An Efficient and Regiospecific Preparation of Trifluoromethyl Substituted 4-(1*H*-Pyrazol-1-yl)-7-chloroquinolines

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A new series of 4-[3-alkyl(aryl)(heteroaryl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-7-chloroquinolines, where [alkyl = CH_3; aryl = C_6H_5, 4-$CH_3C_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$CH_3OC_6H_4$, 4-$NO_2C_6H_4$, 4-biphenyl, 1-naphthyl; heteroaryl = 2-furyl and 2-thienyl] has been regiospecificaly obtained from the reaction of 7-chloro-4-hydrazinoquinoline with 4-substituted-1,1,1-trifluoro-4-methoxybut-3-en-2-ones in 61 – 96 % yield. Subsequently, dehydration reaction of 4,5-dihydropyrazolylquinolines under acid conditions furnished a new series of 4-(3-substituted-5-trifluoromethyl-1*H*-pyrazol-1-yl)-7-chloroquinolines in 73 – 96 % yield.

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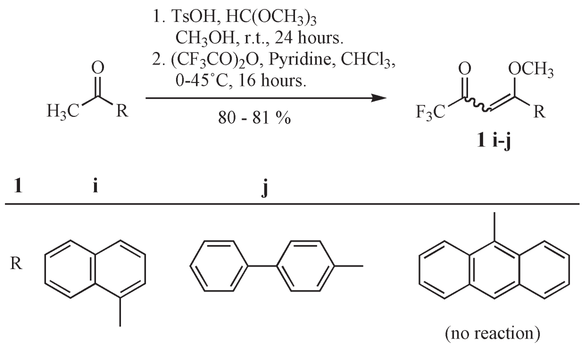
Fluorine-containing quinolines are of significant interest due to biological properties of fluorine that play a pivotal role in bioactive compounds [1,2] The routes to aromatic heterocycles are of ongoing interest, especially methods of placing fluorine selectively on heterocycle moieties since these derivates often exhibit bioactivity [3]. Many substituted pyrazolines and pyrazoles are important biological agents and a significant amount of research has been directed to this class [4]. These compounds are used as antibacterial, antifungal, anti-inflammatory, antitumor, antiviral, antiparasitic, anti-tubercular, anti-diabetic, agrochemicals and insecticidal agents, anesthetic, and analgesic properties [3-7]. Specifically, trichloromethyl substituted pyrazoles obtained recently have demonstrated hypothermic, antipyretic, and antinociception activity, according to biological tests in mice [8,9].

Recently, Singh *et al.* [6,7,10] reported structural and mechanistic studies about the synthesis of pyrazolylquinolines. Specifically, when 4-hydrazino-2-methyl- and 4-hydrazino-7-chloroquinoline, in a synthetic method with limited scope, were allowed to react with 1,1,1-trifluoropentane-2,4-dione in boiling ethanol for 6 hours [7], only stable crystalline trifluoroacetyl hydrazone derivatives were obtained in good yields (70 – 72 %). The elimination of the second molecule of water from the respective hydrazones to obtain the aromatic pyrazole was effected only by treatment with hot acetic acid for 4 hours in 72 – 75 % yields. This procedure allowed to synthesize and isolate the corresponding mixtures of 5(3)-trifluoromethyl-5(3)-hydroxy-4,5-dihydropyrazolylquinolines. On the other hand, the reactions of 2-hydrazino-4-methylquinoline with aliphatic and aromatic trifluoromethyl-β-diketones have been reported [7]. It was determined that aliphatic trifluoromethyl-β-diketones (alkyl = CH_3, CF_3) gave only 2-(3-alkyl-5-trifluoromethyl-5-hydroxy-4,5-dihydropyrazolyl)quinolines. However, by similar reaction conditions (refluxing ethanol for 3 hours), the aryl trifluoromethyl-β-diketones (aryl = C_6H_5, thien-2-yl) gave not only a mixture of aromatic and non-aromatic products, but also the corresponding isomers such as 5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazolylquinolines and 3-trifluoromethyl-pyrazolylquinolines. In accordance with biological screening was demonstrated that β-diketones, trifluoromethylated or not, were less interesting to obtain new compounds with pharmaceutical application, due to the possibility of loosing the regiochemistry during the cyclocondensation reaction, when these 1,3-dicarbonyl compounds are non-symmetrical.

The aim of our research is to report a facile, efficient and regiospecific synthesis of 4-(3-substituted-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl)-7-chloroquinolines (**2**) from the reaction of 7-chloro-4-hydrazinoquinoline with 1,1,1-trifluoro-4-methoxybut-3-en-2-ones (**1**) to generate new compounds for further antimalarial screening. Subsequently, the quinolines **2** were submitted to dehydration reaction to obtain a new series of 4-(3-substituted-5-trifluoromethyl-1*H*-pyrazol-1-yl)-7-chloroquinolines (**3**).

