yl]-amine (7c). Yield 96%; oil; IR (neat) ν_{max} 3377, 2928, 2853, 1590, 1363; ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.21

(t, 1H, $J=5.25$ Hz, NH), 7.74 (d, 2H, $J=7.8$ Hz, ArH), 7.64 (t, 1H, $J=7.5$ Hz, ArH), 7.51 (t, 1H, $J=7.65$ Hz, ArH), 7.35 (m, 4H, ArH), 7.02 (s, 1H, thiazole H), 4.36 (d, 2H, $J=5.4$ Hz, CH_2); ^{13}C NMR (75 MHz, DMSO) $\delta=168.4$, 149.2, 145.2, 138.6, 132.2, 131.9, 130.26, 129.8, 129.0, 128.6, 123.8, 105.5, 47.3; mass (ES^+) m/z 346 (M^++1). Anal. Calcd for $C_{16}H_{12}ClN_3O_2S$: C, 55.57; H, 3.50; N, 12.15. Found: C, 55.79; H, 3.53; N, 12.20.

4.2. General method for the preparation of (2-amino-phenyl)-thiazolo-phenyl-amine (3)

Tin (II) chloride dihydrate (2.28 g, 10.13 mmol) was added to a solution of **7a** (0.60 g, 2.03 mmol) in ethanol (15 mL) at 80 °C. The reaction mixture was stirred for 2 h and then poured in cold water and basified with 5% sodium bicarbonate (pH 8). The mixture was extracted with ethyl acetate, washed with brine (100 mL), dried over sodium sulfate, and evaporated to dryness under reduced pressure to afford a crude material, which was purified on a silica gel column using hexane–ethyl acetate (70/30, v/v) as eluent to afford **3a** as an oil.

4.2.1. (Amino-phenyl)-thiazol-2-yl]-phenyl-amine (3a). Yield 96%; oil; IR (neat) ν_{max} 3450 (br, NH), 1593; ^1H NMR (300 MHz, DMSO) $\delta=10.26$ (s, 1H, NH), 7.56 (d, 2H, $J=7.8$ Hz, ArH), 7.45 (d, 1H, $J=7.5$ Hz, ArH), 7.32 (t, 2H, $J=7.5$ Hz, ArH), 6.98 (m, 2H, ArH), 6.71 (d, 1H, $J=8.1$ Hz, ArH), 6.57 (t, 1H, $J=7.5$ Hz, ArH), 5.92 (s, 2H, CH_2), ^{13}C NMR (50 MHz, DMSO) $\delta=163.3$, 150.7, 146.3, 141.4, 130.1, 129.4, 128.9, 128.6, 121.8, 118.3, 117.3, 116.5, 108.8, 103.1; mass (ES^+) m/z 268.32 (M^++1). Anal. Calcd for $C_{15}H_{13}N_3S$: C, 67.39; H, 4.90; N, 15.72. Found: C, 67.49; H, 4.73; N, 15.53.

4.2.2. [4-(2-Amino-phenyl)-thiazol-2-yl]-benzyl-amine (3b). Yield 95%; oil; IR (neat) ν_{max} 3450 (br, NH), 2836, 2700, 1592; ^1H NMR (300 MHz, $CDCl_3$) $\delta=7.41$–7.33 (m (o), 6H, ArH), 7.09 (t, 1H, $J=7.8$ Hz, ArH), 6.69 (t, 1H, $J=8.25$ Hz, ArH), 6.58 (s, 1H, thiazole H), 5.47 (br s, 1H, NH), 4.52 (d, 2H, $J=6.0$ Hz, CH_2); mass (ES^+) m/z 282 (M^++1). Anal. Calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.32; H, 5.51; N, 14.84.

4.2.3. [4-(2-Amino-phenyl)-thiazol-2-yl]-(4-chloro-benzyl)-amine (3c). Yield 96%; white solid; mp 182–184 °C; IR (KBr) ν_{max} 3420 (br, NH), 2920, 2860, 1598; ^1H NMR (300 MHz, DMSO) $\delta=8.27$ (t, 1H, $J=5.4$ Hz, NH), 7.36 (m, 5H, ArH), 6.96 (t, 1H, $J=7.35$ Hz, ArH), 6.75 (s, 1H, thiazole H), 6.64 (d, 1H, $J=7.8$ Hz, ArH), 6.51 (t, 1H, $J=7.35$ Hz, ArH), 5.86 (br s, 2H, NH_2), 4.45 (d, 2H, $J=5.7$ Hz, CH_2); ^{13}C NMR (50 MHz, DMSO) $\delta=168.7$, 150.8, 146.3, 138.7, 131.8, 129.5, 128.67, 128.2, 118.3, 116.3, 116.1, 101.1, 101.2, 47.4; mass (ES^+) m/z 316 (M^++1). Anal. Calcd for $C_{16}H_{14}ClN_3S$: C, 60.85; H, 4.47; N, 13.31. Found: C, 60.77; H, 4.51; N, 13.50.

4.3. General procedure for the Pictet–Spengler reaction on substrate 3

A mixture of **3a** (0.10 g, 0.39 mmol) and *p*-*N*,*N*-dimethyl-aminobenzaldehyde (0.058 g, 0.39 mmol) in DCM (2 mL) was treated with 2% TFA in DCM. The completion of Pictet–Spengler cyclization was monitored by TLC. After 30 min, the reaction mixture was evaporated, and the residue so obtained was triturated with 5% $NaHCO_3$. It was then extracted with EtOAc, washed with brine (10 mL), and dried over sodium sulfate. EtOAC was evaporated to dryness under reduced pressure and the crude obtained was purified by column chromatography to afford **8a(i)** as a white solid.

4.3.1. [4-(4-Dimethylamino-phenyl)-thiazolo [5,4-*c*] quinolin-2-yl]-phenyl-amine [8a(i)]. Yield 83%; white solid, mp 218–220 °C; IR (KBr) ν_{max} 3246 (br, NH), 2923, 2830, 1478, 1400, 1355 cm^{-1}; ^1H NMR (300 MHz, DMSO): $\delta=11.05$ (s, NH), 8.48 (d, $J=7.8$ Hz, 1H), 8.04 (d, $J=8.4$ Hz, 1H), 7.99 (d, $J=7.8$ Hz, 2H), 7.91 (d, $J=7.8$ Hz, 2H), 7.73 (t, $J=7.35$ Hz, 1H), 7.61 (t, $J=7.5$ Hz, 1H), 7.47 (t, $J=7.2$ Hz, 2H), 7.13 (t, $J=7.23$ Hz, 1H), 6.90 (t, $J=8.1$ Hz, 2H), 3.02 (s, 6H); ^{13}C NMR (75 MHz, DMSO) $\delta=166.0$, 154.8, 150.9, 150.8, 146.2, 139.9, 129.0, 128.6, 126.4, 125.1, 123.1, 122.7, 120.1, 118.2, 112.3, 111.4, 39.8; mass (ES^+) m/z 397 (M^++1). Anal. Calcd for $C_{24}H_{20}N_4S$: C, 72.70; H, 5.08; N, 14.33. Found: C, 72.68; H, 5.10; N, 14.30.

