Cycloaromatization Reaction of 4-Alkoxy-1,1,1-trifluoroalk-3-en-2-ones with 2,6-Diaminotoluene: The Unexpected Regioselective Synthesis of 2,4,7,8-Tetrasubstituted Quinolines

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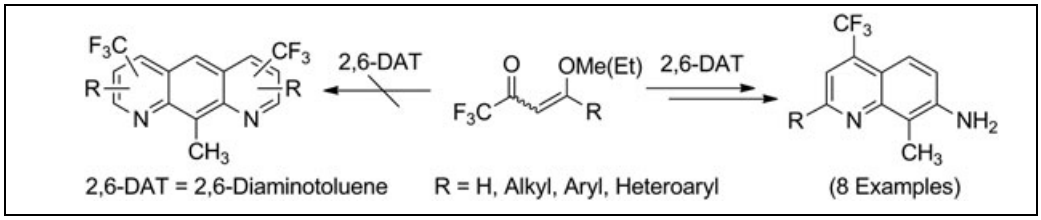

This article reports a convenient and general method for the regioselective synthesis of a new series of 2-alkyl(aryl)-8-methyl-4-trifluoromethyl-7-aminoquinolines in 86–93% yields, from cycloaromatization reactions of *N*-(oxotrifluoroalkenyl)-2,6-diaminotoluenes in a strongly acidic medium polyphosphoric acid and absence of solvent. The enaminoketone intermediates were easily isolated from the reaction of 4-alkoxy-4-alkyl(aryl)-1,1,1-trifluoroalk-3-en-2-ones [$CF_3C(O)CH{=}C(R)OR^1$, where R = H, Me, Ph, 4-FPh, 4-BrPh, 4-MePh, and R^1 = Me, Et] with 2,6-diaminotoluene (2,6-DAT) in methanol under mild conditions, in 46–70% yields. Another synthetic route also allowed the regioselective synthesis of 2-aryl(heteroaryl)-4-methyl-4-trifluoromethyl-7-aminoquinolines from direct cyclocondensation reactions of 4-alkoxy-4-aryl (heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones with 2,6-diaminotoluene in methanol under mild conditions, in 21–36% yields.

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INTRODUCTION

Because the discovery of the beneficial effects of fluorine incorporation into organic molecules due to the unique properties exhibited by such substrates, the synthesis and application of organofluorine compounds has significantly increased [1,2]. Trifluoromethyl-substituted molecules constitute an important class because of specific properties such as high lipophilicity and resistance to enzyme degradation by the CF_3 group [3]. One of the most satisfactory methods for introducing a trifluoromethyl group into heterocycles is based on the trifluoromethylated building block approach. This building block relies on the trifluoroacetylation of enolethers or acetals to give, in one step and good yields, 4-alkoxy-4-alkyl(aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones (**1**) that have proven to be useful starting materials for the regioselective synthesis of numerous heterocyclic compounds [4].

The quinoline ring system occurs in numerous natural products, especially in alkaloids, and a wide spectrum of physiological activities is displayed by this class of compounds [5]. Much attention is still being given to the synthesis of quinoline derivatives because of their industrial applications, pharmacological properties (antimalarials, antibacterials, and protein kinase inhibitors), NADH models, and agrochemical applications, in addition to their use as general synthetic blocks [6]. Quinoline moieties are structural elements of many drugs, as for example, antimalarial agents [7]. Because the classical antimalarial molecules are encountering increased drug resistance and adverse effects, for example, Halofantrine, a nonnatural antimalarial agent possessing a trifluoromethyl substituted phenanthrene skeleton (Fig. 1), considerable efforts have been directed toward the synthesis of new fluorinated quinolines that can provide improved antiparasitic activity [8–10]. Therefore, trifluoromethyl-substituted quinolines are the subject of considerable growing interest because of their medicinal importance, particularly as antimalarial agents (e.g., Mefloquine, Figure 1) [7,9].

Several synthetic routes are well documented in the literature for the formation of quinolines through many different strategies, such as the Skraup [11], Doebner-von Miller [12], Friedländer [13], Pfitzinger [14], Conrad-Limpach [15], Combes [16] and Knorr [17] syntheses. These classical syntheses are well known and still frequently used for the preparation of pharmaceutical agents, ligands, and functional materials bearing a quinoline backbone. However, current methods for quinoline synthesis often do not allow for adequate diversity and substitution on the quinoline ring system [18]. Recent developments in the chemistry of quinoline derivatives have demonstrated that new metal-catalyzed coupling cyclizations or acid catalyzed cycloaddition of appropriate precursors could compete with classical syntheses

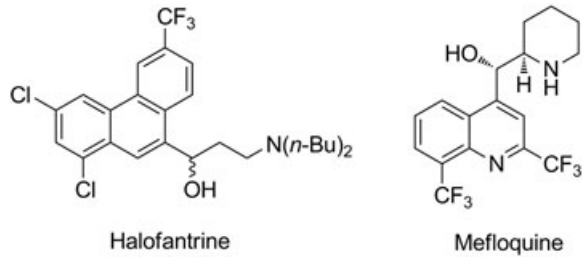


Figure 1. Structures of the antimalarial compounds Halofantrine and Mefloquine [9].

in the efficacy and rapidity of the quinoline construction [7]. The most important and general approaches (both old and new) to quinoline compounds are based on the use of non-heterocyclic precursors. Analysis of the structure of the quinoline ring suggests two general synthetic routes: either the utilization of mono-substituted anilines or the use of ortho-substituted anilines. In some classical syntheses, the substituted enamines and azomethines are intermediate products and generally not isolated [7,10c].

