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A new approach to fluorinated 4(3*H*)-quinazolinones

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Dedicated to 100-anniversary of Prof. I. L. Knunyants.

Abstract

A new approach for the synthesis of fluorinated 1*H*-quinazolin-4-ones and 4-substituted quinazolines has been developed. 6-Fluoro-1*H*-quinazolin-4-ones were obtained by intramolecular cyclization of fluorine-containing *S*-ethyl *N*-benzoylisothioureas. Nucleophilic substitution reactions at positions 2 and 7, as well as alkylation at 1-position of quinazolinones were investigated. In addition, the synthesis of fluorine-containing 4-aminoquinazolines was carried out.

Keywords: Fluorine-containing quinazolinones; Intramolecular cyclization; Nucleophilic substitution; *S*-Ethyl *N*-benzoylisothioureas

1. Introduction

4(3*H*)-Quinazolinones belong to a well known class of heterocyclic compounds exhibiting antihypertensive, antidiabetic, anti-inflammatory, anticonvulsant and antibacterial properties [1]. On the other hand, it has been established that incorporation of one or several fluorine atoms into organic molecules enhances their biological potency, bioavailability and metabolic stability [2].

The synthesis of the quinazolinone system has been extensively studied and described in the literature [3]. There are three general approaches to 1*H*-quinazolin-4-ones deriving from different starting materials, such as anthranilic acid, anthranilonitrile or aniline derivatives [4]. The most straightforward procedure was developed by Niementowski in 1895 and improved later by Grimmel et al. in 1946. They found that 4(3*H*)-quinazolinones could be obtained from *N*-acetylanthranilic acid and anilines in toluene or xylene with phosphorus oxychloride as condensing agent [4].

To our knowledge, the synthesis of 1*H*-quinazolin-4-ones from fluorinated benzoyl chlorides has not so far been described, although, 2-halogenobenzoyl chlorides can be used for preparation of [*a*]-annelated quinazolinones [5]. We wish to report here a new approach to the 1*H*-quinazolin-4-ones based on the reaction of *ortho*-halogen substituted benzoyl chlorides with *S*-ethyl isothiourea, as *N*,*N*′-dinucleophile.

2. Results and discussion

In order to obtain fluorinated quinazolinones bearing fluorine atoms we have studied interaction of tetrafluorobenzoyl, 2,5-difluoro-4-chlorobenzoyl, 2-chloro-4,5-difluorobenzoyl and 2-chloro-4-fluorobenzoyl chlorides (**1a–d**) with *S*-ethyl isothioureum iodide **2** (Scheme 1). Benzoyl chlorides (**1a–d**) were reacted with *S*-ethyl isothioureum iodide (**2**) in methylene chloride at room temperature in the presence of triethyl amine to give *S*-ethyl *N*-aroylisothioureas (**3a–d**) in good yields (71–82%), as evidenced by their ^{1}H NMR spectra. In case of tetrafluorobenzoyl chloride diaroyl derivative (**4a**) was found to be formed when the reaction mixture was slightly heated. Use of *S*-benzyl derivative (**2b**) instead of *S*-ethyl isothiourea in the reaction with tetrafluorobenzoyl chloride

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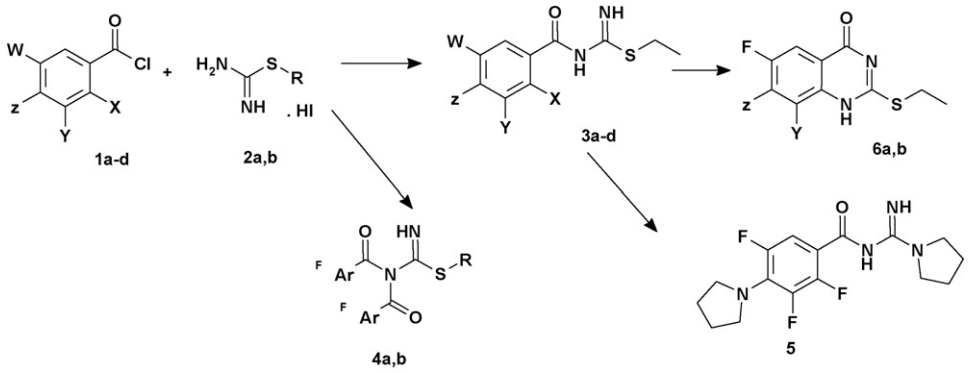


Scheme 1. **1**, **3**: X = Y = Z = W = F (**a**); X = W = F, Z = Cl, Y = H (**b**); X = Cl, W = Z = F, Y = H (**c**); X = Cl, Z = F, W = Y = H (**d**); **2**, **4**: R = Et (**a**), CH_2Ph (**b**). **6**: Z = Y = F (**a**), Z = Cl, Y = H (**b**).

gave diaroyl compound (**4b**) even at room temperature. For this reason *S*-ethyl isothiourea was chosen for further studies.

