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An efficient synthesis of fluorine-containing substituted spiro[piperidine-4, 4′-pyrano[3,2-c]quinoline]-3′-carbonitrile by nonconventional methods

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Abstract

A series of fluorine-containing substituted spiro[piperidine-4,4′-pyrano[3,2-c]quinolines] were synthesized through a rapid one-pot multi-component reaction under microwave irradiation and sonication. The method has the advantages of excellent yields (80–96%) and short reaction time (3–10 min). We provide a series of fluorinated quinoline derivatives interesting for biological screening tests.

Keywords: Fluorinated pyrano[3,2-c]quinoline; Spiropiperidine; Microwave irradiation; Ultrasound waves

1. Introduction

Substituted pyrano quinolines have been synthesized in a search for new physiologically active compounds, drugs, pesticides and other compounds of practical significance [1,2]. Pyrano quinoline moiety is also present in many naturally occurring bioactive alkaloids such as *flindersine*, *oricine* and *vesprisine* [3], *simulenoline* [4,5], *huajiaosimuline* [6] and *zanthodioline*.

Among several scaffolds, spiropiperidines showed to be an interesting and promising class of nociceptin (NOP) ligands. They are structurally related to lofentanyl, a μ-selective opiate ligand having also affinity for the NOP (nociceptin) receptor. Spiropiperidines [7] are also useful tools for the elucidation of the mechanism of interaction of small nonpeptidic molecules. Most of the spiropiperidines have been reported to possess high agonistic activity and selectivity as Ro64-6198[14], which also exhibited anxiolytic properties [8]. Substituted piperidin-4-ones are important synthetic intermediate for the preparation of various alkaloids and pharmaceuticals [9]. This nucleus is also frequently recognized in the structure of numerous naturally occurring alkaloid and synthetic compounds with interesting biological and pharmacological properties [10].

The fluorine-containing heterocycles are now widely recognized as important organic materials showing interesting biological activities for their potential use in medicinal and agricultural scientific fields [11–14]. The fluoro quinolones have proven to be the most successful economically and clinically, notable clinical examples are world wide patented drugs, e.g., norfloxacin, ciprofloxacin, ofloxacin, enooxacin, perfloxacin, grepafloxacin, etc., as antimicrobial, antibacterial [15], anticonvulsant, CNS depressing [16] and hypotensive agents. They are orally and parenterally active, have a broad antimicrobial spectrum that includes many frequently encountered pathogens, are bactericidal in clinically achievable doses, generate comparatively tolerable resistance levels, and possess a fascinating molecular mode of action. That is not to say that they are perfect drugs [17].

Inspite of the immense biological activities of pyrano quinolines and spiropiperidine derivatives no report is yet available on the synthesis of fluorinated spiro derivatives incorporating both biolabile nuclei in a single framework.

Hence, promoted by this observation and in continuation of our earlier interest on the green chemical synthesis of biodynamic spiro derivatives using a nontraditional approach [18] an attempt has been made to synthesize fluorinated novel 2′-amino-1,7′,9′-trimethyl-5′-*oxo*-spiro[piperidine-4,4′-pyrano[3,2-c]quinoline]-3′-carbonitrile with the assumption that the incorporation of more than one bioactive heterocycle moiety into a single framework may result in the production of novel heterocycles with enhance/altered bioactivity.

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2. Results and discussion

For synthesis of novel spiro derivatives, at first we attempted to obtain unsaturated nitrile (Scheme 1) by the condensation of piperidin-4-one (**2a**) and malononitrile (**3**), but the resulting compound is unstable and dimerized at room temperature to form spiropiperidinoisoquinoline (**4a**)[19,20] within 2–3 min after mixing the reactants (chromatographic monitoring).