Similarly, enaminones like **2** are versatile readily obtainable reagents, and their chemistry has received much attention in recent years [19–30]. These enamino-carbonyl compounds represent versatile synthetic precursors that combine the ambident nucleophilicity of enamines with the ambident electrophilicity of enones presenting three nucleophilic and two electrophilic sites. Recently, we reported an addition/elimination sequence leading to trifluoracetyl and trichloroacetyl acyclic enamines from the reactions of 1-naphthylamine [20], *o*-phenylenediamine [21], *m*-phenylenediamine [22,23], *o*-aminophenol [24], *S*,*S*-dimethylsulfoximide [25], and 2,6-diaminopyridine [26] with 4-alkoxy-4-alkyl(aryl/heteroaryl)-1,1,1-trihaloalk-3-en-2-ones. Although the reactions of β-alkoxyvinyl trifluoromethyl ketones **1** with primary and secondary amines have been well documented [19–32], there are no reports in the literature dealing with 2,6-diaminotoluene (2,6-DAT) as a nucleophilic precursor in reactions with **1**.

Recently, we described reactions of **1** with 1,3-phenylenediamine to obtain a variety of *N*,*N*′-bis(oxotrifluoroalkenyl)-1,3-phenylenediamines. When these bis-enamino compounds were heated in the presence of polyphosphoric acid (PPA), selective routes of ring closure were observed, including direct cyclocondensations, hydrolyses, and recombinations, which simultaneously furnished fused bis-(trifluoromethyl)-diazatricycles and 2-substituted-4-trifluoromethyl-7-aminoquinolines [22,23]. The interesting results reported previously showed that the cyclization mode for unsubstituted bis-enaminone (R = H) differs from substituted bis-enaminones (R ≠ H) under the same reaction conditions. Subsequently, we described the reactions of **1** with 2,6-diaminopyridine and demonstrated the achievement of naphthyridines instead of pyrimidines because there was no cyclization in the endocyclic nitrogen atom of the π-deficient pyridine ring [26]. Now, we present the first results obtained so far from the reactions of **1** with 2,6-DAT, a symmetrical diamine that contains a methyl substituent hindering the obtainment of the angular structure and allowing the synthesis of derivatives with linear structures as pyrido[3,2-*g*]quinolines (acridines).

Thus, considering that the quinoline nucleus plays an important role as an intermediate in many pharmacologically active compounds, as an extension of our research, the purpose of this article is to report a general method for the synthesis of a new series of trifluoroacetyl-substituted enamines **2a–f** from the reaction of enones **1a–f** with 2,6-DAT (Scheme 2) as well as to investigate the chemical behavior of alkyl, aryl, and heteroaryl-substituted enamino intermediates (**2**) for their application in the regioselective synthesis of new 4-trifluoromethyl-7-aminoquinolines (**3**) instead of the expected linear tricyclic compounds (Schemes 1 and 3).

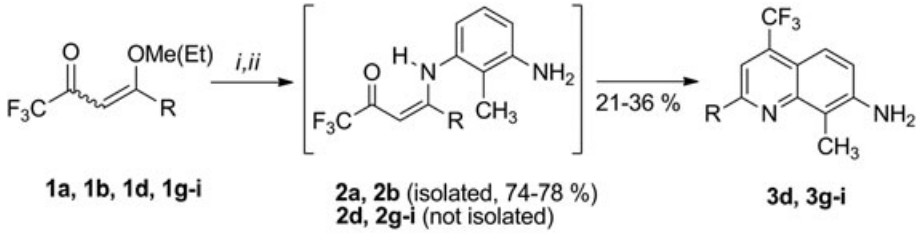
RESULTS AND DISCUSSION

Initially, a series of nine examples of 4-alkoxy-4-alkyl (aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones (**1a–i**), which are readily available 1,3-dielectrophiles (*CCC* synthetic blocks), were prepared from trifluoroacetylation reactions of enol ethers commercially available (for **1a–b**) or generated *in situ* from the respective acetophenone dimethyl acetals (for **1c–g**) [33], 2-(1,1-dimethoxyethyl)furan (**1h**), and 2-(1,1-dimethoxyethyl)thiophene (**1i**) [34] with trifluoroacetic anhydride, respectively, in the presence of pyridine, as described in the literature [33–37].

In an attempt to obtain 7-aminoquinolines from direct cyclocondensation reactions, under mild conditions similar to the method recently described by us for the synthesis of some trifluoromethyl-substituted naphthyridines [26], reactions were carried with some enones **1** and 2,6-DAT. We found that enones **1d** and **1g–i** when added to 2,6-DAT at a molar ration of 1:1, respectively, in pure methanol as solvent at 0°C for 2 h and then heated under reflux for 24 h, allowed us to obtain 7-aminoquinolines **3d** and **3g–i** in low yields (21–36%). Unfortunately, the reaction using **1a** and **1b** under the same conditions described earlier only resulted in the isolation of trifluoroacetyl enamine derivatives **2a** and **2b** in 74% and 78% yields, respectively, and only traces of the 7-aminoquinolines **3a** and **3b**.