Scheme I

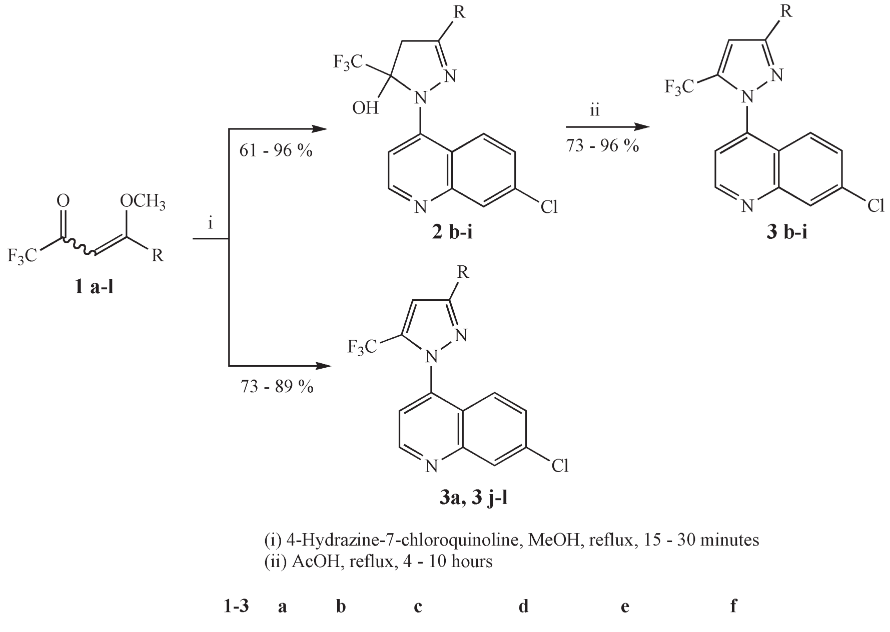


β-Alkoxyvinyl trifluoromethyl ketones (**1a-l**) were prepared as previously reported [11-14], with the exception of **1i** and **1j**, which were prepared as described in this paper (Scheme I). In order to obtain compounds, bearing a new aromatic substituent at the 3-position of pyrazole rings (**2, 3**), new 4-aryl-4-methoxy-1,1,1-trifluoro-3-buten-2-ones (**1**) were prepared from the reaction of 4-acetylbiphenyl and 1-acetylnaphthalene, respectively, with trimethyl orthoformate in the presence of *p*-toluenesulfonic acid. The acylation reaction of acetals with trifluoroacetic anhydride in pyridine and chloroform as solvent was carried out in a molar ratio of 1:2:2, respectively. An exception using this methodology 9-acetylanthracene did not furnish the acetal, as well the respective vinyl ketone (Scheme I). We suggest that the steric effect is the main factor to explain the results of the reaction from acetophenone, 4-acetylbiphenyl, 1-acetylnaphthalene and 9-acetylanthracene with trimethyl orthoformate. As an exception, only 9-acetylanthracene presents H-1 and H-8 hindering a nucleophilic attack to the carbonyl carbon of the acetyl group. The other three above mentioned ketones have the carbonyl carbon with at least one free face for the reaction with trimethyl orthoformate to take place.

The reactions of **1** with 4-hydrazino-7-chloroquinoline, in a molar ratio of 1:1, were carried out in methanol for 15 to 30 minutes under reflux to give a novel series of pure 5-hydroxy-dihydropyrazolylquinolines (**2**) in 61 – 96 % yield (Scheme II). Using this method we were unable to isolate the corresponding pyrazoline **2a** and **2j-l**. When these reactions were carried out in refluxing methanol only aromatic heterocycles **3a** and **3j-l** could be isolated and no traces of **2a**, **2j-l** (2-pyrazolines) are detected. Compounds **2b-i** were converted in the respective aromatic system **3** by an easy treatment of **2** with acetic acid at reflux for 4 hours (73 – 96 % yields). As expected, the dehydration reaction of *p*-nitrophenyl substituted pyrazoline derivative **2h** was very difficult (reflux for 10 hours) but resulted in 82 % yield. It is well-known that, in most cases, 5-hydroxy-4,5-dihydro-1*H*-pyrazoles have been obtained, as stable compounds, when some pyrazoline atoms are substituted with a strong electron-withdrawing group. This electronic effect hinders the elimination of water and makes the subsequent aromatization of the pyrazoline ring difficult [15].

Complementary, to confirm that the pyrazoles **3** could be obtained regiospecificaly and directly from the reaction of **1** with 7-chloro-4-hydrazinoquinoline, the synthesis of **3b** was also performed in a single step reaction without the isolation of the quinoline **2b** (Scheme III). This was possible when the respective reaction was carried out in methanol under reflux for 15 min. After this time, the methanol was evaporated and the reaction treated with acetic acid at reflux for 4 hours to give **3b** in 84% yield.

Scheme II

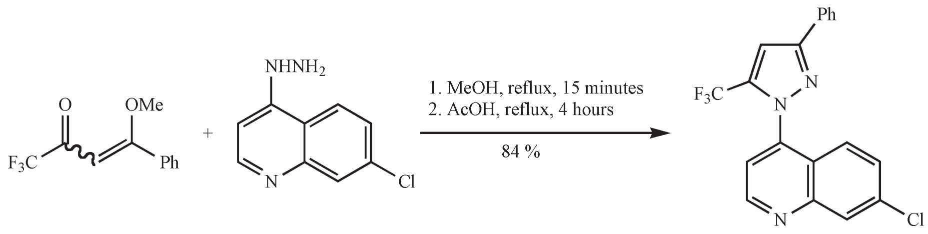


(i) 4-Hydrazine-7-chloroquinoline, MeOH, reflux, 15 - 30 minutes
(ii) AcOH, reflux, 4 - 10 hours

1-3	**a**	**b**	**c**	**d**	**e**	**f**
R	CH_3	C_6H_5	4-$CH_3C_6H_4$	4-FC_6H_4	4-ClC_6H_4	4-BrC_6H_4

1-3	**g**	**h**	**i**	**j**	**k**	**l**
R	4-$OCH_3C_6H_4$	4-$NO_2C_6H_4$	4-biphenyl	1-naphtyl	2-thienyl	2-furyl

Scheme III



The unambiguous ^{1}H- and ^{13}C-NMR chemical shift assignments of compounds **1-3** were obtained with the help of homo- and heteronuclear COSY, HMQC and HMBC 2D-NMR experiments and by comparison with NMR data of other 2-pyrazolines formerly synthesized in our laboratory.

The structures of 4-(5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl)quinolines (**2**) were deduced from their NMR spectra. Compounds **2** show the ^{1}H chemical shifts of the methylene protons (H4a and H4b) as a characteristic AB system with a doublet in average at δ 3.70 and the other doublet at δ 4.07, respectively, with a *geminal* coupling constant ^2J 18.7 Hz. Compounds **2** present the typical ^{13}C chemical shifts of the pyrazoline ring at δ *ca.* 113.8 (C3) and 43.7 (C4). The C5 presents a characteristic quartet at δ *ca.* 93.90 with $^2J_{C\text{-}F}$ 31.78 Hz, due to the OH and the CF$_3$ group that are attached. The CF$_3$ group shows a typical quartet at δ *ca.* 123.7 with $^1J_{C\text{-}F}$ 285.4 Hz.