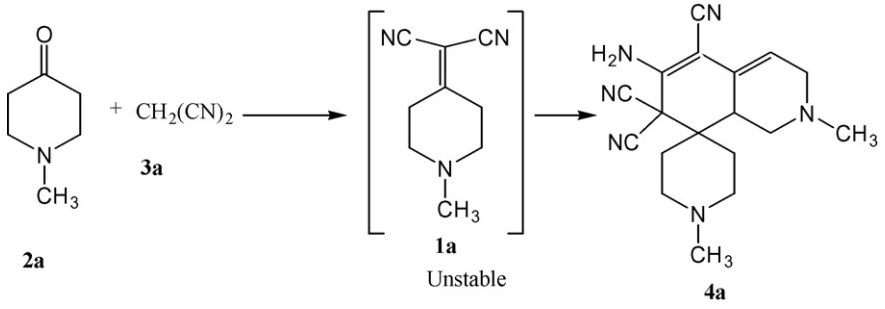
To overcome this problem and encouraged by the potential of multi-component reactions (MCR) [21,22] in organic synthesis specially when intermediates are unstable, we studied the three component condensation of substituted piperidin-4-ones (**2**), malononitrile (**3a**) and substituted 4-hydroxy quinolones (**5**), which afforded the required product spiro[piperidine-4,4′-pyrano[3,2-c]quinoline]-3′-carbonitrile (**6**) exclusively in good yield (80–90%). To optimize the method, the reaction was studied under different reaction conditions to find out the best results (Table 1).

Table 1
Comparative study for synthesis of compound (**6**)

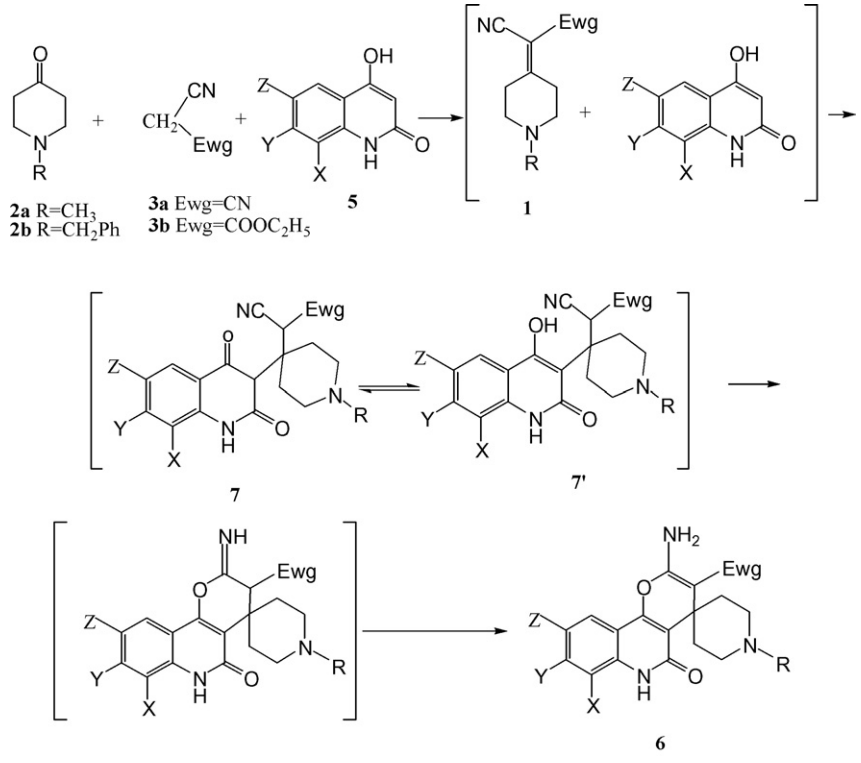
Entry	Reaction conditions	Method	Time/yield
1	Ethanol (MCR)	Δ	No reaction*
2	Ethanol + TEA (MCR)	Δ	12 h/76%
3	Ethanol (MCR)	MW	8 min/92%
4	Ethanol + TEA (MCR)	MW	7 min/94%
5	Ethanol + TEA (MCR)	US (80 °C)	7 h/90%
6	Ethanol (MCR)	US (80 °C)	8 h/86%
7	Neat + ε̇DMF	Δ	5 h/68%
8	Neat + ε̇DMF	MW	7 min/70%

ε̇= few drops of DMF, TEA = triethylamine, US = ultrasound, No reaction* = no reaction after formation of intermediate (**4**).