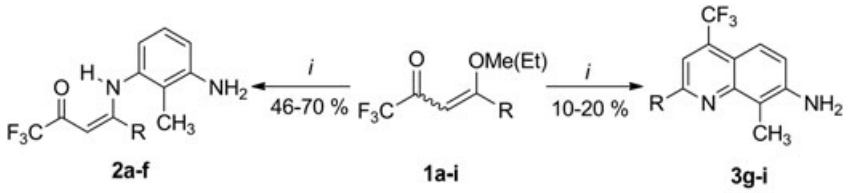
Then, because of the low yields, we aimed to isolate the trifluoroacetyl enamine derivatives (**2a–i**) for subsequent reaction in the presence of a strongly acidic medium (PPA). Fortunately, we found that trifluoromethylated ketones **1a–f** when added to 2,6-DAT at a molar ration of 1:1, respectively, in pure methanol as solvent at 0°C for 2 h, furnished a new series of six enaminone intermediates **2a–f** in 46–70% yields (Scheme 2). Traces of the symmetrical bis-enaminones were obtained as by-products from the reported reactions and were isolated by recrystallization after the work-up of residual reaction mixtures, according to the

Scheme 1. Synthetic route for direct preparation of 7-aminoquinolines **3**. Reagents and condition: (*i*) 2,6-diaminotoluene (1.0 eq), methanol, 0°C, 2 h; (*ii*) methanol, reflux, 24 h.



1-3	a	b	d	g	h	i
R	H	CH_3	4-FPh	4-OMePh	2-Furyl	2-Thienyl

Scheme 2. Synthesis of trifluoracetyl enamines **2a–f** or 7-aminoquinolines **3g–i** from β-alkoxyvinyl trifluoromethyl ketones **1**. Reagents and conditions: (*i*) 2,6-diaminotoluene (1.0 eq), methanol, 0°C, 2 h.



1-3	a	b	c	d	e	f	g	h	i
R	H	Me	Ph	4-FPh	4-BrPh	4-MePh	4-OMePh	2-Furyl	2-Thienyl

procedure described. In addition, we found that enones **1g–i** under the same reaction conditions described earlier allowed us to obtain 7-aminoquinolines **3g–i** instead of the corresponding enaminones **2g–i** (Scheme 2).

Schlosser *et al*. [10], who have investigated the synthesis of 2- and 4-(trifluoromethyl)quinolines and quinolinones in detail and the effect of substituents on the outcome of the reaction, determined that 2-anilinovinyl perfluoroalkyl ketones can be mechanistically correlated with their cyclization products 2-(perfluoroalkyl)quinolones. According to Schlosser *et al*., in a few cases, it is not possible to isolate the intermediates with an electron-rich aromatic nucleus because of the rapid subsequent transformation to quinolines, even under weakly acidic conditions [10c]. As revealed by cross-over experiments, their studies demonstrated a course of reaction featuring a vinylogous amidinium ion (1,3-diaminoallyl cation) as the key intermediate [10a]. Therefore, based on experiments of Schlosser *et al*., we suggest that when R = 4-OMePh, 2-thienyl, and 2-furyl, there is a significant stabilization of the intermediate, accelerating the crucial ring-closure step and, thus, facilitating the formation of products **3g–i** from direct cyclocondensation reactions even under mild conditions.

The structures of compounds **2a–f** were easily established on the basis of ^{1}H NMR and ^{13}C NMR spectroscopy. To obtain structural information about the configuration of the compounds **2a–f**, we have performed an ^{1}H NMR study on (*Z*)-*N*-(4,4,4-trifluoro-3-oxo-1-buten-1-yl)-2,6-diaminotoluene (**2a**). The ^{1}H NMR spectrum of **2a** in $CDCl_3$ showed a *cis* coupling constant for the vicinal olefin protons with *J* ~8 Hz. This is consistent with a *Z*-configuration, as the *E*-form and Z-form can be easily distinguished by their ^{1}H NMR spectra because the N-H signals of the *E*-form (in 4–8 ppm) appear at a much higher field than those of the *Z*-form (in 9–13 ppm), indicating the presence of an intramolecular hydrogen bonding in the latter [38]. The ^{1}H NMR chemical shift of the enamino hydrogens (NH) for **2a–f** were observed on average at 12.36 ppm, allowing one to assume that the enaminones **2a–f** exist in the *Z*-configuration in $CDCl_3$, which is stabilized by an intramolecular hydrogen bond (N-H···O=C).

In a second reaction step, the trifluoroacetyl enamine derivatives **2a–f** were subjected to reactions carried out in the presence of a strongly acidic medium (PPA), in the absence of solvent. For all reactions, initially, PPA ($P_2O_5 + H_3PO_4$) was prepared at 90°C, and the compounds **2a–f** were added to the acid mixture. The cyclization of

2b–f showed that the best results were at 90°C for 6 h, affording the corresponding new series of 7-aminoquinolines **3b–f** in satisfactory yields (86–93, Scheme 3). Unfortunately, by this method only, traces of aminoquinoline **3a** were obtained. Obtaining only traces of compound **3a** by either methods presented in Schemes 1 and 3 is not surprising because a detailed review of the literature shows that enaminone derivatives of β-ethoxyvinyl trifluoromethyl ketone (enone **1a**) present a different chemical behavior from other enones [22,23], leading to heterocycles with lower yields [19,26] and in many cases, the absence of cyclization has been reported [20,22,23,32].

Presumably, the reactions between compounds **1** and 2,6-DAT start with the Michael addition of the amino group of 2,6-DAT at the β-carbon atom of the enones **1a–i** furnishing addition products. The originated aminoether function is unstable in alcohol (reaction solvent), and the alkoxy group (-OR^1) is eliminated as methanol ($R \neq H$) or ethanol ($R = H$). Subsequently, the intramolecular cyclization reaction occurs involving the nucleophilic *ortho*-position of the anilino moiety and the carbonyl function of the β-enaminones **2a–f** (in the presence of PPA) or the non-isolated β-enaminones **2g–i** (in MeOH). The ephemeral dihydroquinolines, after the elimination of one water molecule, lead to the regioselective synthesis of new 4-trifluoromethylated quinolines **3b–i** (Fig. 2).