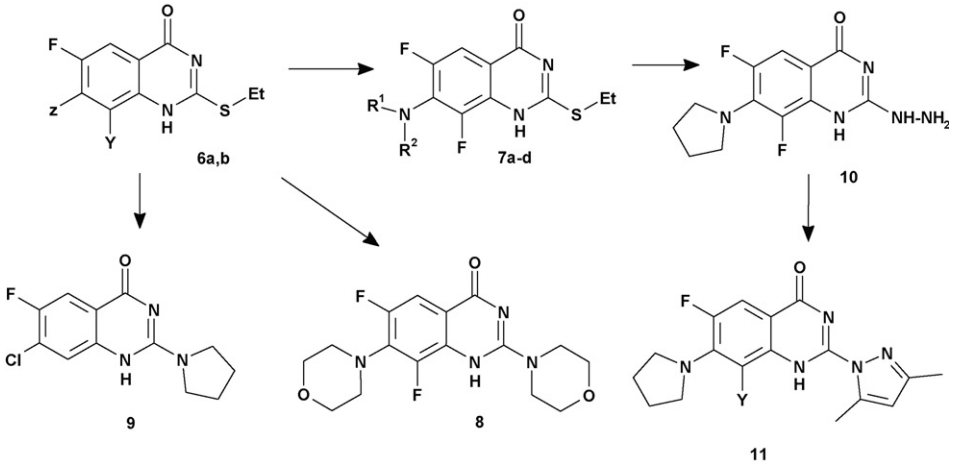
When compounds (**3a**–**d**) were kept on reflux in toluene for 5 h in the presence of NEt_3 only 1*H*-quinazolin-4-one (**6a**) was obtained in 15% yield. Heating of (**3a**) in DMF with pyrrolidine as a base for 5 h failed to give a cyclization product, instead of it the displacement of fluorine atom and the SEt-group by pyrrolidine proved to take place under these conditions (Scheme 1). The structure of compound (**5**) was established by ^{1}H NMR. Isothiourea derivatives bearing fluorine atoms at *ortho*-position (**3a**, **b**) undergo intramolecular cyclization on reflux in DMF for 5 h to give 1*H*-quinazolin-4-ones (**6a**, **b**) in high yields. Attempts to cause intramolecular displacement of chlorine atom at 2-position of (**3c**, **d**) under a variety of conditions (heating in DMF, diphenyl ether, hexadecane, bis(octyl)phthalate, acetic anhydride or in DMF, 1,4-dioxane, toluene in the presence of bases, e.g. potassium carbonate, potassium fluoride, potassium *tert*-butoxide, sodium hydride) have failed.

The structure of quinazolinones (**6a**, **b**) was proved by ^{1}H, ^{19}F NMR data. The ^{1}H NMR spectrum of (**6a**) reveals a characteristic signal of H(5) (ddd, J = 10.0, 8.0, 2.4 Hz), a broadened singlet of NH-group and appropriate signals of the SEt-group. The ^{19}F NMR spectrum of (**6a**) displays signals of three fluorine atoms in the form of ddd, thus indicating the displacement of one F atom and the formation of the cyclic system. Indeed, the double doublet assigned to F(6) has been observed in case of compound (**6b**) in ^{1}H NMR; also the ^{19}F NMR spectrum of (**6b**) reveals the signal of one fluorine atom in the form of dd (J = 8.9, 6.7 Hz). In addition, the peaks with *m*/*z* 260 $[M]^+$ (100%) for (**6a**) and *m*/*z* 258 $[M]^+$ (87%) for (**6b**) in their mass spectra are in full agreement with the suggested structures. The feature of mass spectra of both compounds is the presence of highly intensive peaks of $[M - EtS - CN]^+$ (*m*/*z* 173 (98%) and 171 (100%) for (**6a**) and (**6b**), respectively).

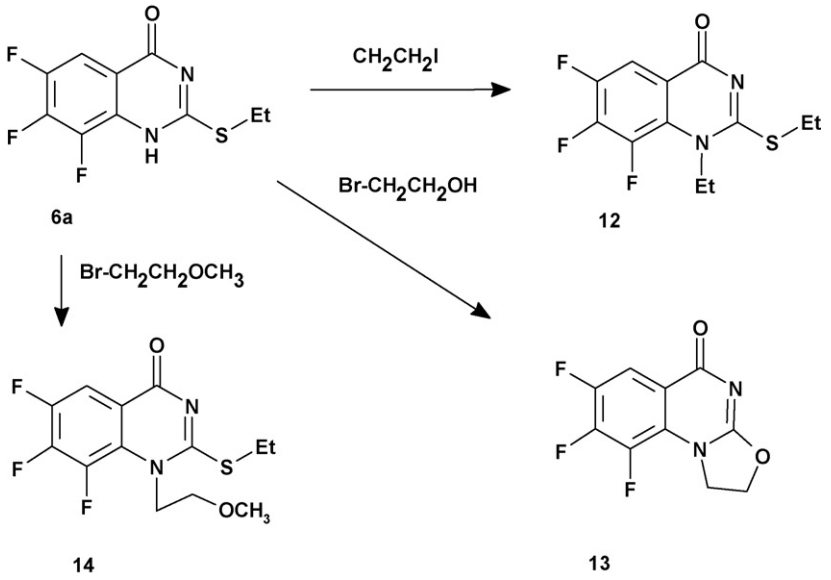
In order to perform some structural modifications of quinazolinone (**6a**) we have studied nucleophilic substitution of atom F(7) and SEt-group at position 2, alkylation at position 1, as well as chlorination and the ability to introduce an amine moiety at position 4 (Scheme 2).