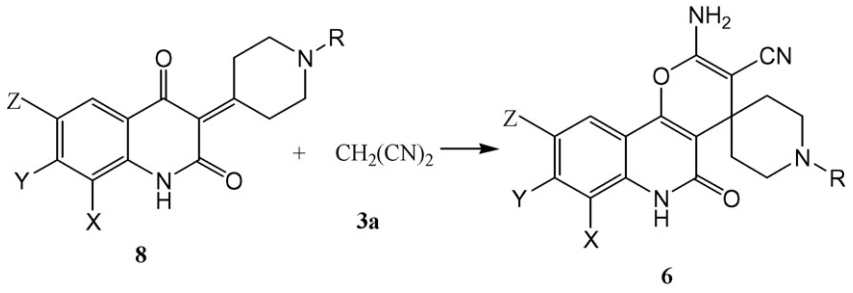
From the results obtained as shown in (Table 1), it is clear that the MCR of (**5**), (**3**) and (**2**) occurred successfully in ethanol without using any catalyst under microwaves and ultrasound, which are well-known nonconventional energy sources for carrying out green chemical synthesis [23–31]. However,



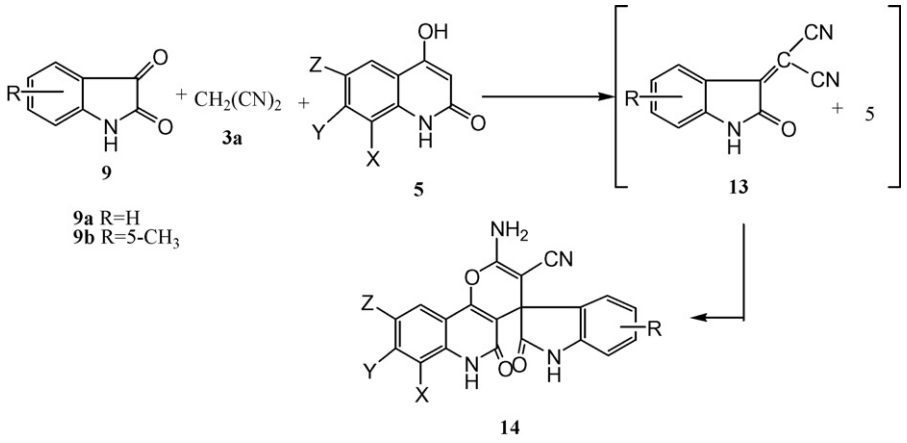
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

formation of spiro product under conventional condition required the prolonged refluxing in ethanol in the presence of triethylamine.

The reaction was also performed under neat conditions in the absence of any solvent or catalyst under microwave irradiation and it was found that at low power level only intermediate was found while at higher power charring occurs. Hence, reaction could be made successful by adding a few drops of DMF, but it can be concluded that under microwaves the reaction is very fast giving required product in 8 min. While, the ultrasonic process is more regioselective, the product of the reaction is analytically pure and does not require further recrystallization.

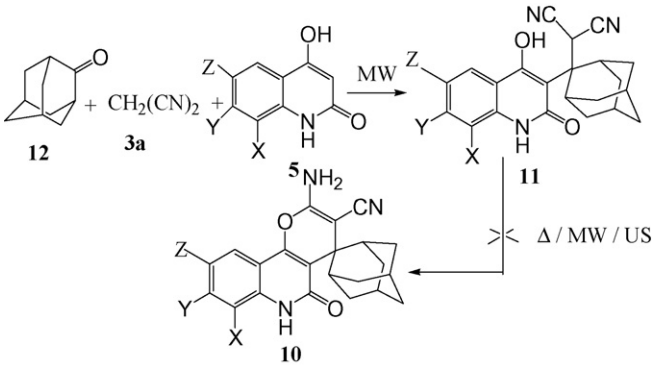
A plausible mechanism for the multi-component reaction of (**5**), (**3**) and (**2**) is given in (Scheme 2). Probably such regioselectivity has been determined by the stringent reaction sequence. That is, the initially formed unsaturated nitrile (**1a**), which acts as electrophile reacts with the ''in situ'' generated nucleophile anion of 4-hydroxy quinolones to give Michael adduct (**7**). Subsequent intramolecular cyclization and tautomeric transformation lead to the desired product (**6**).

In the MCR of (**2**), (**3**) and (**5**) although the another route is also possible as shown in (Scheme 3), which involves the formation of intermediate (**8**), which may react with malononitrile to give finally the spiro[piperidine-4,4′-pyrano[3,2-c]-quinoline (**6**).

But in the present studies the possibility of occurrence of the reaction by path i (Scheme 2) is important and TLC studies also indicated the formation of dimer along with the compound (**6**). Compound (**6**) was obtained in pure form after washing with ethanol.