The structures of the 4-(5-trifluoromethyl-1*H*-pyrazol-1-yl)-7-chloroquinolines (**3**) were also deduced from their NMR spectra. Compounds **3** present the typical ^{13}C chemical shifts of the pyrazole ring in average at δ 151.3 (C3) and 107.0 (C4). The C5 presents a characteristic quartet in average at δ 134.5 with $^2J_{C\text{-}F}$ 38.8 Hz, due to the attached CF$_3$ group. The CF$_3$ group shows a typical quartet in average at δ 119.3 with $^1J_{C\text{-}F}$ 269.5 Hz. Thus, the trifluoromethyl group for compounds **2** and **3** must be attached to the carbon at position 5 of the ring and the regioisomer must be as shown.

Compounds **2** and **3** were also characterized by mass spectroscopic studies in which, significantly, molecular ions were observed corresponding to the 4-(1*H*-pyrazol-1-yl)-7-chloroquinolines. As an exception in the series **2b-i**, compounds **2e-i** underwent thermal dehydration during acquisition of the mass spectrum and mass ions values corresponding to the aromatic pyrazolylquinolines **3e-i** were obtained.

In conclusion, the present methodology allowed to obtain a new series of 4-(5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl)-7-chloroquinolines (**2**) and the bis-heterocyclic and tris-heterocyclic aromatic systems (**3**) from β-alkoxyvinyl trifluoromethyl ketones **1**, in a single reaction step, in a shorter time, and in high yields. In addition, it was possible to introduce regiospecificaly alkyl, aryl or heteroaryl substituents in the 3-position of the pyrazole ring of compounds **2** and **3**. We hope that the new trifluoromethylated compounds describe here contribute to a combinatorial library of 7-chloro-4-pyrazolylquinolines aiming to determine the most potent drug and its action pathway as an antimalarial agent.

EXPERIMENTAL

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined using open capillaries on a Reichert Thermovar apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz), 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in chloroform-d_3 for compounds **1** and methyl sulfoxide-d_6 for **2** and **3** using TMS as internal reference. Mass spectra were registered in a HP 6890 GC connected to a HP 5973 MSD and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, auto sampler, 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).

General Procedure for the Preparation of 4-Aryl-1,1,1-trifluoro-4-methoxybut-3-en-2-ones (**1i-j**).

To a stirred solution of dimethoxy acetals derived from 4-acetylbiphenyl or 1-acetylnaphthalene (30 mmol) and pyridine (60 mmol, 4.8 g) in chloroform (30 ml) kept at 0 ºC (ice bath), trifluoroacetic anhydride (60 mmol) was added drop wise. The mixture was stirred for 16 h at 45 ºC. The mixture was quenched and extracted with 0.1 *M* hydrochloric acid solution (3 x 15 ml) and after with water (1 x 15 ml). The organic layer was dried with magnesium sulfate and filtered. The solvent was evaporated and the products were obtained in high purity by recrystallization from methanol. Yield: 80 – 81%.

4-(4-Biphenyl)-1,1,1-trifluoro-4-methoxybut-3-en-2-one (**1i**).

This compound was obtained as a white solid, yield 80 %, Mp. 68 - 70 ºC.^{1}H NMR (CDCl$_3$) (Biphenyl) δ = 7.62-7.56 (m, 6H, Ph); 7.44-7.37 (m, 2H, Ph); 7.36-7.33 (m, 1H, Ph); 5.83 (s, H3); 3.93 (s, OMe). ^{13}C NMR (CDCl$_3$) (Biphenyl) δ = 140.1; 132.2;

129.4; 128.8; 127.8; 127.1; 126.6 (12C); 177.7 (C=O); 144.1 (C4); 118.2 (q, J_{CF} = 292.4, CF_3); 91.8 (C3); 57.2 (OMe).

Anal. Calcd. for $C_{17}H_{13}F_3O_2$ (306.28): C, 66.67; H, 4.28 %. Found: C, 66.55; H, 4.56 %.

4-(1-Naphthyl)-1,1,1-trifluoro-4-methoxybut-3-en-2-one (**1j**).

This compound was obtained as a yellow solid, yield 81 %, Mp. 75 - 77 ºC. ^{1}H NMR ($CDCl_3$) (Naphthyl) δ = 7.93-7.84 (m, 2H, Ar); 7.70-7.65 (m, 1H, Ar); 7.54-7.36 (m, 4H, Ar); 6.13 (s, H3); 3.91 (s, OMe). ^{13}C NMR ($CDCl_3$) (Naphthyl) δ = 132.1; 131.1; 130.3; 130.0; 128.5; 127.9; 126.9; 126.1; 124.9; 123.8 (10C, Ar); 177.3 (C=O); 133.3 (C4); 116.4 (q, J_{CF} = 292.4, CF_3); 94.6 (C3); 57.2 (OMe).

Anal. Calcd. for $C_{15}H_{11}F_3O_2$ (280.24): C, 64.29; H, 3.96 %. Found: C, 64.55; H, 4.00 %.

General Procedure for the Preparation of 4-(3-Substituted-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-7-chloroquinolines (**2b-i**).

To a magnetically stirred solution of **1b-i** (1 mmol) in MeOH (10 ml), 7-chloro-4-hydrazinoquinoline (1 mmol) was added at room temperature. The mixture was stirred under reflux (64 ºC) for 15 to 30 minutes. The solvent was evaporated under reduced pressure and the solid products **2b-i** recrystallized from a mixture of acetone and water 5:1. Yield: 61 – 96 %.

4-(5-Hydroxy-3-phenyl-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl)-7-chloroquinoline (**2b**).

This compound was obtained as a yellow solid, yield 92%, Mp. 195-198 ºC. ^{1}H NMR (DMSO-d_6) (Pyrazol) δ = 8.59 (s, OH); 3.92 (d, *J*=18.7, Ha); 3.56 (d, *J*= 18.7, Hb); (Quinolyl) δ = 8.70 (d, H2); 8.26 (d, H8); 7.92 (d, H6); 7.68 (d, H5); 7.45 (d, H3); (Phenyl) δ = 7.63-7.61; 7.33-7.31 (m, 5H). ^{13}C NMR (DMSO-d_6) (Pyrazol) δ = 149.0 (C3); 122.2 (q, J_{CF} = 285.3, CF_3); 93.8 (q, $^2J_{CF}$ = 31.7, C5); 43.7 (C4); (Quinolyl) δ = 151.3 (C2); 149.7 (C8a); 146.4 (C4); 133.8 (C7); 129.6 (C8); 128.7 (C6); 125.0 (C5); 122.6 (C4a); 113.7 (C3); (Phenyl) δ = 130.8; 127.5; 126.0; 125.8 (6C). MS (EI, 70 eV): *m/z* (%) = 391 (M^+, 73), 322 (100), 176 (27), 77 (26), 373 (6).