4.3.2. [4-(4-Nitro-phenyl)-thiazolo [5,4-*c*]quinolin-2-yl]-phenyl-amine [8a(ii)]. Yield 80%; yellow solid, mp 234–236 °C; IR (KBr) ν_{max} 3366 (br, NH), 1602, 1454, 1402, 1344; ^1H NMR (300 MHz, DMSO), $\delta=11.20$ (s, 1H, NH), 8.53 (d, 1H, $J=7.8$ Hz, ArH), 8.46 (d, 2H, $J=8.4$ Hz, ArH), 8.32 (d, 2H, $J=8.4$ Hz, ArH), 8.13 (d, 1H, $J=8.1$ Hz, ArH), 7.89 (d, 2H, $J=7.8$ Hz, ArH), 7.80 (t, 1H, $J=7.35$ Hz, ArH), 7.72 (t, 1H, $J=7.35$ Hz, ArH), 7.47 (t, 2H, $J=7.80$ Hz, ArH), 7.15 (t, 1H, $J=7.35$ Hz, ArH); ^{13}C NMR (75 MHz, DMSO d_6), $\delta=166.3$, 155.8, 148.4, 147.8, 146.2, 145.4, 139.9, 129.3, 129.0, 126.8, 123.9, 123.6, 123.3, 120.7, 119.6, 118.6; mass (ES^+) m/z 399 (M^++1). Anal. Calcd for $C_{22}H_{14}N_4O_2S$: C, 66.32; H, 3.54; N, 14.06. Found: C, 66.31; H, 3.55; N, 14.10.

4.3.3. Phenyl-(4-*p*-tolyl-thiazolo [5,4-*c*]quinolin-2-yl)-amine [8a(iii)]. Yield 82%; white solid, mp 128–130 °C; IR (KBr) ν_{max} 3196 (br, NH), 2931, 2835, 1591, 1493, 1363; ^1H NMR (300 MHz, $CDCl_3$), $\delta=8.5$ (d, 1H, $J=8.1$ Hz, ArH), 8.20 (d, 1H, $J=8.4$ Hz, ArH), 7.95 (d, 3H, $J=7.8$ Hz, overlapped with NH, ArH), 7.72 (t, 1H, $J=7.65$ Hz, ArH), 7.58 (m, 3H, ArH), 7.44 (t, 2H, $J=7.8$ Hz, ArH), 7.35 (d, 2H, $J=7.8$ Hz, ArH), 7.22 (t, 1H, $J=7.5$ Hz, ArH), 2.44 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ 155.3, 152.4, 147.0, 139.6, 139.4, 137.3, 129.6, 129.6, 129.0, 128.0, 125.9, 124.7, 123.7, 121.2, 120.2, 21.4; mass (ES^+) m/z 368 (M^++1). Anal. Calcd for $C_{23}H_{17}N_3S$: C, 75.18; H, 4.66; N, 11.44. Found: C, 75.15; H, 4.65; N, 11.45.

4.3.4. (4-Furan-2-yl-thiazolo [5,4-*c*]quinolin-2-yl)-phenyl-amine [8a(iv)]. Yield 85%; white solid, >250 °C; IR (KBr) ν_{max} 3264 (br, NH), 1607, 1472, 1406, 1347. Anal. ^1H NMR (300 MHz, DMSO), $\delta=11.13$ (s, NH), 8.51 (d, 1H, $J=8.1$ Hz, ArH), 8.04 (d, 2H, $J=8.4$ Hz, ArH), 7.92 (d, 2H, $J=8.1$ Hz, ArH), 7.75 (t, 1H, $J=7.5$ Hz, ArH), 7.64 (t, 1H, $J=7.5$ Hz, ArH), 7.48 (t, 2H, $J=7.5$ Hz, ArH), 7.41 (d, 1H, $J=3$ Hz, ArH); ^{13}C NMR (75 MHz, DMSO), $\delta=$ 167.9, 155.9, 152.7, 146.3, 145.3, 147.0, 140.4, 129.6,

128.9, 126.3, 123.8, 123.5, 121.0, 119.0, 116.8, 113.2, 111.1; mass (ES^+) m/z 344 ($M^+ + 1$). Anal. Calcd for $C_{20}H_{13}N_3OS$: C, 69.95; H, 3.82; N, 12.24. Found: C, 69.94; H, 3.81; N, 12.25.

4.3.5. [4-(4-Bromo-phenyl)-thiazolo[5,4-*c*]quinolin-2-yl]-phenyl-amine [8a(v)]. Yield 76%; yellow solid, mp 184–186 °C; IR (KBr) ν_{max} 3288 (br, NH), 1601, 1476, 1406, 1361; ^1H NMR (300 MHz, DMSO), $\delta = 11.16$ (br s, 1H, NH), 8.52 (d, 1H, $J = 7.8$ Hz, ArH), 8.13 (d, 1H, $J = 8.4$ Hz, ArH), 8.03 (d, 2H, $J = 7.2$ Hz, ArH), 7.83 (m, 5H, ArH), 7.70 (t, 1H, $J = 7.2$ Hz, ArH), 7.468 (t, 2H, $J = 7.05$ Hz, ArH), 7.14 (t, 1H, $J = 7.05$ Hz, ArH); ^{13}C NMR (75 MHz, DMSO), δ 166.3, 155.5, 149.7, 146.3, 140.0, 138.8, 131.8, 129.8, 129.0, 126.6, 123.3, 123.2, 120.6, 119.4, 118.6; mass (ES^+) m/z 433 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{14}BrN_3S$: C, 61.12; H, 3.26; N, 9.72. Found: C, 61.10; H, 3.25; N, 9.73.

4.3.6. Benzyl-[4-(4-dimethylamino-phenyl)-thiazolo[5,4-*c*]quinolin-2-yl]-amine [8b(i)]. Yield 81%; pink solid, mp 160–162 °C; IR (KBr) ν_{max} 3209 (br, NH), 2929, 2831, 1599, 1365; ^1H NMR (300 MHz, DMSO), $\delta = 10.20$ (s, NH), 8.48 (d, 1H, $J = 7.8$ Hz, ArH), 8.16 (d, 1H, $J = 8.4$ Hz, ArH), 7.94 (t, 1H, $J = 7.5$ Hz, ArH), 7.85 (d, 2H, $J = 8.4$ Hz, ArH), 7.76 (t, 1H, $J = 7.35$ Hz, ArH), 7.39 (m, 5H, ArH), 6.97 (d, 2H, $J = 8.4$ Hz, ArH), 4.84 (s, 2H, CH_2), 3.08 (s, 6H, $2CH_3$); ^{13}C NMR (50 MHz, DMSO), $\delta = 167.0$, 161.3, 153.6, 148.2, 138.4, 133.2, 130.8, 129.4, 128.6, 128.5, 127.8, 125.2, 120.4, 119.0, 117.8, 112.4, 47.8; mass (ES^+) m/z 411 ($M^+ + 1$). Anal. Calcd for $C_{25}H_{22}N_4S$: C, 73.14; H, 5.40; N, 13.65. Found: C, 73.16; H, 5.38; N, 13.59.