Linderman and Kirollos [39] reported the synthesis of 2-CF_3-substituted quinolines and assigned the chemical shift of the CF_3 group of the ^{13}C NMR spectra as quartets at δ 122.3 ppm (CF_3, $^1J_{CF}$ 275 Hz) and at δ 148.5 ppm (C2, $^2J_{CF}$ 34 Hz). In the same letter, another intramolecular cyclization route was also described, which allowed the synthesis of the 4-(trifluoromethyl)quinoline isomer. With the synthesis of 4-CF_3 quinolines, they reported the ^{13}C NMR spectral data and assigned the chemical shift of the CF_3 group of this regioisomer as quartets at δ 124.2 ppm (CF_3, $^1J_{CF}$ 275 Hz) and δ 134.8 ppm (C4, $^2J_{CF}$ 31 Hz), respectively. In some cases, the reactions resulted in mixtures of both regioisomers 2- and 4-CF_3 quinolines [40].

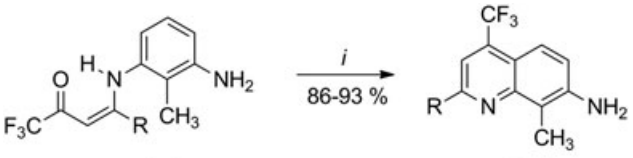
The structures of quinolines **3b–i** were established on the basis of ^1H NMR and ^{13}C NMR spectroscopy and literature data for similar compounds [10,20,22,28,39–41]. The ^{13}C NMR spectra of the compounds 2-alkyl (aryl/heteroaryl)-4-trifluoromethyl-8-methyl-7-aminoquinolines (**3b–i**) showed chemical shifts for C-4 in the range of 133.9–135.1 ppm as a quartet with $^2J_{CF}$ ~31 Hz and for CF_3 groups in the range of 123.7–123.9 ppm as a quartet with $^1J_{CF}$ ~275 Hz. According to the literature, it is well known that the proton in the 5-position of the quinoline nucleus shows long-range coupling with fluorine atoms of the 4-trifluoromethyl substituent, but in some cases, the outer signals of the quartets can appear as shoulders on the inner signals instead of as clearly resolved quartets [42]. This splitting of the H-5 signal is seen in all of the compounds having this structural feature and was clearly seen in ^1H NMR spectra data of the compounds **3b–i**. Any other quinoline analog was not isolated or observed by NMR experiments.

In conclusion, we have described a simple, highly regioselective, and inexpensive route to prepare tetrasubstituted quinolines through cycloaromatization reaction of a variety of enaminones. Our strategy allows efficacy, rapidity, and adequate diversity of substituents in the construction of the quinoline ring system. Furthermore, we have been able to use 2,6-DAT, for the first time, in the synthesis of trifluoromethylated quinolines, which possess free amino and methyl groups for further important derivatizations. This process might lead to greater molecular diversity of trifluoromethyl-substituted nitrogen heterocycles, which are of great potential interest for pharmacological and material applications.

EXPERIMENTAL

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. The melting points were determined using an Electrothermal Mel-Temp 3.0 apparatus (Microquímica Equipamentos Ltda, Brazil). ^1H, ^{13}C, and ^{19}F NMR spectra were acquired on a Bruker DPX 200 spectrometer (^1H at 200.13 MHz) and Bruker DPX 400 (^1H at 400.13 MHz, ^{13}C at 100.32 MHz, and ^{19}F at 376.3 MHz) spectrometer (Bruker Co., Germany), 5 mm

Scheme 3. Synthesis of 7-aminoquinolines **3** from trifluoracetyl enamines **2**. Reagents and conditions: (*i*) (1.2 g P_2O_5 + 0.8 mL H_3PO_4)/mmol (**2**), 90°C, 6 h.



2a-f **3b-f**

2,3	a	b	c	d	e	f
R	H	Me	Ph	4-FPh	4-BrPh	4-MePh

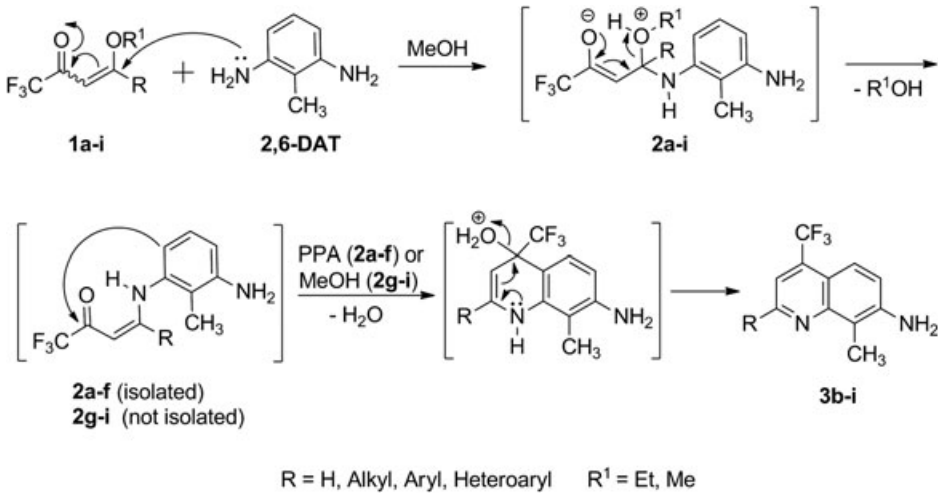


Figure 2. Proposed mechanism for the synthesis of **2a–f** and **3b–i**.

sample tubes, 298 K, digital resolution ± 0.01 ppm, in $CDCl_3$, using TMS as internal reference (^1H and ^{13}C) or fluorobenzene as external reference (^{19}F). Mass spectra were registered in an HP 6890 GC connected to a HP 5973 MSD and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier gas. The CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (São Paulo University, USP/Brazil).