Anal. Calcd. for $C_{19}H_{13}ClF_3N_3O$ (391.77): C, 58.25; H, 3.34; N, 10.73 %. Found: C, 57.98; H, 3.36; N, 10.53 %.

4-[5-Hydroxy-3-(4-methylphenyl)-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-7-chloroquinoline (**2c**).

This compound was obtained as a yellow solid, yield 83 %, Mp. 191 - 193 ºC. ^{1}H NMR (DMSO-d_6) (Pyrazol) δ = 8.73 (s, OH); 4.02 (d, *J*=18.7, Ha); 3.67 (d, *J*= 18.7, Hb); (Quinolyl) δ = 8.83 (d, H2); 8.40 (d, H8); 8.05 (d, H6); 7.80 (d, H5); 7.62 (d, H3); (Phenyl) δ = 7.66-7.63; 7.29-7.27 (m, 4H); 2.35 (s, Me). ^{13}C NMR (DMSO-d_6) (Pyrazol) δ = 149.1 (C3); 122.7 (q, J_{CF} = 284.6, CF_3); 93.7 (q, $^2J_{CF}$ = 31.7, C5); 43.8 (C4); (Quinolyl) δ = 151.3 (C2); 149.8 (C8a); 146.2 (C4); 133.8 (C7); 129.3 (C8); 128.0 (C6); 125.8 (C5); 122.6 (C4a); 113.5 (C3); (Phenyl) δ = 139.5; 127.6; 127.5; 125.9 (6C); 20.8 (Me). MS (EI, 70 eV): *m/z* (%) = 405 (M^+, 67), 336 (100), 115 (41), 176 (15), 91 (13).

Anal. Calcd. for $C_{20}H_{15}ClF_3N_3O$ (405.80): C, 59.20; H, 3.73; N, 10.35 %. Found: C, 59.53; H, 3.91; N, 10.18 %.

4-[3-(4-Fluorophenyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-7-chloroquinoline (**2d**).

This compound was obtained as a yellow solid, yield 96 %, Mp. 169 - 171 ºC. ^{1}H NMR (DMSO-d_6) (Pyrazol) δ = 8.76 (s, OH); 4.07 (d, *J*=18.7, Ha); 3.74 (d, *J*= 18.7, Hb); (Quinolyl) δ = 8.87 (d, H2); 8.42 (d, H8); 8.08 (s, H6); 7.85 (s, H5); 7.62 (d, H3); (Phenyl) δ = 7.32-7.30 (m, 4H). ^{13}C NMR (DMSO-d_6) (Pyrazol) δ = 148.3 (C3); 123.4 (q, J_{CF} = 285.9, CF_3); 93.9 (q, $^2J_{CF}$ = 31.7, C5); 43.8 (C4); (Quinolyl) δ =151.3 (C2); 149.7 (C8a); 146.4 (C4); 133.8 (C7); 129.5 (C8); 128.2 (C6); 126.1 (C5); 122.6 (C4a); 113.8 (C3); (Phenyl) δ = 129.0; 128.1; 127.8; 127.5 (6C). MS (EI, 70 eV): *m/z* (%) = 409 (M^+, 72), 340 (100), 121 (62), 95 (23), 176 (20).

Anal. Calcd. for $C_{19}H_{12}ClF_4N_3O$ (409.77): C, 55.69; H, 2.95; N, 10.25 %. Found: C, 55.40; H, 2.58; N, 9.90 %.

4-[3-(4-Chlorophenyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-7-chloroquinoline (**2e**).

This compound was obtained as a yellow solid, yield 95 %, Mp. 206 - 208 ºC. ^{1}H NMR (DMSO-d_6) (Pyrazol) δ = 8.79 (s, OH); 4.06 (d, *J*=18.7, Ha); 3.68 (d, *J*= 18.7, Hb); (Quinolyl) δ = 8.85 (d, H2); 8.35 (d, H8); 8.06 (d, H6); 7.83-7.76 (m, H5); 7.64-7.61 (m, H3); (Phenyl) δ = 7.83-7.76; 7.55-7.53 (m, 4H). ^{13}C NMR (DMSO-d_6) (Pyrazol) δ = 148.0 (C3); 124.9 (q, J_{CF} = 284.6, CF_3); 94.0 (q, $^2J_{CF}$ = 31.7, C5); 43.6 (C4); (Quinolyl) δ = 151.3 (C2); 149.7 (C8a); 146.2 (C4); 133.8 (C7); 129.7 (C8); 128.7 (C6); 126.1 (C5); 122.1 (C4a); 113.8 (C3); (Phenyl) δ = 134.2; 129.0; 127.5; 127.3 (6C). MS (EI, 70 eV): *m/z* (%) = 407 (M – H_2O, 100), 338 (78), 135 (20), 75 (18), 162 (16).

Anal. Calcd. for $C_{19}H_{12}Cl_2F_3N_3O$ (426.22): C, 53.54; H, 2.84; N, 9.86 %. Found: C, 53.83; H, 2.67; N, 10.12 %.

4-[3-(4-Bromophenyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-7-chloroquinoline (**2f**).

This compound was obtained as a yellow solid, yield 87 %, Mp. 220 - 222 ºC. ^{1}H NMR (DMSO-d_6) (Pyrazol) δ = 8.75 (s, OH); 4.05 (d, *J*=18.5, Ha); 3.68 (d, *J*= 18.5, Hb); (Quinolyl) δ = 8.85 (d, H2); 8.34 (d, H8); 8.06 (d, H6); 7.79 (d, H5); 7.60 (d, H3); (Phenyl) δ = 7.63-7.62 (m, 4H). ^{13}C NMR (DMSO-d_6) (Pyrazol) δ = 148.1 (C3); 124.9 (q, J_{CF} = 285.3, CF_3); 94.1 (q, $^2J_{CF}$ = 31.7, C5); 43.5 (C4); (Quinolyl) δ = 151.8 (C2); 149.7 (C8a); 146.2 (C4); 133.8 (C7); 130.0 (C8); 127.7 (C6); 126.1 (C5); 122.1 (C4a); 113.9 (C3); (Phenyl) δ = 131.7; 127.6; 127.3; 122.9 (6C). MS (EI, 70 eV): *m/z* (%) = 453 (M – H_2O, 100), 384 (45), 135 (25), 75 (20), 162 (17).