4.3.7. Benzyl-[4-(4-nitro-phenyl)-thiazolo[5,4-*c*]-quinolin-2-yl]-amine [8b(ii)]. Yield 79%; white solid, mp 205–207 °C; IR (KBr) ν_{max} 3403 (br, NH), 2924, 2834, 1630, 1569, 1532, 1475, 1403, 1349; ^1H NMR (300 MHz, DMSO), 9.41 (br s, 1H, NH), 8.43 (t, 3H, $J = 7.5$ Hz, ArH), 8.28 (d, 1H, $J = 8.7$ Hz, ArH), 8.08 (d, 1H, $J = 8.4$ Hz, ArH), 7.75 (t, 1H, $J = 7.5$ Hz, ArH) 7.64 (t, 1H, $J = 7.4$ Hz, ArH), 7.47 (d, 2H, $J = 7.2$ Hz, ArH), 7.38 (t, 2H, $J = 7.4$ Hz, ArH), 7.28 (d, 1H, $J = 7.2$ Hz, ArH), 4.77 (d, 2H, $J = 5.1$ Hz, CH_2); ^{13}C NMR (50 MHz, DMSO), δ 170.8, 156.3, 153.3, 148.5, 147.7, 146.3, 145.6, 138.1, 129.1, 129.0, 128.5, 127.7, 127.4, 126.4, 124.0, 123.6, 120.6, 119.8, 47.8; mass (ES^+) m/z 413 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{16}N_4O_2S$: C, 66.97; H, 3.91; N, 13.58. Found: C, 66.98; H, 3.90; N, 13.59.

4.3.8. Benzyl-(4-*p*-tolyl-thiazolo[5,4-*c*]quinolin-2-yl)-amine [8b(iii)]. Yield 85%; white solid, mp 162–164 °C; IR (KBr) ν_{max} 3202, (br, NH), 2925, 2834, 1629, 1585, 1405, 1355; ^1H NMR (300 MHz, DMSO), $\delta = 9.30$ (br s, 1H, NH), 8.38 (d, 1H, $J = 7.8$ Hz, ArH), 8.03 (d, 1H, $J = 8.1$ Hz, ArH), 7.92 (d, 2H, $J = 7.2$ Hz, ArH), 7.69 (t, 1H, ArH), 7.59 (t, 1H, ArH), 7.36 (m, 7H, ArH), 4.75 (s, 2H, CH_2), 2.41 (s, 3H, CH_3; ^{13}C NMR (50 MHz, DMSO), $\delta =$ 167.2, 160.0, 144.6, 142.6, 141.2, 134.0, 133.2, 131.9, 130.5, 129.8, 129.4, 129.0, 128.6, 127.9, 127.5, 127.4, 125.7, 122.4, 118.6, 117.7, 117.0, 114.6, 55.4, 51.6, 48.4, 34.0; mass (ES^+) m/z 382 ($M^+ + 1$). Anal. Calcd for $C_{24}H_{19}N_3S$: C, 75.56; H, 5.02; N, 11.01. Found: C, 75.56; H, 5.03; N, 11.00.

4.3.9. Benzyl-(4-furan-2-yl-thiazolo[5,4-*c*]quinolin-2-yl)-amine [8b(iv)]. Yield 83%; solid, mp 180–182 °C; IR (KBr) ν_{max} 3202 (br, NH), 2930, 2832, 1592, 1489, 1364; ^1H NMR (300 MHz, DMSO), $\delta = 7.67$ (d, 1H, $J = 8.1$ Hz, ArH), 7.23 (d, 2H, $J = 8.4$ Hz, ArH), 7.02 (s, 1H, ArH), 6.88 (t, 1H, $J =$ 7.2 Hz, ArH), 6.72 (m, 3H, ArH), 6.57–6.48 [m (o), 5H, ArH), 5.92 (s, 2H, CH_2); mass (ES^+) m/z 358 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{15}N_3OS$: C, 70.57; H, 4.23; N, 11.76. Found: C, 70.59; H, 4.55; N, 11.45.

4.3.10. Benzyl-[4-(4-bromo-phenyl)-thiazolo[5,4-*c*]-quinolin-2-yl]-amine [8b(v)]. Yield 78%; white solid, mp 175–178 °C; IR (KBr) ν_{max} 3170 (br, NH), 2963, 2833, 1629, 1590, 1352; ^1H NMR (300 MHz, DMSO), $\delta = 7.67$ (d, 1H, $J = 7.8$ Hz, ArH), 7.24 (d, 1H, $J = 8.7$ Hz, ArH), 7.05 (d, 2H, $J = 8.4$ Hz, ArH), 6.91 (t, 3H, $J = 8.4$ Hz, ArH), 6.77 (t, 1H, $J = 7.5$ Hz, ArH), 6.66 (d, 2H, $J = 7.2$ Hz, ArH), 6.55 (t, 2H, $J = 7.2$ Hz, ArH), 6.48 (d, 1H, $J = 7.2$ Hz, ArH), 3.97 (s, 2H,CH_2); ^{13}C NMR (50 MHz, DMSO), $\delta = 156.4$, 146.5, 138.2, 131.7, 129.8, 128.9, 128.6, 128.5, 127.7, 127.3, 125.9, 123.7, 123.2, 120.8, 119.9, 47.6; mass (ES^+) m/z 447 ($M^+ + 1$). Anal. Calcd for. $C_{23}H_{16}BrN_3S$. C, 61.89; H, 3.61; N, 9.41. Found: C, 61.90; H, 3.69; N, 9.42.

4.3.11. (4-Chloro-benzyl)-[4-(4-dimethylamino-phenyl)-thiazolo[5,4-*c*]quinolin-2-yl]-amine [8c(i)]. Yield 80%; white solid, mp 134–136 °C; IR (KBr) ν_{max} 3383 (br, NH), 2925, 2833, 1629, 1589, 1360; ^1H NMR (300 MHz, DMSO), $\delta = 10.26$ (br s, 1H, NH), 8.44 (d, 1H, $J = 9$ Hz, ArH), 8.16 (d, 1H, $J = 9$ Hz, ArH), 7.92 (t, 1H, $J = 7.35$ Hz, ArH), 7.84 (d, 2H, $J = 8.7$ Hz, ArH), 7.73 (t, 1H, $J =$ 7.35 Hz, ArH), 7.47 (q, 4H, ArH), 6.95 (d, 2H, $J = 8.7$ Hz, ArH), 4.82 (s, 2H, CH_2), 3.07 (s, 6H, $2 \times CH_3$); ^{13}C NMR (50 MHz, DMSO), $\delta = 160.0$, 152.9, 148.3, 139.1, 136.7, 132.5, 130.4, 130.08, 128.9, 127.3, 124.7, 121.4, 120.0, 118.7, 112.1, 47.7, 40.0; mass (ES^+) m/z 445 ($M^+ + 1$). Anal. Calcd for $C_{25}H_{21}ClN_4S$: C, 67.48; H, 4.76; N, 12.59. Found: C, 67.49; H, 4.74; N, 12.58.