Further, to study this reaction more thoroughly, we introduced indol-2,3-dione (**9**) (isatin) and model cage compound adamantan-2-one (**12**) into the described three-component condensation instead of the piperidin-4-ones. In case of isatin, the reaction occurs successfully to give expected spiro derivative (**14**) involving the intermediate formation of (2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)malononitrile (**13**), which can be separated out and did not dimerize after prolonged refluxing in ethanol (Scheme 4).

While in case of adamantan-2-one (**12**), the reaction occurs, to form stable Michael adduct (**11**), but due to some steric



Scheme 5.

Table 2
Method and yield of substituted spiro[piperidine-4,4′-pyrano[3,2-c]quinoline] **6**

Entry	Reactant 2/9/12	Reactant 3	Reactant 5	Method	Time	Product 6/11/14	Yield (%)
1	**2b**	**3a**	**5a** X = F, Y = Z = H	A	5 h	**6a**	82
				B	8 min		86
				C	12 min		70
				D	10 min		87
2	**2a**	**3a**	**5a** X = F, Y = Z = H	A	5 h	**6b**	72
				B	5 min		82
				C	15 min		75
				D	8 min		76
3	**2a**	**3a**	5b Y = F, X = Z = H	A	4 h	**6c**	86
				B	4 min		96
				C	16 min		80
				D	8 min		92
4	**2a**	**3a**	**5c** Y = CF_3, X = Z = H	A	5 h	**6d**	81
				B	5 min		92
				C	9 min		85
				D	8 min		90
5	**2a**	**3a**	**5d** X = CF_3, Y = Z = H	A	9 h	**6e**	80
				B	6 min		94
				C	11 min		80
				D	9 min		90
6	**2a**	**3a**	**5e** Z = F, X = Y = H	A	6 h	**6f**	80
				B	10 min		90
				C	9 min		85
				D	9 min		91
7	**2a**	**3a**	**5f** Y = H, X = Z = CH_3	A	6 h	**6g**	76
				B	3 min		92
				C	5 min		70
				D	5 min		86
8	**2a**	**3b**	**5f** Y = H, X = Z = CH_3	A	7 h	**6h**	75
				B	6 min		82
				C	8 min		76
				D	11 min		81
9	**2b**	**3a**	**5g** Y = X = Z = H	A	4 h	**6i**	81
				B	4 min		90
				C	6 min		76
				D	7 min		88
10	**2b**	**3a**	**5h** Z = Cl, X = Y = H	A	6 h	**6j**	83
				B	7 min		92
				C	12 min		72
				D	9 min		90
11	**9a**	**3a**	**5g** Y = X = Z = H	B	5 min	**14a**	80%
12	**9b**	**3a**	**5g** Y = X = Z = H	B	2 min	**14b**	81%
13	**12**	**3a**	**5g** Y = X = Z = H	A	9 h	**11a**	70%
				B	9 min		80%
				D	12 min		82%
14	**12**	**3a**	**5a** X = F, Y = Z = H	A	5 h	**11b**	88%
				B	10 min		92%
				D	17 min		89%

Method A: reflux in EtOH, TEA, Method B: MW in EtOH, Method C: MW in DMF, Method D: sonication.

hindrance Michael adduct (**11**) did not cyclized to pyran derivative (**10**) upon prolonged refluxing in ethanol in the presence of triethylamine or under microwave irradiation/sonication (Scheme 5) (Table 2).

3. Conclusion

In conclusion, the reported one pot procedure is attractive methodology for the facile rapid synthesis of novel

spiro[piperidine-4,4′-pyrano[3,2-c]quinolines] involving the Michael and Knoevenagel condensations.

The reaction course, that is formation of either compound **4** or **6** depends on the structure of the intermediate and the conditions. It is difficult to predict the reaction course unambiguously but on the basis of comparative studies with other cyclic ketone, e.g., isatin and adamantan-2-one and isolation of intermediates it appears that reaction occur regioselectively by path i. We can say that the study of cross-condensation of this type is very important because it leads to the development of one-pot methods for synthesis of complicated and interesting organic compounds.