When compound (**6a**) was refluxed in anhydrous DMF with pyrrolidine for 2 h substitution of fluorine atom at 7-position by pyrrolidine moiety occurred, as evidenced by the presence of signals of pyrrolidine protons and the signal of H(5) as double doublet in ^{1}H NMR spectrum. In contrast, the displacement of SEt-group of 7-chloro derivative (**6b**) by pyrrolidine takes place under similar conditions, ^{1}H NMR and mass spectroscopy data being in agreement with the structure (**9**).

It was found that quinazolinone (**6a**) was reacted with morpholine to give a mixture of 7-morpholino derivative (**7b**)



Scheme 2. **6**: Z = Y = F (**a**), Z = Cl, Y = H (**b**); **7**: NR^1R^2 = pyrrolidin-1-yl (**a**), morpholin-4-yl (**b**), 3-(morpholin-4-yl)-1-propylamine (**c**), 3-methylpipyridin-1-yl (**d**).



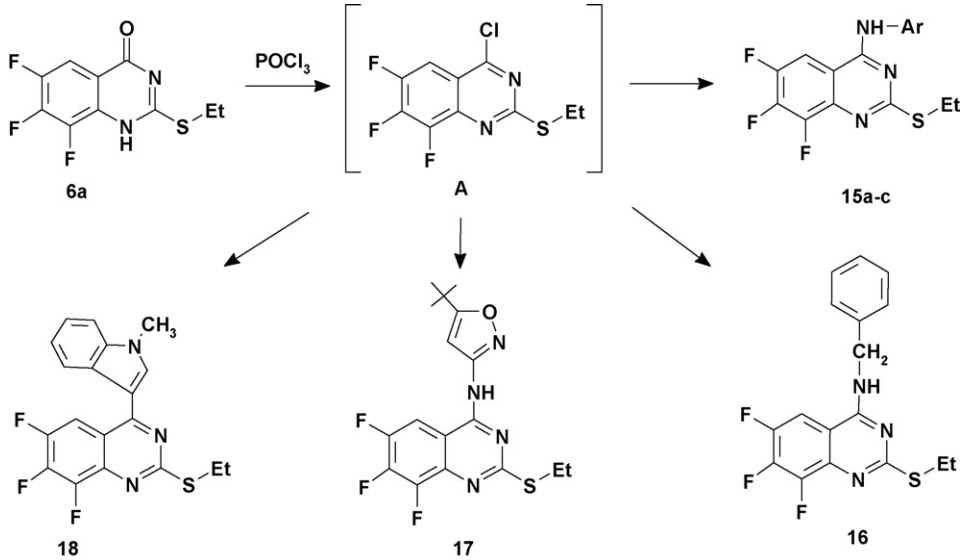
Scheme 3.

and 2,7-bis(morpholino) derivative (**8**), and it became possible to separate the compounds from each other using treatment of the mixture with hot ethanol. In the reaction of (**6a**) with 3-(4-morpholino)-1-propanamine and 3-methylpiperidine only fluorine atom at 7-position was replaced with nucleophiles to afford (**7c**) and (**7d**), respectively.

The ethylthio group at position 2 of (**6a**) was smoothly replaced by the hydrazino moiety to give compound (**10**) upon heating under reflux with hydrazine hydrate for 1 h. Compound (**10**) can be used for preparation of quinazolinones bearing a heterocyclic substituent at 2-position. For example, the reaction of (**10**) with acetylacetone takes place in refluxing acetonitrile in the presence of acetic acid, thus leading to 2-pyrazolylquinazolinone (**11**).

N-Alkylation of (**6a**) with ethyl iodide in the presence of NaOH gave (**12**) (Scheme 3). When quinazolin-4-one (**6a**) was reacted with 2-bromoethanol under similar conditions compound (**13**) was formed, as evidenced by the presence of two CH_2-signals together with the absence of SEt-signals in the ^{1}H NMR spectrum. The formation of (**13**) probably proceeds via *N*-alkylation of (**6a**) with 2-bromoethanol followed by intramolecular nucleophilic substitution of SEt-group. The reaction of (**6a**) with 2-bromoethyl methyl ether gave quinazolin-4-one (**14**).

Since 4-anilinoquinazolines are known as inhibitors of neurominidasa of smallpox virus [6], it was of interest to convert quinazolinone (**6a**) into fluorinated 4-anilinoquinazolines (**15a–c**) (Scheme 4). Compound (**6a**) was treated with phosphorus oxychloride and the chloro compound A was reacted with aniline in CH_3CN to give (**15a**). Quinazolines (**15b**, **c**), (**16**), (**17**) were prepared similarly. This procedure proved to be effective for incorporation of C-nucleophile in positions 4 of quinazolin-4-one (**6a**) to afford 4-(*N*-methylindole-3-yl)-quinazoline (**18**). Interestingly, the reaction of



Scheme 4. **15**: Ar = Ph (**a**); 3,4-$F_2C_6H_3$ (**b**); 2-ClC_6H_4 (**c**).

compound A with *N*-methylindole proceeds without any base or any catalyst.