Anal. Calcd. for $C_{19}H_{12}BrClF_3N_3O$ (470.67): C, 48.49; H, 2.57; N, 8.93 %. Found: C, 48.78; H, 2.79; N, 8.71 %.

4-[5-Hydroxy-3-(4-Methoxyphenyl)-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-7-chloroquinoline (**2g**).

This compound was obtained as a yellow solid, yield 94 %, Mp. 221 - 223 ºC. ^{1}H NMR (DMSO-d_6) (Pyrazol) δ = 8.67 (s, OH); 4.01 (d, *J*=18.7, Ha); 3.66 (d, *J*= 18.7, Hb); (Quinolyl) δ = 8.82 (d, H2); 8.43 (d, H8); 8.05 (d, H6); 7.80 (d, H5); 7.62-7.59 (m, H3); (Phenyl) δ = 7.72-7.70; 7.05-7.02 (m, 4H); 3.82 (s, OMe). ^{13}C NMR (DMSO-d_6) (Pyrazol) δ = 148.9 (C3); 123.7 (q, J_{CF} = 285.0, CF_3); 93.6 (q, $^2J_{CF}$ = 31.7, C5); 43.9 (C4); (Quinolyl) δ = 151.2 (C2); 149.7 (C8a); 146.5 (C4); 133.6 (C7); 130.3 (C8); 128.4 (C6); 125.0 (C5); 123.3 (C4a); 113.3 (C3); (Phenyl) δ = 127.6; 127.5; 127.3; 125.8 (6C); 55.1 (OMe). MS (EI, 70 eV): *m/z* (%) = 403 (M – H_2O, 100), 334 (21), 69 (18), 162 (17), 135 (16).

Anal. Calcd. for $C_{20}H_{15}ClF_3N_3O_2$ (421.80): C, 56.95; H, 3.58; N, 9.96 %. Found: C, 57.13; H, 3.29; N, 9.75 %.

4-[5-Hydroxy-3-(4-Nitrophenyl)-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-7-chloroquinoline (**2h**).

This compound was obtained as a yellow solid, yield 61 %, Mp. 217 - 219 ºC. ^{1}H NMR (DMSO-d_6) (Pyrazol) δ = 8.98 (s, OH); 4.17 (d, J=18.8, Ha); 3.80 (d, J= 18.8, Hb); (Quinolyl) δ = 8.91 (d, H2); 8.35 (d, H8); 8.10 (d, H6);7.69-7.63 (m, H5); 7.86 (d, H3); (Phenyl) δ = 8.34-8.30; 8.04-7.99; 7.69-7.63 (m, 4H). ^{13}C NMR (DMSO-d_6) (Pyrazol) δ = 147.4 (C3); 124.8 (q, J_{CF} = 283.9, CF$_3$); 94.4 (q, $^{2}J_{CF}$ = 31.7, C5); 43.2 (C4); (Quinolyl) δ = 151.4 (C2); 149.7 (C8a); 147.2 (C4); 133.9 (C7); 128.4 (C8); 127.6 (C6); 123.9 (C5); 122.6 (C4a); 114.0 (C3); (Phenyl) δ = 136.9; 127.0; 126.8; 126.4 (6C). MS (EI, 70 eV): *m/z* (%) = 418 (M – H_2O, 100), 349 (70), 135 (21), 162 (13), 75 (10).

Anal. Calcd. for $C_{19}H_{12}ClF_3N_4O_3$ (436.77): C, 52.25; H, 2.77; N, 12.83 %. Found: C, 52.32; H, 2.51; N, 12.55 %.

4-[3-(4-Biphenyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-7-chloroquinoline (**2i**).

This compound was obtained as a yellow solid, yield 80 %, Mp. 219 - 221 ºC. ^{1}H NMR (DMSO-d_6) (Pyrazol) δ = 8.88 (s, OH); 4.14 (d, J=18.6, Ha); 3.80 (d, J= 18.6, Hb); (Quinolyl) δ = 8.92 (d, H2); 8.50 (d, H8); 8.13 (s, H6); 7.92 (s, H5); 7.70 (d, H3); (Biphenyl) δ = 7.89-7.78; 7.54-7.37; (m, 9H). ^{13}C NMR (DMSO-d_6) (Pyrazol) δ = 148.6 (C3); 123.6 (q, J_{CF} = 285.4, CF$_3$); 93.9 (q, $^{2}J_{CF}$ = 31.7, C5); 43.7 (C4); (Quinolyl) δ = 151.3 (C2); 149.8 (C8a); 146.4 (C4); 133.8 (C7); 129.8 (C8); 128.8 (C6); 126.0 (C5); 122.6 (C4a); 114.0 (C3); (Biphenyl) δ = 139.1; 129.8; 127.9; 127.7; 127.6; 127.5; 126.8; 126.4 (12C). MS (EI, 70 eV): *m/z* (%) = 449 (M – H_2O, 100), 207 (26), 152 (25), 380 (22), 135 (19).

Anal. Calcd. for $C_{25}H_{17}ClF_3N_3O$ (467.87): C, 64.18; H, 3.66; N, 8.98 %. Found: C, 64.48; H, 3.75; N, 8.53 %.

General Procedure for the Preparation of 4-(3-Substituted-5-trifluoromethyl-1*H*-pyrazol-1-yl)-7-chloroquinolines (**3a, 3j-l**).

To a magnetically stirred solution of **1a, 1j-l** (1 mmol) in MeOH (10 ml), 7-chloro-4-hydrazinoquinoline (1 mmol) was added at room temperature. The mixture was stirred under reflux (64 ºC) for 15 to 30 minutes (**3a, 3j-l**). The solvent was evaporated under reduced pressure and the solid products **3** recrystallized from a mixture of ethanol and water 5:1. Yield: 73 – 89 %.