4. Experimental

4.1. General

Melting points were determined on a Toshniwal apparatus. The purity of compounds was checked by thin layer of silica gel. IR spectra (KBr) were recorded on a Shimadzu FT IR-8400s spectrophotometer and ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-300 instrument at 300.15 MHz for ^{1}H and 89.55 MHz for ^{13}C NMR, respectively, in $CDCl_3$ relative to tetramethylsilane as a internal reference. The mass spectrum of a representative compound was recorded on a Kratos 50 mass spectrometer at 70 eV. The microwave-assisted reactions were carried out in a multimode MW oven (Panasonic-NN-781JF) equipped with inverter technology (generating fixed frequency throughout the required time) for realistic control of the microwave operating at 1000 W generating 2450 MHz frequency and ultrasound enhanced reactions were carried out in an ultrasonic bath (Bandelin Sonorex) operating at 230 V and generating 33 KHz output frequency.

Substituted 4-hydroxy quinolines (**5a**–**h**) were prepared by improved method under microwaves developed in our laboratory [32].

4.2. General procedures for the synthesis of compounds (*6a–j*)

4.2.1. Method A

An equimolar mixture of ketone (**2**), (1 mmol) malononitrile (1 mmol) and corresponding 4-hydroxy quinoline (1 mmol) and triethylamine (0.5 ml) in absolute ethanol was refluxed for 6 h or stirred for 12 h at room temperature. TLC monitored the progress of the reaction. The precipitate that formed was filtered off, indicated intermediate along with required product. This precipitate was passed through a silica gel column with a mixture of ethyl acetate and petroleum ether (1:15, v/v) as an eluent to give pure product.

4.2.2. Method B

An equimolar mixture (1 mmol) of (**5**), (**2**) and (**3**) was introduced in a beaker and minimum quantity of ethanol sufficient to make slurry was added in the absence of catalyst. The mixture was placed in a microwave oven and irradiated for appropriate time at 300 W. The mixture was then cooled and product separated was filtered and washed with ethanol thoroughly. It was found that the product is pure by TLC analysis in most cases.

4.2.3. Method C

An equimolar mixture (1 mmol) of (**5**), (**2**) and (**3**) with few drops of DMF, in an open tall beaker was irradiated inside microwave oven for an appropriate time (monitored by TLC). The solid mass obtained poured into water to give product, which was recrystallized from ethanol.

4.2.4. Method D

An equimolar mixture (1 mmol) of (**5**), (**2**) and (**3**) dissolved in minimum quantity of ethanol in a conical flask, which was immersed in the water bath of an ultrasonic cleaner. The flask was positioned 0.5 cm above the bottom of the bath and the level of the water was adjusted to that of the solvent level inside the flask. The mixture was treated with ultrasound (operating at 230 V generating 33 KHz output frequencies) for appropriate time (TLC). The product started to separate out during the course of the reaction The solid that separate out was filtered, washed with ethanol and found to be pure by TLC analysis.

Although pure crystalline product was obtained under microwaves and sonication (TLC), for analytical purpose the product was further recrystallized from ethanol.

The identification of substituted 2′-amino-1-benzyl/methyl-5′-*oxo*-spiro[piperidine-4,4′-pyrano[3,2-c]quinoline]-3′-carbonitrile or carboxyethyl synthesized was established by their mp, IR, ^{1}H NMR, ^{13}C NMR and Mass (representative compound) spectral studies.

6a. Mp: 310 °C. ^{1}H NMR ($CDCl_3$) δ 10.69 (s, 1H, NH, D_2O exchangeable), 8.07–6.83 (m, 10H, Ar–H, NH_2 D_2O exchangeable), 3.54 (s, 2H, CH_2Ph), 2.59 (m, 2H), 2.42 (m, 2H), 2.16 (m, 2H), 1.81 (m, 2H). IR (cm^{-1}) 3395, 3350 (NH_2), 2345 (C≡N), 1687 (C=O), 1180 (C–O), 760 (C–F). ^{13}C NMR δ 171.22, 161.87, 154.36, 137.81, 135.96, 128.81, 127.21, 126.91, 126.61, 125.46, 123.41, 120.32, 107,36, 65.71, 58.49, 46.10, 45.96, 26.56, 26.54, 19.18. ^{19}F NMR δ 120.42 (s, C–F). Anal calcd. for $C_{24}H_{21}FN_4O_2$: C, 69.22; H, 5.08; N,13.45. Found C, 69.02; H, 5.06; N, 13.41.