4.3.12. (4-Chloro-benzyl)-[4-(4-nitro-phenyl)-thiazolo[5,4-*c*]quinolin-2-yl]-amine [8c(ii)]. Yield 77%; white solid, mp 220–222 °C; IR (KBr) ν_{max} 3320 (br, NH), 2963, 2833, 1629, 1590, 1352; ^1H NMR (300 MHz, DMSO), $\delta = 9.44$ (s, 1H, NH), 8.43 (t, 3H, ArH), 8.28 (d, 2H, $J = 8.1$ Hz, ArH), 8.08 (d, 1H, $J = 8.1$ Hz, ArH), 7.76 (t, 1H, $J = 7.35$ Hz, ArH), 7.64 (t, 1H, $J = 7.05$ Hz, ArH), 7.61 (t, 1H, $J = 7.2$ Hz, ArH), 7.49 (d, 2H, $J = 8.4$ Hz, ArH), 7.43 (d, 2H, $J = 8.4$ Hz, ArH), 4.75 (d, 2H, $J = 5.1$ Hz, CH_2); ^{13}C NMR (75 MHz, DMSO), $\delta = 171.2$, 156.6, 148.2, 148.1, 146.6, 145.9, 137.5, 131.3, 129.9, 129.4, 128.8, 126.8, 124.3, 123.9, 120.9, 120.2, 47.4; mass (ES^+) m/z 447 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{15}ClN_4O_2S$: C, 61.81; H, 3.38; N, 12.54. Found: C, 61.82; H, 3.36; N, 12.56.

4.3.13. (4-Chloro-benzyl)-(4-*p*-tolyl-thiazolo[5,4-*c*]-quinolin-2-yl)-amine [8c(iii)]. Yield 81%; white solid, mp 90–92 °C; IR (KBr) ν_{max} 3313 (br, NH), 2922, 2830, 1583, 1484, 1402, 1351, ^1H NMR (300 MHz, DMSO), $\delta = 9.31$ (s, 1H, NH), 8.37 (d, 1H, $J = 8.1$ Hz, ArH), 8.03 (d, H, $J = 8.4$ Hz, ArH), 7.92 (d, 2H, $J = 7.8$ Hz, ArH), 7.71 (t, 1H, $J = 7.65$ Hz, ArH), 7.58 (t, 1H, $J = 7.5$ Hz, ArH), 7.44 (m, 6H, ArH), 4.74 (d, 2H, $J = 4.8$ Hz, CH_2), 2.41 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO d_6), $\delta = 171.2$, 156.1,

151.3, 146.8, 139.5, 137.7, 137.5, 132.3, 129.6, 129.0, 128.7, 128.0, 125.9, 123.9, 120.8, 120.0, 47.4, 21.3; mass (ES^+) *m/z* 416 ($M^+ + 1$). Anal. Calcd for $C_{24}H_{18}ClN_3S$: C, 69.30; H, 4.36; N, 10.10. Found: C, 69.28; H, 4.35; N, 10.13.

4.3.14. (4-Chloro-benzyl)-(4-furan-2-yl-thiazolo[5,4-*c*]quinolin-2-yl)-amine [8c(iv)]. Yield 83%; white solid, mp 164–166 °C; IR (KBr) ν_{max} 3225 (br, NH), 2928, 2833, 1585, 1488, 1401, 1360; ^1H NMR (300 MHz, DMSO), δ= 9.35 (s, 1H, NH), 8.386 (d, 1H, *J*=8.1 Hz, ArH), 8.04 (s, 1H, furan H), 7.97 (d, 1H, *J*=8.4 Hz, ArH), 7.69 (t, 2H, *J*= 7.8 Hz, ArH), 7.56 (d, 1H, *J*=7.8 Hz, ArH), 7.50 (d, 2H, *J*=8.4 Hz, ArH), 7.44 (d, 2H, *J*=8.4 Hz, ArH), 7.34 (d, 1H, *J*=3 Hz, furan H), 6.79 (t, 1H, *J*=1.65 Hz, furan H), 4.76 (d, 2H, *J*=5.4 Hz, CH_2); ^{13}C NMR (75 MHz, DMSO), δ= 172.2, 156.4, 152.8, 146.4, 145.2, 141.9, 137.7, 132.3, 129.9, 129.3, 128.8, 125.9, 123.9, 120.9, 116.9, 113.1, 110.9, 47.4; mass (ES^+) *m/z* 392 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{14}ClN_3OS$: C, 64.36; H, 3.60; N, 10.72. Found: C, 64.35; H, 3.60; N, 10.75.

4.3.15. [4-(4-Bromo-phenyl)-thiazolo[5,4-*c*]quinolin-2-yl]-(4-chloro-benzyl)-amine [8c(v)]. Yield 75%; white solid, mp 156–158 °C; IR (KBr) ν_{max} 3219 (br, NH), 2930, 2832, 1599, 1482, 1355; ^1H NMR (300 MHz, DMSO), δ 9.37 (s, 1H, NH), 8.38 (d, 1H, *J*=7.8 Hz, ArH), 8.05 (d, H, *J*=8.4 Hz, ArH), 7.97 (d, 2H, *J*=8.4 Hz, ArH), 7.80 (d, 2H, *J*=8.4 Hz, ArH), 7.73 (t, 1H, *J*= 7.05 Hz, ArH), 7.61 (t, 1H, *J*=7.2 Hz, ArH), 7.49 (d, 2H, *J*=8.4 Hz, ArH), 7.43 (d, 2H, *J*=8.4 Hz, ArH), 4.75 (d, 2H, *J*=5.1 Hz, CH_2); ^{13}C NMR (75 MHz, CD_3COCD_3), δ= 150.0, 146.9, 139.5, 137.4, 132.7, 131.7, 129.8, 129.6, 129.2, 128.7, 128.5, 125.8, 123.8, 123.1, 121.2, 47.4; mass (ES^+) *m/z* 481 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{15}BrClN_3S$: C, 57.45; H, 3.14; N, 8.74. Found: C, 57.43; H, 3.15; N, 8.75.

4.4. General procedure for the synthesis of 5-(2-nitro-phenyl)-1-phenyl-3-aryl-4,5-dihydro-1*H*-pyrazole (10)

A mixture of 3-(2-nitro-phenyl)-1-*p*-tolyl-propenone **9a** (1.00 g, 3.74 mmol), and phenyl hydrazine (0.808 mL, 7.48 mmol) was refluxed in ethanol for 7 h. Ethanol was evaporated in vacuo and the residue so obtained was purified on a silica gel column using hexane: ethyl acetate (70:30, v/v) as eluent to afford **10a** as a red solid.

4.4.1. 5-(2-Nitro-phenyl)-1-phenyl-3-*p*-tolyl-4,5-dihydro-1*H*-pyrazole (10a). Yield 82%; red solid; mp 142–144 °C; IR (KBr) ν_{max} 1521, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.23 (d, *J*=7.8 Hz, 1H, ArH), 7.63 (d, *J*=8.1 Hz, 2H, ArH), 7.53–7.44 (m, 3H, ArH), 7.19 (t, *J*=7.8 Hz, 4H, ArH), 6.94 (d, *J*=8.1 Hz, 2H, ArH), 6.80 (t, *J*=7.5 Hz, 1H, ArH), 5.88–5.82 (m, 1H, –CHPh), 4.11 (dd, *J*=17.5, 12.4 Hz, 1H, $-CH_2-$), 3.14 (dd, *J*=17.5, 6.6 Hz, 1H, $-CH_2-$), 2.38 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=147.85, 144.68, 139.49, 138.12, 134.92, 130.91, 130.01, 129.75, 129.55, 128.95, 128.69, 126.25, 125.86, 124.99, 123.50, 119.73, 113.36, 61.05, 43.66, 21.86; mass *m/z* 358.25 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{19}N_3O_2$. C, 73.93; H, 5.36; N, 11.76. Found: C, 73.71; H, 5.42; N, 11.64.