The structure of quinazolines (**15**)–(**18**) was established on the basis of ^{1}H NMR and mass spectrum data.

In summary, a new approach for the synthesis of fluorinated 1*H*-quinazolin-4-ones and 4-substituted quinazolines has been developed. Also, it has been shown that the presence of three fluorine atoms in quinazoline-4-ones enhances the reactivity of positions 2 and 4 toward N,C,O-nucleophilic reagents.

3. Experimental

3.1. General

^{1}H NMR spectra were recorded on Bruker WM-250 and Bruker DRX-400 spectrometers operating at 250.14 and 400.13 MHz, respectively. ^{19}F NMR spectra were recorded on Bruker DRX-500 spectrometer operating at 376.45 MHz. All spectral data are reported in ppm in the δ scale relative to internal TMS (^{1}H NMR) or hexafluorobenzene (^{19}F NMR), respectively. Mass spectra were recorded on a Varian MAT 311A spectrometer (accelerating voltage 3 kV, cathode emission current 300 μA, energy of ionizing electrons 70 eV, direct inlet probe).

3.2. Typical procedure for the synthesis of 2-ethyl-1-(2-X-3-Y-4-Z-5-W-benzoyl)isothioureas (**3a–d**)

A solution of tetrafluorobenzoyl chloride (**1a**) (0.92 g, 4.3 mmol) in 1 mL of toluene was added to a suspension of *S*-ethylisothiourea hydroiodide (1 g, 4.3 mmol) in 15 mL of CH_2Cl_2 to which 1.2 mL (8.6 mmol) of NEt_3 had been added. After a day at room temperature the mixture was evaporated. The residue was washed with water and recrystallized from ethanol to give 0.85 g (71%) of (**3a**).

3.2.1. 2-Ethyl-1-(2,3,4,5-tetrafluorobenzoyl)isothiourea (**3a**)

A white solid; mp 70–72 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, 250 MHz): δ 1.35 (3H, t, CH_3), 3.11 (2H, q, SCH_2), 7.72 (1H, m, C_6HF_4), 9.5 (2H, br s, NH). Anal. Calcd for $C_{10}H_8F_4N_2OS$, C 42.86; H 2.86; N 10.00. Found: C 42.89; H 2.83; N 10.09.

3.2.2. 2-Ethyl-1-(2,5-difluoro-4-chlorobenzoyl)isothiourea (**3b**)

A white solid; mp 115–117 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, 250 MHz): δ 1.33 (3H, t, CH_3), 3.05 (2H, q, SCH_2), 7.35 (1H, dd, J = 9.7, 6.1 Hz, H-6′ or H-3′), 7.80 (1H, dd, J = 9.3, 6.4 Hz, H-3′ or H-6′), 9.4 (2H, br s, NH). Anal. Calcd for $C_{10}H_9ClF_2N_2OS$, C 43.10; H 3.25; N 10.0. Found: C 43.15; H 3.24; N 10.07.

3.2.3. 2-Ethyl-1-(4,5-difluoro-2-chlorobenzoyl)isothiourea (**3c**)

A white solid; mp 90–92 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, 250 MHz): δ 1.36 (3H, t, CH_3), 3.10 (2H, q, SCH_2), 7.45 (1H, dd, J = 9.8, 6.9 Hz, H-3′ or H-6′), 7.83 (1H, dd, J = 10.9, 8.9 Hz, H-6′ or H-3′), 9.5 (2H, br s, NH). Anal. Calcd for $C_{10}H_9ClF_2N_2OS$, C 43.10; H 3.25; N 10.05. Found: C 43.11; H 3.22; N 10.07.

3.2.4. 2-Ethyl-1-(4-fluoro-2-chlorobenzoyl)isothiourea (**3d**)

A white solid; mp 88–90 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, 250 MHz): δ 1.32 (3H, t, CH_3), 3.06 (2H, q, SCH_2), 7.09 (1H, ddd, J = 10.9, 8.5, 2.5 Hz, H-6′), 7.20 (1H, dd, J = 9.0, 2.5 Hz, H-3′), 7.92 (1H, dd, J = 9.0, 7.0 Hz, H-5′), 9.4 (2H, br s, NH). Anal. Calcd for $C_{10}H_{10}ClFN_2OS$, C 46.07; H 3.87; N 10.74. Found: C 46.10; H 3.84; N 10.77.

3.3. 2,3,5-Trifluoro-N-(iminopyrrolidin-1-ylmethyl)-4-(pyrrolidin-1-yl)benzamide (**5**)

A white solid; mp 83–85 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, 250 MHz): δ 1.90 (8H, m, $2(CH_2)_2$), 3.57 (8H, m, $2N(CH_2)_2$), 7.38 (1H, ddd, J = 15.7, 6.7, 2.5 Hz, H-6′).

