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UNEXPECTED HIGHLY CHEMOSELECTIVE NUCLEOPHILIC SUBSTITUTION REACTION OF 4-DIMETHYLAMINO-2-METHOXY-3-TRIFLUOROACETYLQUINOLINE WITH VARIOUS NUCLEOPHILES

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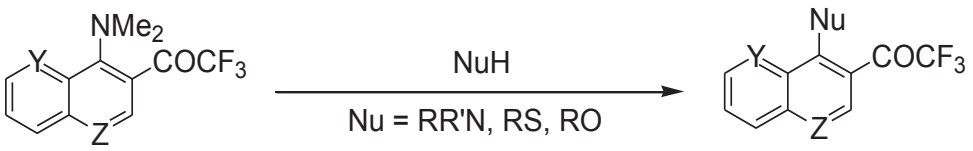
Abstract – Aromatic nucleophilic substitution reaction of 4-dimethyl-amino-2-methoxy-3-trifluoroacetylquinoline with various nucleophiles (NuH) such as amines, thiols, and alcohols proceeded chemoselectively to give the corresponding *Me2N-Nu* exchanged products, 2-methoxy-3-trifluoroacetyl-4-quinolylamines, sulfides, and ethers without any formation of *MeO-Nu* exchanged products in spite of the common knowledge that alkoxy group is the better leaving group than amino group.

In the course of our systematic investigation as to nucleophilic substitution reactions on aromatic systems activated by trifluoroacetyl group, we found that dimethylamino group which is hardly substituted by nucleophiles (NuH) in general is easily substituted by various nucleophiles on 2,4-bis(trifluoroacetyl)-1-dimethylaminonaphthalene (**1**),[1] 5,7-bis(trifluoroacetyl)-8-dimethylaminoquinoline (**2**),[2] and 4-dimethylamino-3-trifluoroacetylquinoline (**3**)[3] to afford the corresponding *Me2N-Nu* exchanged products (**4-6**) in high yields (Scheme 1).



1: (Y, Z) = (CH, C-$COCF_3$)
2: (Y, Z) = (N, C-$COCF_3$)
3: (Y, Z) = (CH, N)

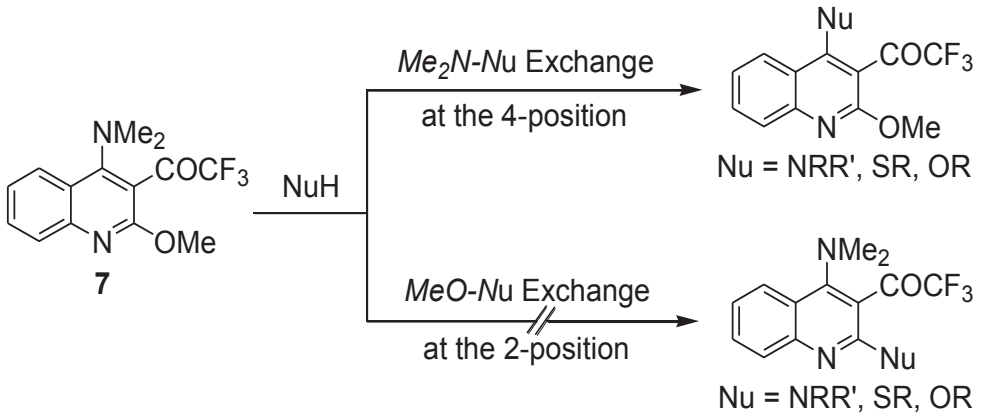
4: (Y, Z) = (CH, C-$COCF_3$)
5: (Y, Z) = (N, C-$COCF_3$)
6: (Y, Z) = (CH, N)

Scheme 1

Meanwhile, it is commonly known that alkoxy group such as methoxy group is better leaving group than amino group on nucleophilic substitution reaction.[4] It is also known that nucleophilic substitution occurs at the 2-position more easily than the 4-position on quinoline ring system[5] except for the special case that the leaving group at the 4-position is especially active relative to that at the 2-position.[6]

These findings prompted us to examine the aromatic nucleophilic substitution on quinoline derivatives which have two leaving groups at the 2- and 4-positions on the quinoline ring.

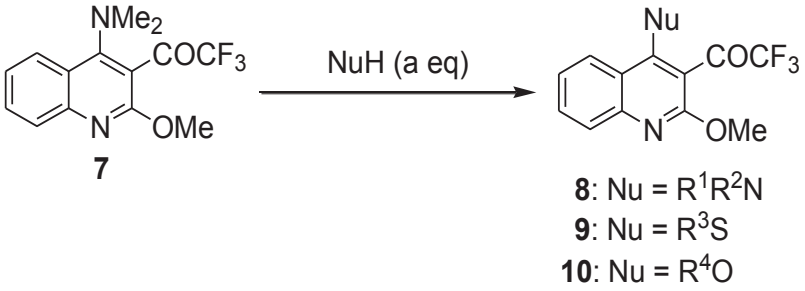
Here, we wish to report an unexpected highly chemoselective nucleophilic substitution reaction on 4-dimethylamino-2-methoxy-3-trifluoroacetylquinoline (**7**) in which dimethylamino group at the 4-position, the poor leaving group relative to methoxy group at the 2-position, is exclusively substituted by various nucleophiles (Scheme 2).