4.4.2. 3-(4-Chloro-phenyl)-5-(2-nitro-phenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole (10b). Yield 87%; red solid; mp 150–152 °C; IR (KBr) ν_{max} 1516, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.13 (d, *J*=8.1 Hz, 1H, ArH), 7.66 (d, *J*=8.1 Hz, 2H, ArH), 7.55–7.51 (m, 1H, ArH), 7.46–7.42 (m, 2H, ArH), 7.35 (d, *J*=8.1 Hz, 2H, ArH), 7.19 (t, *J*=7.5 Hz, 2H, ArH), 6.94 (d, *J*=7.8 Hz, 2H, ArH), 6.82 (t, *J*=7.2 Hz, 1H, ArH), 5.91–5.85 (m, 1H, –CHPh), 4.09 (dd, *J*=18.0, 12.3 Hz, 1H, $-CH_2-$), 3.13 (dd, *J*=18.0, 6.6 Hz, 1H, $-CH_2-$); mass *m/z* 378.20 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{16}ClN_3O_2$ C, 66.76; H, 4.27; N, 11.12. Found: C, 66.62; H, 4.22; N, 11.43.

4.4.3. 5-(5-Fluoro-2-nitro-phenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazole (10c). Yield 85%; red solid; mp 132–134 °C; IR ν_{max} (KBr) 1524, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.28–8.24 (m, 1H, ArH), 7.74 (d, *J*=7.2 Hz, 2H, ArH), 7.43–7.36 (m, 3H, ArH), 7.25–7.17 (m, 3H, ArH), 7.13 (t, *J*=7.5 Hz, 1H, ArH), 6.95 (d, *J*= 8.1 Hz, 2H, ArH), 6.85 (t, *J*=7.2 Hz, 1H, ArH), 5.94–5.87 (m, 1H, –CHPh), 4.15 (dd, *J*=18.0, 12.6 Hz, 1H, $-CH_2-$), 3.16 (dd, *J*=17.5, 6.6 Hz, 1H, $-CH_2-$); mass *m/z* 362.40 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{16}FN_3O_2$: C, 69.80; H, 4.46; N, 11.63. Found: C, 69.74; H, 4.32; N, 11.74.

4.5. General procedure for the synthesis of 5-(2-nitro-phenyl)-1-phenyl-3-aryl-1*H*-pyrazole (11)

A solution of 5-(2-nitro-phenyl)-1-phenyl-3-*p*-tolyl-4,5-dihydro-1*H*-pyrazole **10a** (0.80 g, 2.25 mmol) in DCM–THF (1/1, 7 mL) was treated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 1.02 g, 4.50 mmol) at rt. The reaction mixture was stirred for 4 h. The solvent was removed under reduced pressure and the crude red residue was chromatographed on silica gel (5:1 hexane/ethyl acetate) to afford **11a** as a yellow solid.

4.5.1. 5-(2-Nitro-phenyl)-1-phenyl-3-*p*-tolyl-1*H*-pyrazole (11a). Yield 87%; yellow solid; mp 90–92 °C; IR (KBr) ν_{max} 1521, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=7.90 (d, 1H, *J*=7.8 Hz, ArH), 7.79 (d, *J*=7.8 Hz, 2H, ArH), 7.60 (t, *J*=6.9 Hz, 1H, ArH), 7.52 (t, *J*=6.9 Hz, 1H, ArH), 7.45 (d, *J*=7.5 Hz, 1H, ArH), 7.28–7.22 (m, 7H, ArH), 6.75 (s, 1H, =CH), 2.38 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=152.66, 149.18, 139.85, 139.58, 138.35, 133.29, 133.12, 130.29, 129.77, 129.44, 127.92, 126.18, 124.93, 106.07, 21.70; mass *m/z* 356.13 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.54; H, 4.72; N, 11.74.

4.5.2. 3-(4-Chloro-phenyl)-5-(2-nitro-phenyl)-1-phenyl-1*H*-pyrazole (11b). Yield 88%; yellow solid; mp 102–104 °C; IR (KBr) ν_{max} 1530, 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=7.93 (d, *J*=8.1 Hz, 1H, ArH), 7.84 (d, *J*=8.4 Hz, 2H, ArH), 7.64–7.52 (m, 2H, ArH), 7.45 (d, *J*=7.2 Hz, 1H, ArH), 7.39 (d, *J*=8.4 Hz, 2H, ArH), 7.28 (s, 5H, ArH), 6.75 (s, 1H, =CH); mass *m/z* 376.20 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{14}ClN_3O_2$: C, 67.12; H, 3.75; N, 11.18. Found: C, 67.22; H, 3.82; N, 11.70.

4.5.3. 5-(5-Fluoro-2-nitro-phenyl)-1,3-diphenyl-1*H*-pyrazo (11c). Yield 83%; yellow solid; mp 165–167 °C; IR (KBr) ν_{max} 1529, 1596 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ=8.01–7.97 (m, 1H, ArH), 7.91 (d, J=7.5 Hz, 2H, ArH), 7.44 (t, J=7.5 Hz, 2H, ArH), 7.36 (d, J=7.5 Hz, 1H, ArH), 7.30 (s, 5H, ArH), 7.20 (d, J=8.1 Hz, 2H, ArH), 6.79 (s, 1H, =CH), mass m/z 360.43 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{14}FN_3O_2$: C, 70.19; H, 3.93; N, 11.69. Found: C, 70.22; H, 3.80; N, 11.79.

4.6. General procedure for the reduction of 5-(2-nitro-phenyl)-1-phenyl-3-aryl-1*H*-pyrazole to get 4

Tin (II) chloride dihydrate (2.28 g, 9.25 mmol) was added to a solution of 5-(2-nitro-phenyl)-1-phenyl-3-*p*-tolyl-1*H*-pyrazole **11a** (0.65 g, 1.84 mmol) in ethanol (15 mL) at 80 °C. The reaction mixture was stirred for 1.5 h. After that the reaction mixture was poured in cold water and basified with 5% aqueous sodium bicarbonate solution (pH 8). The mixture was extracted with ethyl acetate, washed with brine (100 mL), dried over sodium sulfate, and evaporated to dryness under reduced pressure to afford **4a**

4.6.1. 2-(2-Phenyl-5-*p*-tolyl-2*H*-pyrazol-3-yl)-phenyl-amine (4a). Yield 92%; yellow oil; IR (neat) ν_{max}, 1596, 3473 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=7.82 (d, J=7.8 Hz, 2H, ArH), 7.41 (d, J=7.5 Hz, 2H, ArH), 7.33–7.23 (m, 5H, ArH), 7.17 (t, J=7.5 Hz, 1H, ArH), 6.98 (d, J=7.5 Hz, 1H, ArH), 6.81 (s, 1H, =CH), 6.72 (t, J=6.9 Hz, 2H, ArH), 3.84 (br s, 2H, NH_2), 2.40 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=152.57, 145.19, 141.40, 140.49, 138.30, 131.56, 130.53, 129.84, 129.25, 127.43, 126.13, 124.25, 118.62, 116.48, 115.96, 106.23, 21.78; mass m/z 326.80 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91. Found: C, 81.37; H, 5.62; N, 12.78.