3.4. Typical procedure for the synthesis of 2-ethylthio-6-fluoro-7-Z-8-Y-1H-quinazolin-4-ones (**6a, b**)

Compound **3a** (0.6 g, 2.1 mmol) in 10 mL of anhydrous DMF was refluxed for 4 h. The reaction mixture was then evaporated and the residue was recrystallized from ethanol to give 0.42 g (76%) of **6a**.

3.4.1. 2-Ethylthio-6,7,8-trifluoro-1H-quinazolin-4-one (**6a**)

A white solid; mp 207–209 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, 250 MHz): δ 1.36 (3H, t, CH_3), 3.18 (2H, q, SCH_2), 7.64 (1H, ddd, J = 10.0, 8.0, 2.4 Hz, H-5), 12.6 (1H, br s, NH). ^{19}F NMR ([^{2}H$_6$]DMSO, 376.45 MHz): δ_F 10.84 (1F, ddd, J = 19.3, 22.4, 8.1 Hz, F-7), 15.94 (1F, ddd, J = 19.3, 4.0, 2.3 Hz, F-8), 25.6 (1F, ddd, J = 22.4, 10.0, 4.0 Hz, F-6). MS, *m/z*: 260 $[M]^+$ (100), 173 $[M - EtS - CN]^+$ (98), 174 $[M - 86]^+$ (58), 144 $[M - 116]^+$ (58). Anal. Calcd for $C_{10}H_7F_3N_2OS$, C 46.15; H 2.71; N 10.76. Found: C 46.18; H 2.68; N 10.70.

3.4.2. 2-Ethylthio-6-fluoro-7-chloro-1H-quinazolin-4-one (**6b**)

A white solid; mp 210–212 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, 250 MHz): δ 1.39 (3H, t, CH_3), 3.17 (2H, q, SCH_2), 7.61 (1H, d, J = 6.7 Hz, H-8), 7.78 (1H, d, J = 8.9 Hz, H-5), 12.5 (1H, br s, NH). ^{19}F NMR ([^{2}H$_6$]DMSO, 376.45 MHz): δ_F 43.66 (1F, dd, J = 8.9, 6.7 Hz). MS, *m/z*: 258 $[M]^+$ (87), 171 $[M - EtS - CN]^+$ (100), 142 $[M - 116]^+$ (97), 225 $[M - 33]^+$ (81), 172 $[M - 86]^+$ (60). Anal. Calcd for $C_{10}H_8ClFN_2OS$, C 46.43; H 3.12; N 10.83. Found: C 46.40; H 3.10; N 10.81.

3.5. Typical procedure for the synthesis of 2-ethylthio-6,8-difluoro-7-(alkylimino)-1H-quinazolin-4-ones (**7a, c, d**) and 7-chloro-6-fluoro-2-(pyrrolidin-1-yl)-1H-quinazolin-4-one (**9**)

Pyrrolidine (0.7 mL, 8.5 mmol) was added to a solution of (**6a**) (0.6 g, 2.3 mmol) in 4 mL of anhydrous DMF. The reaction mixture was refluxed for 2 h. After the mixture was cooled the

precipitate formed was collected by filtration and recrystallized from DMSO to give 0.5 g (70%) of (**7a**).

*3.5.1. 2-Ethylthio-6,8-difluoro-7-(pyrrolidin-1-yl)-1H-quinazolin-4-one (**7a**)*

A white solid; mp 246–248 °C. ^{1}H NMR ([$^2H_6$]DMSO, 250 MHz): δ 1.38 (3H, t, CH_3), 1.92 (4H, m, $(CH_2)_2$), 3.19 (2H, q, SCH_2), 3.65 (4H, m, $N(CH_2)_2$), 7.32 (1H, dd, J = 13.8, 2.0 Hz, H-5), 12.19 (1H, br s, NH). ^{19}F NMR ([$^2H_6$]DMSO, 376.45 MHz): δ_F 23.27 (1F, d, J = 13.1 Hz), 39.63 (1F, m). MS, *m/z*: 311 $[M]^+$ (100), 310 $[M - H]^+$ (48), 278 $[M - 33]^+$ (31), 282 $[M - Et]^+$ (26). Anal. Calcd for $C_{14}H_{15}F_2N_3OS$, C 54.01; H 4.86; N 13.50. Found: C 54.05; H 4.80; N 13.53.

*3.5.2. 2-Ethylthio-6,8-difluoro-7-(3-(morpholie-4-yl)-1-propylamine)-1H-quinazolin-4-one (**7c**)*

A white solid; mp 214–216 °C. ^{1}H NMR ([$^2H_6$]DMSO, 250 MHz): δ 1.43 (3H, t, CH_3), 1.77 (2H, m, CH_2), 2.40 (2H, m, CH_2), 2.54 (2H, m, CH_2), 3.21 (2H, q, SCH_2), 3.47 (4H, m, $N(CH_2)_2$), 3.61 (4H, m, $O(CH_2)_2$), 7.35 (1H, dd, J = 11.8, 1.5 Hz, H-5), 12.19 (1H, br s, NH). ^{19}F NMR ([$^2H_6$]DMSO, 376.45 MHz): δ_F 16.58 (1F, d, J = 12.8 Hz), 32.96 (1F, m). MS, *m/z*: 384 $[M]^+$ (7), 100 $[M - 284]^+$ (100). Anal. Calcd for $C_{17}H_{22}F_2N_4O_2S$, C 53.11; H 5.77; N 14.57. Found: C 53.15; H 5.70; N 14.53.