4-(3-Methyl-5-trifluoromethyl-1*H*-pyrazol-1-yl)-7-chloroquinoline (**3a**).

This compound was obtained as a yellow solid, yield 80 %, Mp. 58 - 60 ºC. ^{1}H NMR (DMSO-d_6) (Pyrazol) δ = 7.10 (s, H4); (Quinolyl) δ = 9.17 (d, H2); 8.29 (d, H8); 7.80-7.72 (m, H6 and H3); 7.41 (d, H5); 2.38 (s, Me). ^{13}C NMR (DMSO-d_6) (Pyrazol) δ = 150.8 (C3); 133.3 (q, $^{2}J_{CF}$ = 38.5, C5); 118.7 (q, J_{CF} = 269.1, CF$_3$); 105.7 (C4); (Quinolyl) δ = 152.1 (C2); 148.2 (C8a); 143.4 (C4); 136.7 (C7); 129.9 (C8); 128.4 (C6); 125.7 (C5); 120.2 (C4a); 110.0 (C3); 13.2 (Me). MS (EI, 70 eV): *m/z* (%) = 312 (M^+, 7), 260 (100), 176 (30), 242 (10), 75 (9).

Anal. Calcd. for $C_{14}H_9ClF_3N_3$ (311.69): C, 53.95; H, 2.91; N, 13.48 %. Found: C, 53.64; H, 3.25; N, 13.30 %.

4-[3-(2-Naphthyl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]-7-chloroquinoline (**3j**).

This compound was obtained as a yellow solid, yield 76%, Mp. 102-104 ºC. ^{1}H NMR (DMSO-d_6) (Pyrazol) δ = 7.61-7.48 (m, H4 + H3$_{Quinl}$); (Quinolyl) δ = 9.16 (d, H2); 8.54 (d, H8); 8.25 (d, H6); 7.74-7.68 (m, H5); (Naphthyl) δ = 8.00-7.78 (m, 4H); 7.74-7.68 (m, 2H). ^{13}C NMR (DMSO-d_6) (Pyrazol) δ = 149.1 (C3); 133.7 (q, $^{2}J_{CF}$ = 38.8, C5); 119.6 (q, J_{CF} = 269.1, CF$_3$); 110.2 (C4); (Quinolyl) δ = 152.3 (C2); 142.2 (C8a); 135.4 (C7); 133.4 (C4); 129.8 (C8); 128.4 (C6); 124.5 (C5); 123.0 (C4a); 120.1 (C3); (Naphthyl) δ = 133.6; 129.4; 129.3; 128.1; 128.0; 127.8; 126.9; 125.3; 123.7; 123.3 (10C). MS (EI, 70 eV): *m/z* (%) = 423 (M^+, 100), 354 (25), 127 (35), 166 (12), 192 (9).

Anal. Calcd. for $C_{23}H_{13}ClF_3N_3$ (423.82): C, 65.18; H, 3.09; N, 9.91 %. Found: C, 65.03; H, 3.47; N, 9.94 %.

4-[3-(2-Thienyl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]-7-chloroquinoline (**3k**).

This compound was obtained as a yellow solid, yield 82 %, Mp. 183 - 185 ºC. ^{1}H NMR (DMSO-d_6) (Pyrazol) δ = 7.63 (s, H4); (Quinolyl) δ = 9.20 (d, H2); 8.32 (d, H8); 7.93-7.86 (m, H5 and H6); 7.48 (d, H3); (Thienyl) δ = 7.75 (d, 2H); 7.18-7.29 (m, 1H). ^{13}C NMR (DMSO-d_6) (Pyrazol) δ = 149.0 (C3); 134.0 (q, $^{2}J_{CF}$ = 38.8, C5); 118.5 (q, J_{CF} = 269.1, CF$_3$); 106.7 (C4); (Quinolyl) δ = 152.2 (C2); 147.9 (C8a); 141.8 (C4); 135.4 (C7); 129.2 (C8); 128.5 (C6); 124.4 (C5); 122.9 (C4a); 120.1 (C3); (Thienyl) δ = 133.1; 127.9; 126.9; 126.7 (4C). MS (EI, 70 eV): *m/z* (%) = 379 (M^+, 100), 310 (47), 135 (21), 162 (9), 75 (6).

Anal. Calcd. for $C_{17}H_9ClF_3N_3S$ (379.79): C, 53.76; H, 2.39; N, 11.06%. Found: C, 53.54; H, 2.56; N, 10.86%.

4-[3-(2-Furyl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]-7-chloroquinoline (**3l**).

This compound was obtained as a yellow solid, yield 73%, Mp. 166-168 ºC. ^{1}H NMR (DMSO-d_6) (Pyrazol) δ = 7.75-7.68 (m, H4 + H5$_{Quinl}$); (Quinolyl) δ = 9.20 (d, H2); 8.30 (d, H8); 7.84-7.83 (m, H6); 7.73 (d, H3); (Furyl) δ = 7.90 (d, 1H); 7.05 (d, 1H); 6.67-6.66 (m, 1H). ^{13}C NMR (DMSO-d_6) (Pyrazol) δ = 149.0 (C3); 134.2 (q, $^{2}J_{CF}$ = 39.5, C5); 118.8 (q, J_{CF} = 269.8, CF$_3$); 106.5 (C4); (Quinolyl) δ = 152.2 (C2); 145.7 (C8a); 144.6 (C4); 135.4 (C7); 129.2 (C8); 127.9 (C6); 124.5 (C5); 122.8 (C4a); 120.0 (C3); (Furyl) δ = 143.7; 141.1; 111.7; 108.7 (4C). MS (EI, 70 eV): *m/z* (%) = 363 (M^+, 100), 294 (27), 135 (14), 75 (9), 162 (8).

Anal. Calcd. for $C_{17}H_9ClF_3N_3O$ (363.72): C, 56.14; H, 2.49; N, 11.55%. Found: C, 55.97; H, 2.79; N, 11.50%.

General Procedure for the Preparation 4-(3-Substituted-5-trifluoromethyl-1*H*-pyrazol-1-yl)-7-chloroquinolines (**3b-i**).

To a magnetically stirred pure acetic acid (10 ml), dihydropyrazole **2b-i** (1 mmol) was added at room temperature. The mixture was stirred under reflux (116 ºC) for 4 hours (**3b-g, 3i**) or for 10 hours (**3h**). The solvent was evaporated under reduced pressure and solid products **3** were recrystallized from a mixture of ethanol and water 5:1. Yield: 73 - 96 %.