4.6.2. 2-[5-(4-Chloro-phenyl)-2-phenyl-2*H*-pyrazol-3-yl]-phenylamine (4b). Yield 88%; yellow oil; IR (neat) ν_{max} 1600, 3464 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=7.86 (d, J=8.4 Hz, 2H, ArH), 7.40 (d, J=8.1 Hz, 3H, ArH), 7.34–7.23 (m, 4H, ArH), 7.18 (t, J=7.5 Hz, 1H, ArH), 6.97 (d, J=7.5 Hz, 1H, ArH), 6.81 (s, 1H, =CH), 6.74–6.67 (m, 2H, ArH), 3.82 (br s, 2H, NH_2); mass m/z 346.40 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{16}ClN_3$: C, 72.93; H, 4.66; N, 12.15. Found: C, 72.82; H, 4.82; N, 12.31.

4.6.3. 2-(2,5-Diphenyl-2*H*-pyrazol-3-yl)-4-fluoro-phenyl-amine (4c). Yield 86%; yellow oil; IR (neat) ν_{max} 1595, 3430 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=7.92 (d, J=7.2 Hz, 2H, ArH), 7.50–7.16 (m, 8H, ArH), 6.88 (t, J=8.1 Hz, 1H, ArH), 6.83 (s, 1H, =CH–), 6.73 (d, J=8.7 Hz, 1H, ArH), 6.71–6.63 (m, 1H, ArH), 3.67 (br s, 2H, NH_2); mass m/z 330.32 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{16}FN_3$: C, 76.58; H, 4.90; N, 12.76. Found: C, 76.42; H, 4.86; N, 12.88.

4.7. General procedure for the Pictet–Spengler reaction on substrate 4

A mixture of 2-(2-phenyl-5-*p*-tolyl-2*H*-pyrazol-3-yl)-phenylamine **4a** (0.10 g, 0.32 mmol), 4-N, *N*-dimethyl-benzaldehyde (0.048 g, 0.32 mmol) and *p*-tolylsulphonic acid (6.08 mg, 0.032 mmol) was refluxed in toluene for 4 h. Toluene was evaporated in vacuo and residue so obtained was dissolved in ethyl acetate (25 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 was dissolved in DCM–THF (1/1) 10 mL and DDQ (18 mg, 0.08 mmol) was added. The resulting mixture was stirred at rt for 2 h. Then solvent was evaporated in vacuo and the residue so obtained was purified on column chromatography on silica gel with hexane: ethyl acetate (80:20, v/v) as eluent to afford **12a(i)** as a white solid.

4.7.1. Dimethyl-[4-(1-phenyl-3-*p*-tolyl-1*H*-pyrazolo[4,3-*c*]quinolin-4-yl)-phenyl]-amine [12a(i)]. Yield 79%; off white solid; mp 190–192 °C; IR (KBr) ν_{max} 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.27 (d, J=8.4 Hz, 1H, ArH), 7.70–7.56 (m, 7H, ArH), 7.36 (d, J=8.4 Hz, 2H, ArH), 7.30 (d, J=7.5 Hz, 1H, ArH), 7.17 (d, J=7.5 Hz, 2H, ArH), 6.96 (d, J=7.8 Hz, 2H, ArH), 6.49 (d, J=8.7 Hz, 2H, ArH), 2.92 [s, 6H, –$N(CH_3)_2$], 2.31 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=156.90, 151.31, 149.00, 146.32, 141.81, 141.23, 137.31, 130.90, 130.21, 129.90, 129.72, 129.01, 128.42, 127.60, 127.31, 125.41, 121.75, 115.34, 111.93, 40.80, 21.40; mass m/z 455.40 ($M^+ + 1$). Anal. Calcd for $C_{31}H_{26}N_4$: C, 81.91; H, 5.77; N, 12.33. Found: C, 81.81; H, 5.84; N, 12.43.

4.7.2. 4-(4-Nitro-phenyl)-1-phenyl-3-*p*-tolyl-1*H*-pyrazolo[4,3-*c*]quinoline [12a(ii)]. Yield 75%; yellow solid; mp 235–237 °C; IR (KBr) ν_{max} 1524, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.30 (d, J=8.4 Hz, 1H, ArH), 8.02 (d, J=8.4 Hz, 2H, ArH), 7.71–7.63 (m, 9H, ArH), 7.42 (t, J=7.5 Hz, 1H, ArH), 7.09 (d, J=7.8 Hz, 2H, ArH), 6.94 (d, J=7.8 Hz, 2H, ArH), 2.29 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=154.15, 148.56, 148.07, 146.13, 145.42, 141.92, 141.04, 138.96, 130.96, 130.27, 129.95, 129.80, 129.65, 128.93, 127.74, 127.15, 123.12, 122.06, 116.03, 114.47, 21.59; mass m/z 457.30 ($M^+ + 1$). Anal. Calcd for $C_{29}H_{20}N_4O_2$: C, 76.30; H, 4.42; N, 12.27. Found: C, 76.42; H, 4.22; N, 12.43.

4.7.3. 4-(4-Bromo-phenyl)-1-phenyl-3-*p*-tolyl-1*H*-pyrazolo[4,3-*c*]quinoline [12a(iii)]. Yield 76%; off white solid; mp 210–212 °C; IR (KBr) ν_{max} 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.28 (d, J=8.1 Hz, 1H, ArH), 7.73–7.60 (m, 7H, ArH), 7.39–7.30 (m, 5H, ArH), 7.09 (d, J=7.8 Hz, 2H, ArH), 6.97 (d, J=7.8 Hz, 2H, ArH), 2.35 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=155.58, 148.88, 146.27, 141.86, 141.21, 138.47, 138.19, 131.57, 131.14, 130.79, 130.21, 129.98, 129.84, 129.56, 128.84, 127.78, 126.56, 123.42, 122.00, 115.8, 114.57, 21.69; mass m/z 490.78 ($M^+ + 1$). Anal. Calcd for $C_{29}H_{20}BrN_3$: C, 71.03; H, 4.11; N, 8.57. Found: C, 71.42; H, 4.22; N, 8.43.

4.7.4. 4-(2-Methoxy-phenyl)-1-phenyl-3-*p*-tolyl-1*H*-pyrazolo[4,3-*c*]quinoline [12a(iv)]. Yield 82%; off white; mp 216–218 °C; IR (KBr) ν_{max} 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.30 (d, J=8.4 Hz, 1H, ArH), 7.71–7.61 (m, 8H, ArH), 7.36–7.26 (m, 2H, ArH), 7.09 (d, J=7.2 Hz, 3H, ArH), 6.88 (d, J=7.5 Hz, 2H, ArH), 6.40 (d, J=8.1 Hz, 1H, ArH), 3.18 (s, 3H, –OCH_3), 2.28 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=157.35, 154.73, 149.72, 146.51, 141.40, 141.02, 137.70, 130.90, 130.83, 130.66, 130.17, 129.92, 129.44, 129.31, 129.17, 128.25, 127.85, 126.31, 122.04, 121.14, 116.29, 115.95, 110.57, 55.10, 21.67; mass

m/z 442.20 ($M^+ + 1$). Anal. Calcd for $C_{30}H_{23}N_3O$: C, 81.61; H, 5.25; N, 9.52. Found: C, 81.47; H, 5.22; N, 9.43.