6b. Mp: 223 °C. ^{1}H NMR ($CDCl_3$) δ 9.61 (s, 1H, NH, D_2O exchangeable), 7.16–6.89 (m, 5H, Ar–H, NH_2, D_2O exchangeable), 2.60 (m, 2H), 2.57 (s, 3H, CH_3), 2.42 (m, 2H), 2.11 (m, 2H), 1.81 (m, 2H). IR (cm^{-1}) 3380, 3310 (NH_2) 2352 (C≡N), 1685 (C=O), 1180 (C–O), 780 (C–F). ^{13}C NMR δ 171.16, 162.80, 154.39, 134.91, 126.96, 125.47, 123.49, 116.26, 107.32, 65.74, 48.79, 48.46, 38.01, 25.26, 26.16, 19.22. ^{19}F NMR δ 119.20 (s, C–F). Anal calcd. for $C_{18}H_{17}FN_4O_2$: C, 63.52; H, 5.03; N,16.46. Found C, 63.33; H, 5.02; N, 16.41.

6c. Mp; 265 °C. ^{1}H NMR ($CDCl_3$) δ 10.51 (s, 1H, NH, D_2O exchangeable), 7.89–7.51 (m, 5H, Ar–H, NH_2, D_2O exchangeable), 2.61 (m, 2H), 2.60 (s, 3H, CH_3), 2.41 (m, 2H), 2.15 (m, 2H), 1.50 (m, 2H). IR (cm^{-1}) 3392, 3320 (NH_2), 2347 (C≡N), 1688 (C=O), 1185 (C–O), 760 (C–F). ^{13}C NMR δ170.81, 160.82, 152.19, 133.96, 126.94, 125.49, 122.49, 119.34,

116.24, 107.34, 65.94, 48.79, 48.64, 38.34, 26.19, 19.11. ^{19}F NMR δ 118.05 (s, C–F). Anal calcd. for $C_{18}H_{17}FN_4O_2$: C, 63.52; H, 5.03; N, 16.46. Found C, 63.51; H, 5.04; N, 16.42.

6d. Mp: 280 °C. ^{1}H NMR ($CDCl_3$) δ 10.16 (s, 1H, NH, D_2O exchangeable), 7.50–7.47 (m, 5H, Ar–H, NH_2, D_2O exchangeable), 2.60 (m, 2H), 2.50 (s, 3H, CH_3), 2.38 (m, 2H), 2.30 (m, 2H), 1.87 (m, 2H). IR (cm^{-1}) 3390, 3350 (NH_2), 2355 (C≡N), 1695 (C=O), 1195 (C–O), 770 (C–F). ^{13}C NMR δ 170.92, 160.84, 153.94, 132.96, 125.41, 124.96, 123.49, 119.39, 116.29, 112.64, 107.39, 65.99, 48.79, 48.26, 39.12, 26.24, 26.02, 19.11. ^{19}F NMR δ 64.01 (s, C–CF_3). Anal calcd. for $C_{19}H_{17}F_3N_4O_2$: C, 58.46; H, 4.39; N, 14.60. Found C, 58.65; H, 4.38; N, 14.56.

6e. Mp: 145 °C. ^{1}H NMR ($CDCl_3$) δ 10.16 (s, 1H, NH, D_2O exchangeable), 7.50–7.47 (m, 5H, Ar–H, NH_2, D_2O exchangeable), 2.61 (m, 2H), 2.52 (s, 3H, CH_3), 2.38 (m, 2H), 2.30 (m, 2H), 1.87 (m, 2H). IR (cm^{-1}) 3390, 3350 (NH_2), 2355 (C≡N), 1695 (C=O), 1195 (C–O), 760 (C–F). ^{13}C NMR δ171.01, 162.81, 154.91, 132.54, 128.79, 125.69, 123.19, 116.24, 109.65, 107.91, 65.64, 48.59, 48.26, 38.04, 26.64, 26.51, 19.07. ^{19}F NMR δ 63.24 (s, C–CF_3). Anal calcd. for $C_{19}H_{17}F_3N_4O_2$: C,60.59; H, 4.39; N, 15.70. Found C, 58.63; H, 4.40; N, 60.40.