Synthetic procedures: General procedure for the preparation of (*Z*)-*N*-(oxotrifluoroalkenyl)-2,6-diaminotoluenes (2a–f). To a magnetically stirred solution of 2,6-diaminotoluene (0.25 g, 2 mmol) in methanol (20 mL), a solution of **1** (2 mmol) in methanol (20 mL) was added dropwise at 0°C over a period of 2 h. After the end of the reaction, traces of the bis-enaminones were isolated by filtration. The solvent was evaporated under reduced pressure and the products **2a–f** recrystallized from ethanol (46–70% yields).

(3*Z*)-4-(3-Amino-2-methylanilino)-1,1,1-trifluoro-3-buten-2-one (2a). This compound was obtained as a yellow solid, yield 70%, mp 118–120°C. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 12.12$ (s, 1H, NH), 7.66 (dd, $J_1 = 8$, $J_2 = 12$ Hz, 1H, H-1), 7.06 (t, $J = 8$ Hz, 1H, H-7), 6.64 (d, $J = 8$ Hz, 1H, H-6), 6.57 (d, $J = 8$ Hz, 1H, H-8), 5.67 (d, $J = 8$ Hz, 1H, H-2), 3.78 (s, 2H, NH_2), 2.17 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 178.9$ (q, $^2J = 34$ Hz, C=O), 151.1 (C-1), 146.0 (C-9), 138.0 (C-5), 127.4 (C-10), 117.1 (q, $^1J = 288$ Hz, CF_3), 112.8 (C-7), 112.0 (C-6), 106.1 (C-8), 89.7 (C-2, $^3J = 2$ Hz), 10.5 (CH_3) ppm; GC–MS (EI, 70 eV): *m/z* (%) = 244 (M^+, 100), 227 (5), 175 (98), 160 (50), 147 (49), 133 (70), 77 (30), 69 (8), 66 (15). *Anal.* Calcd for $C_{11}H_{11}F_3N_2O$ (244.08): C, 54.10; H, 4.54; N, 11.47%. Found: C, 54.29; H, 4.55; N, 11.22%.

(3*Z*)-4-(3-Amino-2-methylanilino)-1,1,1-trifluoro-3-penten-2-one (2b). This compound was obtained as a brown solid, yield 53%, mp 113–115°C. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 12.39$ (s, 1H, NH), 7.05 (t, $J = 8$ Hz, 1H, H-7), 6.67 (d, $J = 8$ Hz, 1H, H-6), 6.54 (d, $J = 8$ Hz, 1H, H-8), 5.55 (s, 1H, H-3), 3.65 (s, 2H, NH_2), 2.05 (s, 3H, CH_3), 1.98 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 176.5$ (q, $^2J = 34$ Hz, C=O), 169.3 (C-2), 146.0 (C-10), 136.2 (C-6), 126.8 (C-11), 117.6 (q, $^1J = 288$ Hz, CF_3), 118.1 (C-8), 116.5 (C-7), 114.5 (C-9), 89.9 (C-3, $^3J = 2$ Hz), 19.8, 11.5 (2 CH_3) ppm; GC–MS (EI, 70 eV): *m/z* (%) = 258 (M^+, 100), 241 (10), 189 (90), 175 (20), 161 (91), 146 (55). *Anal.* Calcd for $C_{12}H_{13}F_3N_2O$ (258.10): C, 55.81; H, 5.07; N, 10.85%. Found: C, 55.66; H, 5.03; N, 10.94%.

(3*Z*)-4-(3-Amino-2-methylanilino)-1,1,1-trifluoro-4-phenyl-3-buten-2-one (2c). This compound was obtained as a yellow solid, yield 50%, mp 122–124°C. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 12.47$ (s, 1H, NH), 7.34–7.24 (m, 5H, Ph), 6.72 (t, $J = 8$ Hz, 1H, H-7), 6.46 (d, $J = 8$ Hz, 1H, H-6), 6.11 (d, $J = 8$ Hz, 1H, H-8), 5.70 (s, 1H, H-2), 3.58 (s, 2H, NH_2), 2.11 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 177.2$ (q, $^2J = 34$ Hz, C=O), 167.8 (C-1), 145.5 (C-9), 137.1 (C-5), 134.1, 130.4, 128.7, 128.3, 127.9 (6C-Ph), 127.2 (C-7), 126.2 (C-10), 120.3 (q, $^1J = 288$ Hz, CF_3), 116.7 (C-6), 113.4 (C-8), 91.7 (C-2), 11.6 (CH_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -75.05$ ppm; GC–MS (EI, 70 eV): *m/z*(%) = 320 (M^+, 33), 303 (5), 251 (65), 236 (3), 223 (100), 208 (64), 69 (2). *Anal.* Calcd for $C_{17}H_{15}F_3N_2O$ (320.11): C, 63.75; H, 4.72; N, 8.75%. Found: C, 63.71; H, 4.57; N, 8.94%.