4.7.5. 4-(3,4-Dimethoxy-phenyl)-1-phenyl-3-*p*-tolyl-1*H*-pyrazolo[4,3-*c*]quinoline [12a(v)]. Yield 80%; yellow solid; mp 158–160 °C; IR (KBr) ν_{max} 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.29 (d, J=8.4 Hz, 1H, ArH), 7.71–7.65 (m, 6H, ArH), 7.58 (d, J=8.1 Hz, 1H, ArH), 7.34 (t, J=7.5 Hz, 1H, ArH), 7.25 (d, J=6.9 Hz, 1H, ArH), 7.19 (d, J=8.4 Hz, 2H, ArH), 7.00 (s, 1H, ArH), 6.96 (d, J=6.9 Hz, 2H, ArH), 6.77 (d, J=8.4 Hz, 1H, ArH), 3.89 (s, 3H, –OCH_3), 3.55 (s, 3H, –OCH_3), 2.31 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=156.34, 150.09, 148.86, 148.60, 146.27, 142.09, 141.30, 138.20, 132.25, 130.60, 130.41, 130.19, 130.10, 129.42, 128.75, 127.81, 126.77, 126.15, 122.95, 121.92, 115.68, 114.28, 113.77, 111.28, 56.51, 55.86, 21.65; mass *m/z* 472.33 ($M^+ + 1$). Anal. Calcd for $C_{31}H_{25}N_3O_2$: C, 78.96; H, 5.34; N, 8.91. Found: C, 78.49; H, 5.62; N, 8.54.

4.7.6. {4-[3-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazolo[4,3-*c*]quinolin-4-yl]-phenyl}-dimethyl-amine [12b(i)]. Yield 82%; pale yellow solid; mp 244–246 °C; IR (KBr) ν_{max} 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.27 (d, J=8.1 Hz, 1H, ArH), 7.69–7.63 (m, 5H, ArH), 7.56 (d, J=8.1 Hz, 1H, ArH), 7.39–7.20 (m, 6H, ArH), 7.12 (d, J=8.1 Hz, 2H, ArH), 6.50 (d, J=8.4 Hz, 2H, ArH), 2.95 [s, 6H, –$N(CH_3)_2$]. ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=156.87, 151.60, 147.99, 146.60, 142.07, 141.25, 134.04, 132.01, 131.51, 131.07, 130.53, 130.22, 130.16, 129.45, 128.13, 127.77, 127.08, 125.79, 121.88, 115.49, 114.62, 112.06, 41.00; mass *m/z* 475.33 ($M^+ + 1$). Anal. Calcd for $C_{30}H_{23}ClN_4$: C, 75.86; H, 4.88; N, 11.80. Found: C, 75.77; H, 4.99; N, 11.54.

4.7.7. 3-(4-Chloro-phenyl)-4-(4-nitro-phenyl)-1-phenyl-1*H*-pyrazolo[4,3-*c*]quinoline [12b(ii)]. Yield 80%; yellow solid; mp 231–233 °C; IR (KBr) ν_{max} 1520, 1597 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=8.31 (d, J=8.4 Hz, 1H, ArH), 8.09 (d, J=8.6 Hz, 2H, ArH), 7.76–7.61 (m, 9H, ArH), 7.48–7.38 (m, 2H, ArH), 7.15 (d, J=4.2 Hz, 3H, ArH). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=155.27, 153.71, 148.24, 145.33, 140.85, 131.98, 131.33, 131.02, 130.54, 130.39, 130.25, 130.03, 129.65, 129.31, 129.06, 128.98, 128.52, 128.01, 127.68, 127.41, 123.37, 122.05, 115.89; mass *m/z* 477.18 ($M^+ + 1$). Anal. Calcd for $C_{28}H_{17}ClN_4O_2$: C, 70.52; H, 3.59; N, 11.75. Found: C, 70.42; H, 3.75; N, 11.53.

4.7.8. 4-(4-Bromo-phenyl)-3-(4-chloro-phenyl)-1-phenyl-1*H*-pyrazolo[4,3-*c*]quinoline [12b(iii)]. Yield 76%; white solid; mp 242–244 °C; IR (KBr) ν_{max} 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.28 (d, J=8.4 Hz, 1H, ArH), 7.74–7.67 (m, 6H, ArH), 7.60 (d, J=8.1 Hz, 1H, ArH), 7.40–7.34 (m, 5H, ArH), 7.16 (s, 4H, ArH). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=155.18, 147.50, 146.25, 142.05, 141.00, 138.06, 134.83, 131.55, 131.41, 131.37, 131.36, 130.80, 130.39, 130.33, 129.80, 128.38, 127.72, 126.79, 123.79, 121.98, 115.75, 114.32; mass *m/z* 510.33 ($M^+ + 1$). Anal. Calcd for $C_{28}H_{17}BrClN_3$: C, 65.84; H, 3.35; N, 8.23. Found: C, 65.73; H, 3.39; N, 8.54.

4.7.9. 3-(4-Chloro-phenyl)-4-(2-methoxy-phenyl)-1-phenyl-1*H*-pyrazolo[4,3-*c*]quinoline [12b(iv)]. Yield 79%; pale yellow solid; mp 242–244 °C; IR (KBr) ν_{max} 1597 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=8.31 (d, J=8.2 Hz, 1H, ArH), 7.72–7.59 (m, 9H, ArH), 7.39–7.29 (m, 1H, ArH), 7.17–7.03 (m, 5H, ArH), 6.46 (d, J=8.2 Hz, 1H, ArH), 3.22 (s, 3H, –OCH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=157.21, 154.33, 148.40, 146.52, 141.22, 134.15, 131.99, 131.42, 130.99, 130.91, 130.85, 130.68, 130.19, 130.12, 129.36, 129.18, 128.96, 127.73, 126.50, 122.00, 121.31, 116.17, 115.81, 110.61, 55.06; mass *m/z* 462.15 ($M^+ + 1$). Anal. Calcd for $C_{29}H_{20}ClN_3O$: C, 75.40; H, 4.36; N, 9.10. Found: C, 75.42; H, 3.55; N, 9.31.

4.7.10. 3-(4-Chloro-phenyl)-4-(3,4-dimethoxy-phenyl)-1-phenyl-1*H*-pyrazolo[4,3-*c*]quinoline [12b(v)]. Yield 82%; pale yellow solid; mp 212–214 °C; IR (KBr) ν_{max} 1609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.30 (d, J=8.1 Hz, 1H, ArH), 7.73–7.67 (m, 5H, ArH), 7.53 (d, J=7.2 Hz, 1H, ArH), 7.35 (t, J=7.8 Hz, 1H, ArH), 7.28–7.22 (overlapped, 2H, ArH), 7.16 (m, 2H, ArH), 7.05 (m, 2H, ArH), 6.67 (m, 2H, ArH), 3.89 (s, 3H, –OCH_3), 3.68 (s, 3H, –OCH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=156.15, 150.36, 148.99, 146.34, 141.14, 134.52, 131.98, 131.88, 131.40, 130.68, 130.27, 129.78, 129.61, 129.32, 129.02, 128.22, 127.74, 126.71, 126.34, 123.29, 121.90, 115.60, 113.36, 111.21, 56.59, 56.05; mass *m/z* 492.20 ($M^+ + 1$). Anal. Calcd for $C_{30}H_{22}ClN_3O_2$: C, 73.24; H, 4.51; N, 8.54. Found: C, 73.57; H, 5.89; N, 8.59.