6f. Mp: 275 °C. ^{1}H NMR ($CDCl_3$) δ 10.70 (s, 1H, NH, D_2O exchangeable), 7.80–7.02 (m, 5H, Ar–H, NH_2, D_2O exchangeable), 2.60 (m, 2H), 2.56 (s, 3H, CH_3), 2.35 (m, 2H), 2.20 (m, 2H), 1.87 (m, 2H). IR (cm^{-1}) 3385, 3300 (NH_2), 2350 (C≡N), 1692 (C=O) 1180 (C–O), 780 (C–F). ^{13}CNMR δ 170.71, 162.72, 156.72, 154.09, 130.86, 126.64, 122.59, 116.34, 106.24, 65.64, 48.76, 48.61, 38.21, 26.21, 26.09, 19.10. Anal calcd. for $C_{18}H_{17}FN_4O_2$: C, 63.52; H, 5.03; N, 16.46. Found C, 63.71; H, 5.02; N, 16.41.

6g. Mp: 140 °C. ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 1H, NH, D_2O exchangeable), 7.84–7.49 (m, 4H, Ar–H, NH_2, D_2O exchangeable), 2.62 (m, 2H), 2.50 (s, 3H, N–CH_3), 2.40 (m, 2H), 2.27, 2.26 (2s, 6H, Ar–CH_3), 2.20 (m, 2H), 1.87 (m, 2H). IR (cm^{-1}) 3380, 3300 (NH_2), 2350 (C≡N), 1690 (C=O), 1190 (C–O). ^{13}C NMR δ 170.11, 161.01, 154.64, 132.91, 128.46, 123.11, 116.21, 107.32, 65.74, 48.74, 48.21, 39.54, 26.21, 26.01, 21.64, 19.17, 12.54. *m/z* (%) 350 (15, M^+), 349 (10), 323 (20), 311 (100), 293 (40), 288 (30), 190 (60), 105 (35). Anal calcd. for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99. Found C, 68.34; H, 6.31; N, 15.94.

6h. Mp: 300 °C. ^{1}H NMR ($CDCl_3$) δ 10.69 (s, 1H, NH, D_2O exchangeable), 8.55–7.20 (m, 4H, Ar–H, NH_2, D_2O exchangeable) 4.41 (q, 2H, CH_2), 2.62 (m, 2H), 2.38 (m, 2H), 2.58 (s, 3H, CH_3), 2.27,2.26 (2s, 6H, CH_3), 2.14 (m, 2H), 1.81 (m, 2H), 1.44 (t, 3H, CH_3). IR (cm^{-1}) 3385, 3350 (NH_2), 1685, 1680 (2C=O), 1170 (C–O). ^{13}C NMR δ164.94, 163.84, 160.94, 153.09, 132.64, 128.49, 124.64, 107.64, 88.94, 58.91, 49.24, 49.16, 38.91, 26.94, 26.64, 20.69, 19.07, 12.74, 11.51. Anal calcd. for $C_{22}H_{27}N_2O_4$: C, 66.48; H, 6.85; N, 10.57. Found C, 66.28; H, 6.83; N, 10.54.

6i. Mp: 181 °C. ^{1}H NMR ($CDCl_3$) δ 9.50 (s, 1H, NH, D_2O exchangeable), 8.56–7.21 (m, 9H, Ar–H), 6.50 (s, 2H, NH_2, D_2O exchangeable), 3.72 (s, 2H, CH_2Ph), 2.62 (m, 2H), 2.37 (m, 2H), 2.12 (m, 2H), 1.80 (m, 2H). IR (cm^{-1}) 3390, 3300 (NH_2), 2355 (C≡N), 1696 (C=O), 1190 (C–O). ^{13}C NMR δ171.26, 162.87. 154.10, 135.35, 133.21, 129.36, 128.01, 127.36, 126.72, 125.27, 124.06, 116.21, 107.06, 65.74, 57.46, 47.19, 47.12, 27.56, 27.42, 19.30. Anal calcd. for $C_{24}H_{22}N_4O_2$: C, 72.34; H, 5.57; N, 14.02. Found C, 72.13; H, 5.55; N, 14.02.