(3*Z*)-4-(3-Amino-2-methylanilino)-1,1,1-trifluoro-4-(4-fluorophenyl)-3-buten-2-one (2d). This compound was obtained as a yellow solid, yield 46%, mp 99–101°C. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 12.47$ (s, 1H, NH), 7.30–7.22 (m, 2H, Ph), 7.01–6.91 (m, 2H, Ph), 6.77 (t, $J = 8$ Hz, 1H, H-7), 6.51 (d, $J = 8$ Hz, 1H, H-6), 6.10 (d, $J = 8$ Hz, 1, H-8), 5.69 (s, 1H, H-2), 3.70 (s, 2H, NH_2), 2.14 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 178.3$ (q, $^2J = 34$ Hz, C=O), 166.2 (C-1), 163.9 (d, $^1J = 253$ Hz, C-FPh), 145.7 (C-9), 138.1 (C-5), 130.4 (d, $^3J = 9$ Hz, 2C-FPh), 129.7 (d, $^4J = 3$ Hz, C-FPh), 127.7 (C-7), 126.2 (C-10), 124.8 (C-6), 117.2 (q, $^1J = 288$ Hz, CF_3), 116.0 (d, $^2J = 22$ Hz, 2C-FPh), 113.6 (C-8), 92.7 (C-2), 13.2 (CH_3) ppm; GC–MS (EI, 70 eV): *m/z* (%) = 338 (M^+, 20), 321 (5), 269 (60), 254 (5), 241 (100), 226 (70), 96 (5), 69 (6). *Anal.* Calcd for $C_{17}H_{14}F_4N_2O$ (338.1): C, 60.36; H, 4.17; N, 8.28%. Found: C, 60.72; H, 3.83; N, 8.67%.

(3*Z*)-4-(3-Amino-2-methylanilino)-4-(4-bromophenyl)-1,1,1-trifluoro-3-buten-2-one (2e). This compound was obtained as a yellow solid, yield 48%, mp 165–167°C. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 12.43$ (s, 1H, NH), 7.42 (d, $J = 8$ Hz, 2H, Ph), 7.13

(d, J = 8 Hz, 2H, Ph), 6.76 (t, J = 8 Hz, 1H, H-7), 6.51 (d, J = 8 Hz, 1H, H-6), 6.11 (d, J = 8 Hz, 1H, H-8), 5.68 (s, 1H, H-2), 3.70 (s, 2H, NH_2), 2.13 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5 (q, ^2J = 34 Hz, C=O), 166.5 (C-1), 145.6 (C-9), 136.9 (C-5), 133.0 (C-7), 131.7, 129.6, 126.5 (6C-Ph), 125.1 (C-10), 117.4 (q, ^1J = 288 Hz, CF_3), 116.8 (C-6), 113.6 (C-8), 91.7 (C-2), 11.7 (CH_3) ppm; GC–MS (EI, 70 eV): m/z (%) = 398 (M^+, 30), 381 (12), 329 (49), 301 (100), 286 (38). *Anal*. Calcd for $C_{17}H_{14}BrF_3N_2O$ (398.02): C, 51.15; H, 3.53; N, 7.02%. Found: C, 51.00; H, 3.27; N, 6.71%.

(3*Z*)-4-(3-Amino-2-methylanilino)-1,1,1-trifluoro-4-(4-methylphenyl)-3-buten-2-one (2f). This compound was obtained as a yellow solid, yield 45%, mp 147–149°C. ^1H NMR (200 MHz, $CDCl_3$): δ = 12.53 (s, 1H, NH), 7.17 (d, J = 8, 2H, Ph), 7.07 (d, J = 8, 2H, Ph), 6.76 (t, J = 8 Hz, 1H, H-7), 6.49 (d, J = 8 Hz, 1H, H-6), 6.14 (d, J = 8 Hz, 1H, H-8), 5.71 (s, 1H, H-2), 3.69 (s, 2H, NH_2), 2.31 (s, 3H, CH_3), 2.13 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9 (q, ^2J = 34 Hz, C=O), 167.9 (C-1), 145.5 (C-9), 141.0 (C-Ph), 137.3 (C-5), 131.1 (C-7), 129.1, 128.1 (5C-Ph), 126.3 (C-10), 117.5 (q, ^1J = 288 Hz, CF_3), 116.8 (C-6), 113.3 (C-8), 91.6 (C-2, ^3J = 2 Hz), 21.3, 11.8 (2 CH_3) ppm; GC–MS (EI, 70 eV): m/z (%) = 334 (M^+, 30), 316 (60), 265 (80), 237 (100), 222 (50). *Anal*. Calcd for $C_{18}H_{17}F_3N_2O$ (334.13): C, 64.66; H, 5.13; N, 8.38%. Found: C, 64.49; H, 5.02; N, 8.46%.

Synthetic procedures: General procedure for the preparation of 2-alkyl(aryl)-4-trifluoromethyl-8-methyl-7-aminoquinolines (3b–f). To a stirred mixture of P_2O_5 (1.2 g) and H_3PO_4 (0.8 mL) (PPA) at 90°C, **2a–f** (1 mmol) was added. The reaction mixture was stirred for an additional 6 h. After cooling, the reaction mixture was treated with crushed ice and with concentrated NH_4OH until the pH was 8. The compounds **3b–f** were isolated of the solution by filtration at reduced pressure (86–93% yields).

4-Trifluoromethyl-2,8-dimethyl-7-aminoquinoline (3b). This compound was obtained as a beige solid, yield 86%, mp 81–83°C. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.77 (dq, J_1 = 2, J_2 = 9 Hz, 1H, H-5), 7.28 (s, 1H, H-3), 7.00 (d, J = 9 Hz, 1H, H-6), 4.02 (s, 2H, NH_2), 2.73 (s, 3H, CH_3), 2.59 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3 (C-2), 148.7 (C-8a), 145.3 (C-7), 133.9 (q, ^2J = 30 Hz, C-4), 123.9 (q, ^1J = 275 Hz, CF_3), 121.9 (q, ^4J = 2 Hz, C-5), 118.5 (C-6), 115.4 (C-8), 114.9 (C-4a), 117.7 (q, ^3J = 5 Hz, C-3), 25.6, 10.4 (2 CH_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −61.24 ppm; GC–MS (EI, 70 eV): m/z (%) = 240 (M^+, 100), 221 (2), 212 (8). *Anal*. Calcd for $C_{12}H_{11}F_3N_2$ (240.09): C, 60.00; H, 4.62; N, 11.66%. Found: C, 60.14; H, 4.60; N, 11.54%.