4.7.11. [4-(8-Fluoro-1,3-diphenyl-1*H*-pyrazolo[4,3-*c*]-quinolin-4-yl)-phenyl]-dimethyl-amine [12c(i)]. Yield 80%; pale yellow solid; mp 193–195 °C; IR (KBr) ν_{max} 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=8.26 (m, 1H, ArH), 7.68–7.67 (overlapped, 5H, ArH), 7.56–7.26 (m, 5H, ArH), 7.23–7.16 (m, 4H, ArH), 6.48 (d, J=8.1 Hz, 2H, ArH), 2.92 [s, 6H, –$N(CH_3)_2$]. ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=162.36, 156.28, 151.53, 149.17, 143.46, 141.73, 140.79, 133.31, 132.79, 132.62, 131.07, 130.29, 128.07, 127.77, 127.14, 118.66, 118.72, 115.90, 114.58, 112.11, 106.95, 106.44, 40.96; mass *m/z* 459.33 ($M^+ + 1$). Anal. Calcd for $C_{30}H_{23}FN_4$: C, 78.58; H, 5.06; N, 12.22. Found: C, 78.87; H, 5.25; N, 12.45.

4.7.12. 8-Fluoro-4-(4-nitro-phenyl)-1,3-diphenyl-1*H*-pyrazolo[4,3-*c*]quinoline [12c(ii)]. Yield 75%; brown solid; mp 196–198 °C; IR (KBr) ν_{max} 1513, 1596 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=8.34–8.26 (m, 1H, ArH), 8.03 (d, J=8.8 Hz, 2H, ArH), 7.70 (s, 5H, ArH), 7.62 (d, J=8.8 Hz, 2H, ArH), 7.48 (td, J=8.4, 2.8 Hz, 1H, ArH), 7.29–7.10 (overlapped, 6H, ArH). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=163.24, 158.31, 153.32, 148.44, 148.13, 143.01, 141.62, 140.36, 133.41, 133.23, 132.42, 130.92, 130.69, 130.45, 130.08, 129.01, 128.34, 127.66, 123.20, 119.38, 118.89, 116.70, 114.47, 107.21, 106.71; mass *m/z* 461.23 ($M^+ + 1$). Anal. Calcd for $C_{28}H_{17}FN_4O_2$: C, 73.04; H, 3.72; N, 12.17. Found: C, 73.42; H, 3.85; N, 12.01.

4.7.13. 4-(4-Bromo-phenyl)-8-fluoro-1,3-diphenyl-1*H*-pyrazolo[4,3-*c*]quinoline [12c(iii)]. Yield 77%; off white solid; mp 194–196 °C; IR (KBr) ν_{max} 1592 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ=8.28 (m, 1H, ArH), 7.68 (s, 5H, ArH), 7.46 (td, J=8.1, 2.7 Hz, 1H, ArH), 7.34–7.26 (overlapped, 6H, ArH), 7.23–7.15 (m, 4H, ArH). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=162.89, 157.98, 154.70, 148.76, 143.13, 140.52, 137.89, 133.19, 133.00, 132.61, 131.51, 131.25, 130.56, 130.39, 130.13, 128.64, 128.22, 127.70, 123.56, 119.09, 118.60, 116.42, 114.52, 107.10, 106.60; mass m/z 494.33 (M^++1). Anal. Calcd for $C_{28}H_{17}BrFN_3$: C, 68.03; H, 3.47; N, 8.50. Found: C, 68.41; H, 3.25; N, 8.67.

4.7.14. 8-Fluoro-4-(2-methoxy-phenyl)-1,3-diphenyl-1*H*-pyrazolo[4,3-*c*]quinoline [12c(iv)]. Yield 79%; off white solid; mp 212–214 °C; IR (KBr) ν_{max} 1594 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=8.33–8.26 (m, 1H, ArH), 7.72–7.58 (m, 6H, ArH), 7.42 (td, J=8.0, 2.8 Hz, 1H, ArH), 7.28–7.18 (overlapped, 6H, ArH), 7.09 (d, J=6 Hz, 2H, ArH), 6.39 (d, J=8.2 Hz, 1H, ArH), 3.17 (s, 3H, –OCH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=162.81, 157.91, 157.27, 153.90, 149.62, 143.41, 140.74, 133.24, 133.06, 132.65, 130.86, 130.28, 129.43, 128.71, 128.11, 127.76, 127.62, 121.19, 118.62, 118.13, 116.85, 115.98, 110.58, 107.08, 106.59, 55.01; mass m/z 446.26 (M^++1). Anal. Calcd for $C_{29}H_{20}FN_3O$: C, 78.19; H, 4.53; N, 9.43. Found: C, 78.47; H, 4.25; N, 9.58.

4.7.15. 4-(3,4-Dimethoxy-phenyl)-8-fluoro-1,3-diphenyl-1*H*-pyrazolo[4,3-*c*]quinoline [12c(v)]. Yield 80%; yellow solid; mp 185–187 °C; IR (KBr) ν_{max} 1598 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.29 (m, 1H, ArH), 7.68 (m, 5H, ArH), 7.44 (td, J=8.1, 5.4 Hz, 1H, ArH), 7.31–7.24 (overlapped, 4H, ArH), 7.20–7.12 (m, 3H, ArH), 6.87 (s, 1H, ArH), 6.82 (d, J=8.4 Hz, 1H, ArH), 3.88 (s, 3H, –OCH_3), 3.52 (s, 3H, –OCH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=157.77, 155.52, 150.14, 148.80, 148.59, 143.14, 140.62, 133.08, 132.79, 131.91, 130.49, 130.37, 130.18, 128.56, 128.11, 127.73, 122.76, 118.92, 118.34, 116.31, 114.37, 113.63, 111.31, 107.00, 106.50, 56.47, 55.85; mass m/z 476.20 (M^++1). Anal. Calcd for $C_{30}H_{22}FN_3O_2$: C, 75.78; H, 4.66; N, 8.84. Found: C, 75.57; H, 4.95; N, 8.67.

4.7.16. 2-(1-Phenyl-3-*p*-tolyl-1*H*-pyrazolo[4,3-*c*]quinolin-4-yl)-phenol [12c(vi)]. Yield 75%; off white solid; mp 201–203 °C; IR (KBr) ν_{max} 1597, 3425 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=8.15 (d, J=8.4 Hz, 1H, ArH), 7.68–7.57 (overlapped, 6H, ArH), 7.55 (d, J=8.2 Hz, 1H, ArH), 7.38–7.27 (m, 3H, ArH), 7.20–7.03 (m, 5H, ArH), 6.26 (t, J=7.4 Hz, 1H, ArH), 2.35 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=158.47, 156.13, 149.27, 143.79, 142.69, 141.13, 138.58, 133.60, 131.50, 130.65, 130.29, 130.11, 129.89, 129.12, 127.84. 127.29, 126.64, 122.04, 120.12, 118.22, 117.45, 115.69, 113.10, 21.72; mass m/z 427.18 (M^++1). Anal. Calcd for $C_{29}H_{21}N_3O$: C, 81.48; H, 4.95; N, 9.83. Found: C, 81.76; H, 4.55; N, 9.53.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.01.063.

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