*3.5.3. 2-Ethylthio-6,8-difluoro-7-(3-methylpipyridin-1-yl)-1H-quinazolin-4-one (**7d**)*

A white solid; mp 150–152 °C. ^{1}H NMR ([$^2H_6$]DMSO, 250 MHz): δ 0.92 (3H, d, CH_3, J = 6.3 Hz), 1.12 (1H, m, CH), 1.41 (3H, t, CH_3), 1.73 (2H, m, CH_2), 1.78 (2H, m, CH_2), 2.81 (2H, m, CH_2), 3.20 (2H, q, SCH_2), 3.33 (2H, m, CH_2), 7.38 (1H, dd, J = 11.5, 1.6 Hz, H-5), 12.15 (1H, br s, NH). MS, *m/z*: 339 $[M]^+$ (100), 284 $[M - 55]^+$ (60), 338 $[M - H]^+$ (58). Anal. Calcd for $C_{16}H_{19}F_2N_3OS$, C 56.62; H 5.64; N 12.38. Found: C 56.65; H 5.60; N 12.53.

*3.5.4. 7-Chloro-6-fluoro-2-(pyrrolidin-1-yl)-1H-quinazolin-4-one (**9**)*

A white solid; mp 308–310 °C. ^{1}H NMR ([$^2H_6$]DMSO, 250 MHz): δ 1.92 (4H, m, $(CH_2)_2$), 3.50 (4H, m, $N(CH_2)_2$), 7.29 (1H, d, J = 5.5 Hz, H-8), 7.62 (1H, d, J = 8.4 Hz, H-5), 11.2 (1H, br s, NH). MS, *m/z*: 267 $[M]^+$ (64), 238 $[M - Et]^+$ (100). Anal. Calcd for $C_{12}H_{11}ClFN_3O$, C 53.88; H 4.15; N 15.71. Found: C 53.85; H 4.10; N 15.53.

*3.6. The procedure for the synthesis of 2-ethylthio-6,8-difluoro-7-(morpholin-4-yl)-1H-quinazolin-4-one (**7b**) and 2,7-bis(morpholino)-6,8-difluoro-1H-quinazolin-4-one (**8**)*

Morpholine (0.86 mL, 9.6 mmol) was added to a solution of (**6a**) (0.6 g, 2.3 mmol) in 4 mL of anhydrous DMF. The reaction mixture was refluxed for 2 h and then evaporated. The residue was added to 6 mL of hot ethanol. The unsolved solid which was filtered off proved to be quinazolinone (**8**). It was then recrystallized from DMSO. The material which was recrystallized from ethanol proved to be quinazilinone (**7b**).

*3.6.1. 2-Ethylthio-6,8-difluoro-7-(morpholin-4-yl)-1H-quinazolin-4-one (**7b**)*

A white solid; mp 190–192 °C. ^{1}H NMR ([$^2H_6$]DMSO, 250 MHz): δ 1.41 (3H, t, CH_3), 3.00 (4H, m, $N(CH_2)_2$), 3.24 (2H, q, SCH_2), 3.30 (2H, m, OCH_2), 3.74 (2H, m, OCH_2), 7.41 (1H, dd, J = 12.8, 2.0 Hz, H-5), 12.10 (1H, br s, NH). MS, *m/z*: 327 $[M]^+$ (15), 285 $[M - 42]^+$ (100). Anal. Calcd for $C_{14}H_{15}F_2N_3O_2S$, C 51.37; H 4.62; N 12.84. Found: C 51.35; H 4.60; N 12.89.

*3.6.2. 2,7-Bis(morpholino)-6,8-difluoro-1H-quinazolin-4-one (**8**)*

A white solid; mp 285–287 °C. ^{1}H NMR ([$^2H_6$]DMSO, 250 MHz): δ 3.13 (8H, m, $2N(CH_2)_2$), 3.64 (8H, m, $2O(CH_2)_2$), 7.25 (1H, m, H(5)), 11.11 (1H, s, NH). MS, *m/z*: 352 $[M]^+$ (9), 310 $[M - 42]^+$ (100). Anal. Calcd for $C_{16}H_{18}F_2N_4O_3$, C 54.49; H 5.11; N 15.89. Found: C 54.35; H 5.60; N 15.89.