4-Trifluoromethyl-8-methyl-2-phenyl-7-aminoquinoline (3c). This compound was obtained as a beige solid, yield 90%, mp 128–130°C. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.24–8.18 (m, 2H, Ph), 7.90 (s, 1H, H-3), 7.80 (dq, J_1 = 2, J_2 = 8 Hz, 1H, H-5), 7.56–7.44 (m, 3H, Ph), 7.02 (d, J = 9 Hz, 1H, H-6), 3.87 (s, 2H, NH_2), 2.67 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1 (C-2), 148.8 (C-8a), 145.5 (C-7), 139.1 (C-Ph), 134.9 (q, ^2J = 31 Hz, C-4), 129.6, 128.8, 127.3 (5C-Ph), 123.9 (q, ^1J = 275 Hz, CF_3), 121.9 (q, ^4J = 2 Hz, C-5), 119.3 (C-6), 116.1 (C-8), 115.7 (C-4a), 111.4 (q, ^3J = 5 Hz, C-3), 10.5 (CH_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −60.54 ppm; GC–MS (EI, 70 eV): m/z (%) = 302 (M+, 100), 286 (5), 274 (10), 233 (5). *Anal*. Calcd for $C_{17}H_{13}F_3N_2$ (302.10): C, 67.54; H, 4.33; N, 9.27%. Found: C, 67.33; H, 4.18; N, 9.41%.

4-Trifluoromethyl-2-(4-fluorophenyl)-8-methyl-7-aminoquinoline (3d). This compound was obtained as a beige solid, yield 96%, mp 140–142°C. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.20–8.17 (m, 2H, FPh), 7.81 (s, 1, H-3), 7.79 (d, J = 9 Hz, 1H, H-5), 7.19–7.17 (m, 2H, FPh), 7.02 (d, J = 9 Hz, 1H, H-6), 4.05 (s, 2H, NH_2), 2.65 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0 (d, ^1J = 249 Hz, C-FPh), 154.1 (C-2), 148.9 (C-8a), 145.7 (C-7), 135.4 (d, ^4J = 3 Hz, C-FPh), 135.1 (q, ^2J = 31 Hz, C-4), 129.2 (d, ^{3} = 9 Hz, 2C-FPh), 123.9 (q, ^1J = 275 Hz, CF_3), 122.0 (C-5), 119.4 (C-6), 116.1 (C-8), 115.7 (C-4a), 115.6 (d, ^2J = 22 Hz, 2C-FPh), 111.0 (q, ^3J = 5 Hz, C-3), 10.4 (CH_3) ppm; GC–MS (EI, 70 eV): m/z (%) = 320 (M^+, 100), 301 (5), 251 (5). *Anal*. Calcd for $C_{17}H_{12}F_4N_2$ (320.09): C, 63.75; H, 3.78; N, 8.75%. Found: C, 63.55; H, 3.70; N, 8.82%.

2-(4-Bromophenyl)-4-trifluoromethyl-8-methyl-7-aminoquinoline (3e). This compound was obtained as a yellow solid, yield 92%, mp 174–176°C. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.08 (d, J = 8 Hz, 2H, Ph), 7.81 (d, J = 9 Hz, 1H, H-5), 7.78 (s, 1H, H-3), 7.62 (d, J = 8 Hz, 2H, Ph), 7.06 (d, J = 9 Hz, 1H, H-6), 4.10 (s, 2H, NH_2), 2.65 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.8 (C-2), 148.7 (C-8a), 145.6 (C-7), 138.0 (C-Ph), 135.1 (q, ^2J 3 = 1 Hz, C-4), 131.9, 128.7, 124.2 (5C-Ph), 123.8 (q, ^1J = 275 Hz, CF_3), 121.9 (q, ^4J = 2 Hz, C-5), 119.6 (C-6), 116.0 (C-8), 115.4 (C-4a), 110.9 (q, ^3J = 5 Hz, C-3), 10.5 (CH_3) ppm; GC–MS (EI, 70 eV): m/z (%) = 380 (M^+, 100), 301 (5). *Anal*. Calcd for $C_{17}H_{12}BrF_3N_2$ (380.01): C, 53.56; H, 3.17; N, 7.35%. Found: C, 53.26; H, 3.00; N, 7.06%.

4-Trifluoromethyl-8-methyl-2-(4-methylphenyl)-7-aminoquinoline (3f). This compound was obtained as a beige solid, yield 93%, mp 121–123°C. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.16 (d, J = 9 Hz, 2H, Ph), 7.92 (s, 1H, H-3), 7.83 (dq, J_1 = 2, J_2 = 9 Hz, 1H, H-5), 7.35 (d, J = 9 Hz, 2H, Ph), 7.06 (d, J = 9 Hz, 1H, H-6), 4.09 (s, 2H, NH_2), 2.71 (s, 3H, CH_3), 2.46 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0 (C-2), 148.7 (C-8a), 145.5 (C-7), 139.7, 136.3 (2C-Ph), 134.7 (q, ^2J = 31 Hz, C-4), 129.5, 127.1 (4C-Ph), 123.9 (q, ^1J = 275 Hz, CF_3), 121.8 (q, ^4J = 2 Hz, C-5), 119.0 (C-6), 116.0 (C-8), 115.5 (C-4a), 111.2 (q, ^3J = 5 Hz, C-3), 21.3, 10.5 (2 CH_3) ppm; GC–MS (EI, 70 eV): m/z (%) = 316 (M^+, 100), 301 (3), 288 (4). *Anal*. Calcd for $C_{18}H_{15}F_3N_2$ (316.12): C, 68.35; H, 4.78; N, 8.86%. Found: C, 68.22; H, 4.61; N, 8.98%.