6j. Mp: 215 °C. ^{1}H NMR ($CDCl_3$) δ 9.52 (s, 1H, NH, D_2O exchangeable), 7.59–7.26 (m, 8H, Ar–H); 6.70 (br, s, 2H, NH_2, D_2O exchangeable), 3.71 (s, 2H, CH_2Ph), 2.63 (m, 2H), 2.38 (m, 2H), 2.20 (m, 2H), 1.81 (m, 2H). IR (cm^{-1}) 3392, 3330 (NH_2), 2356 (C≡N), 1697 (C=O), 1195 (C–O), 735 (C–Cl). ^{13}C NMR δ 170.21, 163.84, 155.90, 135.32, 128.36, 128.32, 127.10, 127.01, 126.36, 125.71, 124.01, 115.20, 106.01, 64.72, 56.41, 47.16, 46.10, 26.51, 26.06, 19.12. Anal calcd. for $C_{24}H_{21}N_4ClO_2$: C, 72.34; H, 5.60; N, 14.05. Found C, 72.11; H, 5.60; N, 14.01.

14a. Mp: 258 °C. ^{1}H NMR ($CDCl_3$) δ 9.19 (s, 1H, NH, D_2O exchangeable), 8.60–7.02 (m, 11H, Ar–H, NH and NH_2, D_2O exchangeable). IR (cm^{-1}) 3370, 3200 (NH_2 and NH), 2100 (C≡N), 1725, 1695 (two C=O), 1170 (C–O). ^{13}C NMR δ 177.06, 166.63, 162.49, 157.91, 141.82, 133.53, 132.33, 129.49, 128.10, 127.41, 127.36, 126.77, 126.12, 121.42, 116.78, 97.04, 56.70, 46.70. Anal calcd. for $C_{20}H_{12}N_4O_3$,: C, 67.41; H, 3.39; N 15.72. Found C, 67.21; H, 3.38; N 15.67.

14b. Mp: 220 °C. ^{1}H NMR ($CDCl_3$) δ 9.24 (s, 1H, NH, D_2O exchangeable), 8.28–6.83 (m, 10H, Ar–H, NH and NH_2, D_2O exchangeable), 2.21 (s, 3H, CH_3). IR (cm^{-1}) 3360, 3200 (NH_2 and NH), 2100 (C≡N), 1720, 1690 (two C=O), 1170 (C–O). ^{13}C NMR δ 176.29, 167.32, 162.78, 158.67, 140.91, 134.29, 133.38, 129.24, 128.73, 127.67, 126.34, 125.49, 123.05, 119.43, 116.72, 98.04, 56.64, 46.61, 20.42. Anal calcd. for $C_{21}H_{14}N_4O_3$: C, 68.10; H, 3.81; N 15.13. Found C, 67.90; H, 3.80; N 15.08.

11a. Mp: 133 °C. ^{1}H NMR ($CDCl_3$) δ 10.93 (bs, 1H, OH, D_2O exchangeable), 9.42 (s, 1H, NH, D_2O exchangeable), 7.60–7.28 (m, 4H, Ar–H), 3.58 (s, 1H, CH), 2.07–1.25 (m, 14H, adamantanyl protons). IR (cm^{-1}) 3275 (NH), 2200 (two C≡N), 1725 (C=O). ^{13}C NMR δ162.81, 160.34, 134.86, 127.41, 126.97, 123.81, 119.32, 117.69, 100.83, 37.27, 31.16, 29.33, 29.21, 28.84, 28.46, 28.06, 19.42. Anal calcd. for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N 11.69. Found C, 73.42; H, 5.87; N 11.65.

11b. Mp: 186 °C. ^{1}H NMR ($CDCl_3$) δ 10.52 (bs, 1H, OH, D_2O exchangeable), 9.62 (s, 1H, NH, D_2O exchangeable), 7.55–6.92 (m, 3H, Ar–H), 3.55 (s, 1H, CH), 2.10–1.52 (m, 14H, adamantanyl protons). IR (cm^{-1}) 3270 (NH), 2210 (two C≡N), 1720 (C=O), 785 (C–F). ^{13}C NMR δ 161.80, 159.54, 134.62, 126.45, 124.91, 124.69, 120.34, 116.40, 101.53, 36.51, 32.45, 30.61, 29.43, 28.54, 28.29, 28.09, 20.05. Anal calcd. for $C_{22}H_{20}FN_3O_2$: C, 70.01; H, 5.34; N 11.13. Found C, 69.81; H, 5.35; N, 11.10.

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