*3.7. The procedure for the synthesis of 2-hydrazino-6,8-difluoro-7-(pyrrolidin-1-yl)-1H-quinazolin-4-one (**10**)*

Compound (**7b**) (0.56 g, 1.8 mmol) in 5 mL of hydrazine hydrate was heated under reflux during 1 h. After the mixture was cooled the precipitate formed was collected by filtration and recrystallized from DMSO to give 0.45 g (88%) of (**10**), mp 329–331 °C. ^{1}H NMR ([$^2H_6$]DMSO, 250 MHz): δ 1.94 (4H, m, $(CH_2)_2$), 3.64 (4H, m, $N(CH_2)_2$), 7.26 (1H, dd, J = 12.9, 1.2 Hz, H-5). MS, *m/z*: 281 $[M]^+$ (100), 280 $[M - H]^+$ (54). Anal. Calcd for $C_{12}H_{13}F_2N_5O$, C 51.24; H 4.66; N 24.90. Found: C 51.25; H 4.60; N 24.53.

*3.8. The procedure for the synthesis of 2-(3,5-dimethylpyrazol-1-yl)-6,8-difluoro-7-(pyrrolidin-1-yl)-1H-quinazolin-4-one (**11**)*

Acetylacetone (0.37 mL, 3.6 mmol) was added to a solution of quinazolinone (**10**) (0.5 g, 1.8 mmol) in 10 mL of anhydrous acetonitrile to which 0.35 mL of acetic acid had been added. The reaction mixture was refluxed for 2. After the mixture was cooled the precipitate formed was collected by filtration and recrystallized from ethanol to give 0.50 g (81%) of (**11**), mp 225–227 °C. ^{1}H NMR ([$^2H_6$]DMSO, 250 MHz): δ 1.92 (3H, s, CH_3), 1.99 (3H, s, CH_3), 2.27 (4H, m, $(CH_2)_2$), 2.71 (4H, m, $N(CH_2)_2$), 6.18 (1H, s, CH), 7.43 (1H, dd, J = 13.5, 1.8 Hz, H-5), 11.22 (1H, br s, NH). MS, *m/z*: 345 $[M]^+$ (100), 344 $[M - H]^+$ (69), 346 $[M + H]^+$ (20). Anal. Calcd for $C_{17}H_{17}F_2N_5O$, C 59.13; H 4.93; N 20.29. Found: C 59.15; H 4.89; N 20.23.

*3.9. Typical procedure for the synthesis of 1-ethyl-2-ethylthio-6,7,8-trifluoro-1H-quinazolin-4-one (**12**)*

Ethyl iodide (0.62 mL, 7.7 mmol) was added to a solution of quinazolinone (**6a**) (0.5 g, 1.9 mmol) in 5 mL of ethanol to which 0.62 mL of 30% aqueous NaOH had been added. The reaction mixture was refluxed for 2. After the mixture was evaporated the residue was washed with water and recrystallized from ethanol to give 0.37 g (68%) of (**12**).

*3.9.1. 1-Ethyl-2-ethylthio-6,7,8-trifluoro-1H-quinazolin-4-one (**12**)*

Mp 95–97 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, 250 MHz): δ 1.28 (3H, t, CH_3), 1.41 (3H, t, CH_3), 3.29 (2H, q, SCH_2), 4.07 (2H, q, NCH_2), 7.80 (1H, ddd, J = 10.3, 8.1, 2.2 Hz, H-5). MS, *m/z*: 288 $[M]^+$ (39), 173 $[M - 115]^+$ (100), 259 $[M - Et]^+$ (81), 200 $[M - 88]^+$ (76). Anal. Calcd for $C_{12}H_{11}F_3N_2OS$, C 50.00; H 3.85; N 9.72. Found: C 50.15; H 3.89; N 10.00.

*3.9.2. 5,6,7-Trifluoro-8,9H-oxazolo[2,3-a]-quinazolin-4-one (**13**)*

Mp 310–312 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, 250 MHz): δ 4.31 (3H, m, CH_2), 4.81 (2H, m, CH_2), 7.73 (1H, ddd, J = 9.9, 7.5, 2.0 Hz, H-5). MS, *m/z*: 242 $[M]^+$ (65), 200 $[M - 42]^+$ (100). Anal. Calcd for $C_{10}H_5F_3N_2O_2$, C 49.60; H 2.08; N 11.57. Found: C 49.61; H 2.31; N 11.53.

*3.9.3. 1-(2-Methoxyethyl)-2-ethylthio-6,7,8-trifluoro-1H-quinazolin-4-one (**14**)*

Mp 190–192 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, 250 MHz): δ 1.33 (3H, t, CH_3), 3.07 (2H, q, SCH_2), 3.20–3.35 (4H, m, $(CH_2)_2$), 3.35 (3H, s, OCH_3), 7.61 (1H, ddd, J = 10.6, 8.5, 2.1 Hz, H-5). MS, *m/z*: 318 $[M]^+$ (2), 173 $[M - 145]^+$ (100), 260 $[M - 58]^+$ (87). Anal. Calcd for $C_{13}H_{13}F_3N_2O_2S$, C 49.05; H 4.12; N 8.80. Found: C 50.10; H 4.09; N 9.00.