Synthetic procedures: General procedure for the preparation of 2-aryl(heteroaryl)-4-trifluoromethyl-8-methyl-7-aminoquinolines (3g–i). To a magnetically stirred solution of 2,6-diaminotoluene (0.49 g, 4 mmol) in methanol (40 mL), a solution of **1g–i** (4 mmol) in methanol (40 mL) was added dropwise at 0°C over a period of 2 h. The mixture was refluxed for an additional 24 h. The crude oily product was dissolved in hot methanol and subsequently cooled (4–8°C, 24 h). The solids **3g–i** were isolated from the cooled solution by filtration under reduced pressure (31–36% yields). The compound **3h** was recrystallized from chloroform (21% yield).

4-Trifluoromethyl-2-(4-methoxyphenyl)-8-methyl-7-aminoquinoline (3g). This compound was obtained as a yellow solid, yield 36%, mp 126–128°C. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.19 (d, J = 8 Hz, 2H, Ph), 7.86 (s, 1H, H-3), 7.80 (d, J = 9 Hz, 1H, H-5), 7.04 (d, J = 9 Hz, 3H, H-6, Ph), 3.88 (s, 2H, NH_2), 3.88 (s, 3H, OCH_3), 2.69 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0 (C-2), 154.7 (C-8a), 148.8 (C-7), 145.5 (C-Ph), 134.8 (q, ^2J = 31 Hz, C-4), 131.8, 128.7 (3C-Ph), 124.0 (q, ^1J = 275 Hz, CF_3), 121.8 (q, ^4J = 2 Hz, C-5), 118.9 (C-6), 116.0 (C-8), 114.2 (2C-Ph),

115.4 (C-4a), 111.0 (q, $^3J = 5$ Hz, C-3), 55.4 (OCH_3), 10.5 (CH_3) ppm; GC–MS (EI, 70 eV): *m/z* (%) = 332 (M^+, 100), 317 (9), 316 (5), 304 (12), 263 (5), 248 (4). *Anal*. Calcd for $C_{18}H_{15}F_3N_2O$ (332.11): C, 65.06; H, 4.55; N, 8.43%. Found: C, 64.86; H, 4.33; N, 8.60%.

4-Trifluoromethyl-2-(2-furyl)-8-methyl-7-aminoquinoline (3h). This compound was obtained as a yellow solid, yield 21%, mp 117–119°C. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.87$ (s,1H, H-3), 7.78 (dq, $J_1 = 2$, $J_2 = 8$ Hz, 1H, H-5), 7.59 (d, $J = 1$ Hz, 1H, furyl), 7.28 (dd, $J_1 = 1$, $J_2 = 3$ Hz, 1H, furyl), 7.06 (d, $J = 9$ Hz, 1H, H-6), 6.58 (dd, $J_1 = 1$, $J_2 = 2$ Hz, 1H, furyl), 4.07 (s, 2H, NH_2), 2.63 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 153.9$ (C-2), 148.7 (C-8a), 147.5 (C-furyl), 145.6 (C-7), 144.8 (C-furyl), 134.8 (q, $^2J = 31$ Hz, C-4), 123.8 (q, $^1J = 275$ Hz, CF_3), 121.9 (q, $^4J = 2$ Hz, C-5), 119.1 (C-6), 115.7 (C-8), 115.5 (C-4a), 112.3 (C-furyl), 110.3 (q, $^3J = 5$ Hz, C-3), 109.9 (C-furyl), 10.4 (CH_3) ppm; GC–MS (EI, 70 eV): *m/z* (%) = 292 (M^+, 100), 273 (5), 263 (12), 223 (3), 206 (4), 193 (6). *Anal*. Calcd for $C_{15}H_{11}F_3N_2O$ (292.08): C, 61.64; H, 3.79; N, 9.59%. Found: C, 61.58; H, 3.70; N, 9.65%.

4-Trifluoromethyl-8-methyl-2-(2-thienyl)-7-aminoquinoline (3i). This compound was obtained as a yellow solid, yield 31%, mp 130–132°C. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.76$ (s, 1H, H-3), 7.73 (d, $J = 2$ Hz, 1H, H-5), 7.69 (dd, $J_1 = 1$, $J_2 = 4$ Hz, 1H, thienyl), 7.43 (dd, $J_1 = 1$, $J_2 = 4$ Hz, 1H, thienyl), 7.13 (t, $J = 4$ Hz, 1H, thienyl), 7.00 (d, $J = 9$ Hz, 1H, H-6), 4.05 (s, 2H, NH_2), 2.62 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 150.5$ (C-2), 148.6 (C-8a), 145.7 (C-7), 145.6 (C-thienyl), 134.8 (q, $^2J = 31$ Hz, C-4), 128.8, 128.1, 125.7 (3C-thienyl), 123.7 (q, $^1J = 275$ Hz, CF_3), 121.9 (q, $^4J = 2$ Hz, C-5), 118.9 (C-6), 115.7 (C-8), 115.6 (C-4a), 110.3 (q, $^3J = 5$ Hz, C-3), 10.3 (CH_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -60.45$ ppm; GC–MS (EI, 70 eV): *m/z* (%) = 308 (M^+, 100), 289 (4), 259 (5), 240 (3), 223 (7), 207 (15), 154 (12). *Anal*. Calcd for $C_{15}H_{11}F_3N_2S$ (308.06): C, 58.43; H, 3.60; N, 9.09%. Found: C, 58.08; H, 3.64; N, 8.90%.

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