4-(3-Phenyl-5-trifluoromethyl-1*H*-pyrazol-1-yl)-7-chloroquinoline (**3b**).

This compound was obtained as a yellow solid, yield 96 %, Mp. 143 - 145 ºC. ^{1}H NMR (DMSO-d_6) (Phenylpyrazol) δ = 8.00-7.92; 7.55-7.49 (m, 6H, H4 + 5H$_{Ar}$); (Quinolyl) δ = 9.24 (d, H2); 8.34 (d, H8); 8.04 (s, H6); 8.00-7.92; (m, H3); 7.78-7.74 (m, H5). ^{13}C NMR (DMSO-d_6) (Pyrazol) δ = 151.1 (C3); 134.5 (q, J_{CF} = 39.5, C5); 118.8 (q, J_{CF} = 269.1, CF$_3$); 106.9 (C4); (Quinolyl) δ = 152.1 (C2); 149.0 (C8a); 142.0 (C4); 135.3 (C7); 129.0 (C8); 127.9 (C6); 124.4 (C5); 122.8 (C4a); 120.4 (C3);

(Phenyl) δ = 127.8; 127.7; 127.2; 126.0 (6C). MS (EI, 70 eV): *m/z* (%) = 373 (M$^+$, 99), 304 (100), 77 (22), 186 (17), 135 (16).

Anal. Calcd. for $C_{19}H_{11}ClF_3N_3$ (373.76): C, 61.06; H, 2.97; N, 11.24 %. Found: C, 60.81; H, 3.07; N, 10.99 %.

4-[3-(4-Methylphenyl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]-7-chloroquinoline (**3c**).

This compound was obtained as a yellow solid, yield 79%, Mp. 133-135 ºC. ^{1}H NMR (DMSO-d$_6$) (pyrazol) δ = 7.39-7.31 (m, H4 + H3$_{\text{Quinl}}$); (Quinolyl) δ = 9.23 (d, H2); 8.36 (d, H8); 7.95 (d, H6); 7.53 (d, H5); (Phenyl) δ = 7.91-7.77 (m, 4H); 2.38 (s, Me). ^{13}C NMR (DMSO-d$_6$) (Pyrazol) δ = 152.1 (C3); 134.6 (q, $^2J_{CF}$ = 38.8, C5); 120.5 (q, J_{CF} = 269.1, CF$_3$); 106.8 (C4); (Quinolyl) δ = 152.2 (C2); 149.0 (C8a); 142.1 (C4); 135.8 (C7); 129.8 (C8); 127.9 (C6); 124.5 (C5); 122.9 (C4a); 119.9 (C3); (Phenyl) δ = 129.7; 129.3; 129.1; 125.5 (6C); 39.4 (Me). MS (EI, 70 eV): *m/z* (%) = 387 (M$^+$, 100), 318 (71), 192 (12), 135 (12), 65 (11).

Anal. Calcd. for $C_{20}H_{13}ClF_3N_3$ (387.79): C, 61.95; H, 3.38; N, 10.84%. Found: C, 61.82; H, 3.54; N, 10.64%.

4-[3-(4-Fluorophenyl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]-7-chloroquinoline (**3d**).

This compound was obtained as a yellow solid, yield 77%, Mp. 117-119 ºC. ^{1}H NMR (DMSO-d$_6$) (Phenylpyrazol) δ = 8.08-8.06; 8.04-7.93; 7.37-7.32 (m, 5H, H4 + 4H$_{\text{Ar}}$); (Quinolyl) δ = 9.24 (d, H2); 8.33 (d, H8); 8.08-8.06 (m, H6); 7.78-7.74 (m, H5); 7.54 (d, H3). ^{13}C NMR (DMSO-d$_6$) (Pyrazol) δ =151.3 (C3); 134.5 (q, $^2J_{CF}$ = 38.8, C5); 119.6 (q, J_{CF} = 269.1, CF$_3$); 106.9 (C4); (Quinolyl) δ = 152.1 (C2); 149.0 (C8a); 142.0 (C4); 135.3 (C7); 129.0 (C8), 127.9 (C6); 124.5 (C5); 122.8 (C4a); 115.8 (C3); (Phenyl) δ = 127.8; 127.7; 125.2; 124.4 (6C). MS (EI, 70 eV): *m/z* (%) = 391 (M$^+$, 100), 322 (88), 135 (19), 195 (15), 75 (14).

Anal. Calcd. for $C_{19}H_{10}ClF_4N_3$ (391.75): C, 58.25; H, 2.57; N, 10.73 %. Found: C, 58.19; H, 2.60; N, 11.05 %.

4-[3-(4-Chlorophenyl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]-7-chloroquinoline (**3e**).

This compound was obtained as a yellow solid, yield 92 %, Mp. 154 - 156 ºC. ^{1}H NMR (DMSO-d$_6$) (Phenylpyrazol) δ = 8.04-7.95; 7.59-7.53 (m, 5H, H4 + 4H$_{\text{Ar}}$); (Quinolyl) δ =9.24 (s, H2); 8.34 (s, H8); 8.04 (s, H6); 7.76 (d, H5); 7.50 (s, H3). ^{13}C NMR (DMSO-d$_6$) (Pyrazol) δ = 151.1 (C3); 134.5 (q, $^2J_{CF}$ = 38.8, C5); 121.9 (q, J_{CF} = 269.1, CF$_3$); 107.2 (C4); (Quinolyl) δ = 152.2 (C2); 149.0 (C8a); 142.0 (C4); 135.4 (C7); 129.2 (C8); 127.9 (C6); 124.5 (C5); 122.8 (C4a); 119.9 (C3); (Phenyl) δ = 129.5; 128.9; 127.4; 127.6 (6C). MS (EI, 70 eV): *m/z* (%) = 407 (M$^+$, 100), 338 (78), 135 (20), 75 (18), 162 (16).

Anal. Calcd. for $C_{19}H_{10}Cl_2F_3N_3$ (408.20): C, 55.90; H, 2.47; N, 10.29 %. Found: C, 55.47; H, 2.38; N, 9.89 %.