*3.10. Typical procedure for the synthesis of 2-ethylthio-4-amino-6,7,8-trifluoroquinazolines (**15a–c**), (**16**), (**17**)*

Compound (**6a**) (0.8 g, 3.1 mmol) in 4 mL of $POCl_3$ was heated under reflux during 2 h. The mixture was then poured into ice water and neutralised with $NaHCO_3$. The aqueous mixture was extracted with ethyl acetate. The extracts were dried (Na_2SO_4) and then evaporated. The residue thus obtained was added to a solution of aniline (0.41 mL, 6.2 mmol) in 8 mL of anhydrous acetonitrile. The mixture was refluxed for 4 h. After the mixture was evaporated the residue was washed with water and recrystallized from ethanol to give (**15a**).

*3.10.1. 2-Ethylthio-4-anilino-6,7,8-trifluoroquinazolines (**15a**)*

Mp 79–81 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, 250 MHz): δ 1.42 (3H, t, CH_3), 3.17 (2H, q, SCH_2), 7.19 (1H, m, Ph), 7.42 (2H, m, Ph), 7.82 (2H, m, Ph), 8.47 (1H, m, H-5), 9.80 (1H, s, NH). MS, *m/z*: 335 $[M]^+$ (97), 274 $[M - SEt]^+$ (100). Anal. Calcd for $C_{18}H_{16}F_3N_3S$, C 59.50; H 4.41; N 11.57. Found: C 59.52; H 4.49; N 11.52.

*3.10.2. 2-Ethylthio-4-(3′,4′-difluoroanilino)-6,7,8-trifluoroquinazolines (**15b**)*

Mp 86–88 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, 250 MHz): δ 1.41 (3H, t, CH_3), 3.13 (2H, q, SCH_2), 7.27 (1H, m, $C_6H_3F_2$), 7.58 (1H, m, $C_6H_3F_2$), 7.99 (1H, ddd, J = 11.0, 7.5, 2.1 Hz, H-5), 8.44 (1H, m, $C_6H_3F_2$), 9.88 (1H, s, NH). MS, *m/z*: 371 $[M]^+$ (100), 310 $[M - SEt]^+$ (74), 338 $[M - 33]^+$ (58). Anal. Calcd for $C_{16}H_{10}F_5N_3S$, C 51.75; H 2.71; N 11.32. Found: C 51.72; H 2.79; N 11.32.

*3.10.3. 2-Ethylthio-4-(2′-chloroanilino)-6,7,8-trifluoroquinazolines (**15c**)*

Mp 158–160 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, 250 MHz): δ 1.20 (3H, t, CH_3), 2.90 (2H, q, SCH_2), 7.29–7.54 (4H, m, C_6H_4Cl), 8.34 (1H, ddd, J = 11.4, 8.5, 1.8 Hz, H-5), 9.92 (1H, br s, NH). MS, *m/z*: 369 $[M]^+$ (100), 274 $[M - 95]^+$ (86). Anal. Calcd for $C_{16}H_{11}ClF_3N_3S$, C 51.97; H 3.00; N 11.36. Found: C 51.92; H 2.99; N 11.32.

*3.10.4. 2-Ethylthio-4-benzylamino-6,7,8-trifluoroquinazolines (**16**)*

Mp 149–151 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, 250 MHz): δ 1.40 (3H, t, CH_3), 3.14 (2H, q, SCH_2), 4.82 (2H, m, CH_2), 7.22–7.39 (5H, m, Ph), 8.18 (1H, m, H-5), 8.85 (1H, s, NH). MS, *m/z*: 349 $[M]^+$ (52), 91 $[CH_2C_6H_5]^+$ (100). Anal. Calcd for $C_{17}H_{14}F_3N_3S$, C 58.45; H 4.01; N 12.03. Found: C 58.42; H 3.99; N 12.00.

*3.10.5. 2-Ethylthio-4-(5′-tert-butylisoxazole-3-yl)-6,7,8-trifluoroquinazolines (**17**)*

Mp 219–221 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, 250 MHz): δ 1.40 (3H, t, CH_3), 1.41 (9H, s, $(CH_3)_3$), 3.20 (2H, q, SCH_2), 6.87 (1H, s, isoxazole), 8.55 (1H, m, H-5), 10.98 (1H, s, NH). MS, *m/z*: 382 $[M]^+$ (34), 57 $[C(CH_3)_3]^+$ (100). Anal. Calcd for $C_{17}H_{17}F_3N_4OS$, C 53.40; H 4.48; N 14.65. Found: C 53.35; H 4.52; N 14.70.

*3.10.6. 2-Ethylthio-4-(N-methylindole-3-yl)-6,7,8-trifluoroquinazolines (**18**)*

Mp 211–213 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, 250 MHz): 1.47 (3H, t, CH_3), 3.28 (2H, q, SCH_2), 3.97 (3H, s, CH_3), 7.19–7.33 (2H, m, H-5′, H-6′), 7.50 (1H, m, H-4′), 8.18 (1H, m, H-5), 8.22 (1H, s, H-2′), 8.26 (1H, m, H-7′). MS, *m/z*: 373 $[M]^+$ (100), 287 $[M - Et - SCN]^+$ (69), 312 $[M - SEt]^+$ (68). Anal. Calcd for $C_{19}H_{14}F_3N_3S$, C 61.12; H 3.78; N 11.25. Found: C 60.35; H 4.00; N 11.20.

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