4-[3-(4-Bromophenyl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]-7-chloroquinoline (**3f**).

This compound was obtained as a yellow solid, yield 87 %, Mp. 162 - 164 ºC. ^{1}H NMR (DMSO-d$_6$) (Phenylpyrazol) δ = 7.96-7.91; 7.72-7.68 (m, 5H, H4 + 4H$_{\text{Ar}}$); (Quinolyl) δ = 9.24 (d, H2); 8.33 (d, H8); 7.99 (s, H6); 7.77 (d, H5); 7.50 (d, H3). ^{13}C NMR (DMSO-d$_6$) (Pyrazol) δ = 151.2 (C3); 134.5 (q, $^2J_{CF}$ = 39.5, C5); 121.7 (q, J_{CF} = 269.1, CF$_3$); 107.2 (C4); (Quinolyl) δ = 152.3 (C2); 149.0 (C8a); 142.1 (C4); 135.4 (C7); 129.9 (C8); 128.0 (C6); 124.5 (C5); 122.3 (C4a); 120.0 (C3); (Phenyl) δ = 131.8; 129.3; 127.7; 124.9 (6C). MS (EI, 70 eV): *m/z* (%) = 453 (M$^+$, 100), 384 (45), 135 (25), 75 (20), 162 (17).

Anal. Calcd. for $C_{19}H_{10}BrClF_3N_3$ (452.66): C, 50.42; H, 2.23; N, 9.28 %. Found: C, 50.58; H, 2.44; N, 9.31 %.

4-[3-(4-Methoxyphenyl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]-7-chloroquinoline (**3g**).

This compound was obtained as a yellow solid, yield 79 %, Mp. 144 - 146 ºC.^{1}H NMR (DMSO-d$_6$) (Pyrazol) δ = 7.07 (s, H4); (Quinolyl) δ = 9.25 (d, H2); 8.35 (d, H8); 7.96-7.89 (m, H6) 7.80-7.74 (m, H5); 7.07 (d, H3); (Phenyl) δ = 7.96-7.89; 7.58-7.53 (m, 4H); 3.84 (s, OMe). ^{13}C NMR (DMSO-d$_6$) (Pyrazol) δ = 151.8 (C3); 134.4 (q, $^2J_{CF}$ = 38.8, C5); 119,5 (q, J_{CF} = 269.8, CF$_3$); 106.4 (C4); (Quinolyl) δ = 152.0 (C2); 148.6 (C8a); 142.3 (C4); 135.3 (C7); 129.0 (C8); 126.9 (C6); 124.5 (C5); 122.8 (C4a); 114.0 (C3); (Phenyl) δ = 127.5; 126.4; 124.6; 123.0 (6C); 54.9 (OMe). MS (EI, 70 eV): *m/z* (%) = 403 (M$^+$, 100), 334 (21), 69 (18), 162 (17), 135 (16).

Anal. Calcd. for $C_{20}H_{13}ClF_3N_3O$ (403.79): C, 59.49; H, 3.25; N, 10.41 %. Found: C, 59.76; H, 3.40; N, 10.52 %.

4-[3-(4-Nitrophenyl)-trifluoromethyl-1*H*-pyrazol-1-yl]-7-chloroquinoline (**3h**).

This compound was obtained as a yellow solid, yield 82 %, Mp. 199 - 200 ºC. ^{1}H NMR (DMSO-d$_6$) (Pyrazol) δ = 7.95 (s, H4); (Quinolyl) δ = 9.22 (d, H2); 8.35 (s, H8); 8.29-8.26 (m, H6); 8.24 (d, H5); 7.51 (d, H3); (Phenyl) δ = 8.33-8.29; 8.29-8.26; 7.76-7.73 (m, 4H). ^{13}C NMR (DMSO-d$_6$) (Pyrazol) δ = 151.3 (C3); 134.4 (q, $^2J_{CF}$ = 38.8, C5); 118.3 (q, J_{CF} = 269.8, CF$_3$); 106.9 (C4); (Quinolyl) δ = 152.1 (C2); 149.0 (C8a); 142.1 (C4); 135.4 (C7); 129.1 (C8); 128.0 (C6); 124.5 (C5); 122.9 (C4a); 115.8 (C3); (Phenyl) δ = 127.9; 127.8; 127.2; 126.4 (6C). MS (EI, 70 eV): *m/z* (%) = 418 (M$^+$, 100), 349 (70), 135 (21), 162 (13), 75 (10).

Anal. Calcd. for $C_{19}H_{10}ClF_3N_4O_2$ (418.76): C, 54.50; H, 2.41; N, 13.38 %. Found: C, 54.08; H, 2.38; N, 13.11 %.

4-[3-(4-Biphenyl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]-7-chloroquinoline (**3i**).

This compound was obtained as a yellow solid, yield 83%, Mp. 127-129 ºC. ^{1}H NMR (DMSO-d$_6$) (Pyrazol) δ = 7.57-7.41 (m, H4 + H3$_{\text{Quinl}}$); (Quinolyl) δ = 9.25 (d, H2); 8.35 (d, H8); 8.13-7.97 (m, H5 and H6); (Biphenyl) δ = 8.13-7.97 (m, 2H); 7.95-7.75 (m, 5H); 7.57-7.41 (m, 2H). ^{13}C NMR (DMSO-d$_6$) (Pyrazol) δ = 151.8 (C3); 134.4 (q, $^2J_{CF}$ = 38.8, C5); 119.8 (q, J_{CF} = 269.8, CF$_3$); 107.0 (C4); (Quinolyl) δ = 152.1 (C2); 149.0 (C8a); 142.1 (C4); 135.4 (C7); 129.7 (C8); 127.9 (C6); 124.5 (C5); 122.9 (C4a); 117.8 (C3); (Biphenyl) δ = 140.5; 139.2; 129.0; 128.9; 127.5; 126.9; 126.4; 126.2; (12C). MS (EI, 70 eV): *m/z* (%) = 449 (M$^+$, 100), 207 (26), 152 (25), 380 (22), 135 (19).

Anal. Calcd. for $C_{25}H_{15}ClF_3N_3$ (449.86): C, 66.75; H, 3.36; N, 9.34 %. Found: C, 66.35; H, 3.38; N, 9.26 %.

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