Scheme 2

Firstly, we examined the reaction of **7** with various amines (Scheme 3, Table 1). The reaction of **7** with *n*-butylamine in refluxing acetonitrile occurred cleanly at the 4-position to give the *Me*$_2$*N-NHBu-n* exchanged product (**8a**) in 94% yield (Entry 1). In spite of careful inspection of the crude materials, no *MeO-NHBu-n* exchanged product was detected in this reaction. The reaction of **7** with benzylamine also proceeded selectively to afford the *N-N* exchanged product (**8b**) in excellent yield with no formation of the *O-N* exchanged product (Entry 2). Quite similarly, the reaction of **7** with cycloalkylamines such as cyclopropylamine and cyclohexylamine yielded the corresponding dimethylamino-cycloalkylamino exchanged products (**8c** and **8d**) solely in excellent yields (Entries 3 and 4). The reaction of **7** with allylamine and propargylamine also occurred at the 4-position to give more functionalized *N*-allyl- and *N*-propargyl-4-quinolylamines (**8e** and **8f**) in high yields, respectively (Entries 5 and 6). Although the reaction of **7** with secondary amines such as pyrrolidine required more enhanced conditions, it introduced pyrrolidyl group only at the 4-position of the quinoline ring to afford **8g** (Entry 7). With less nucleophilic aromatic amines such as *p*-substituted anilines **7** underwent the *N-N* exchange reaction

exclusively under more forced conditions (in refluxing valeronitrile for prolonged time) to give the corresponding *N*-aryl-4-quinolylamines (**8h-k**) in good to high yields (Entries 8-11).[7]



Scheme 3

Next, we examined the reactions of **7** with thiols (Table 2). Interestingly, **7** reacted with aliphatic thiols, such as *n*-butanethiol, *n*-hexanethiol, and phenylmethanethiol at the 4-position in the absence of any catalyst to afford the corresponding 2-methoxy-3-trifluoroacetyl-4-quinolyl sulfides (**9a-c**) in moderate to high yields (Entries 1-3). Also, the reaction with benzenethiols having various *p*-substituent proceeded cleanly under almost similar conditions to give the corresponding *N*-*S* exchanged products (**9d-g**) exclusively in good yields (Entries 4-7).[8] Thus, it was found that the reaction of **7** with thiols proceeded chemoselectively at the 4-position quite similar to the case of that with amines.

Lastly, we tried the reaction of **7** using alcohols as a nucleophile (Table 3). In spite of the weak nucleophilicity of alcohols relative to the corresponding amines and thiols, the reaction of **7** with *n*-propyl,

Table 1. Aromatic nucleophilic substitution of **7** with amines (R^1R^2NH)

Entry	R^1	R^2	a (eq)	Temp. (°C)	Solvent	Time (h)	Product	Yield (%)[a]
1	*n*-Bu	H	3	reflux	MeCN	4	**8a**	94
2	$PhCH_2$	H	3	reflux	MeCN	48	**8b**	91
3	Cyclopropyl	H	5	50	MeCN	24	**8c**	96
4	Cyclohexyl	H	5	reflux	MeCN	24	**8d**	96
5	$H_2C{=}CHCH_2$	H	3	60	MeCN	24	**8e**	95
6	$HC{\equiv}CCH_2$	H	5	reflux	MeCN	24	**8f**	86
7	$-(CH_2)_4-$		20	reflux	MeCN	24	**8g**	47
8	*p*-$MeOC_6H_4$	H	5	reflux	BuCN	72	**8h**	71
9	*p*-MeC_6H_4	H	5	reflux	BuCN	96	**8i**	84
10	Ph	H	10	reflux	BuCN	168	**8j**	88
11	*p*-ClC_6H_4	H	20	reflux	BuCN	168	**8k**	68

[a] Isolated yields.

Table 2. Aromatic nucleophilic substitution of **7** with Thiols (R^3SH)

Entry	R^3	a (eq)	Temp. (°C)	Solvent	Time (h)	Product	Yield (%)[a]
1	*n*-Bu	40	160[b]	mesitylene	120	**9a**	84
2	*n*-Hexyl	40	reflux	mesitylene	120	**9b**	73
3	$PhCH_2$	5	reflux	mesitylene	96	**9c**	57
4	*p*-$MeOC_6H_4$	5	reflux	*p*-xylene	72	**9d**	79
5	*p*-MeC_6H_4	5	reflux	mesitylene	96	**9e**	79
6	Ph	5	reflux	mesitylene	96	**9f**	66
7	*p*-ClC_6H_4	5	reflux	mesitylene	96	**9g**	65

[a] Isolated yields. [b] In a sealed tube.

n-butyl, and *n*-pentyl alcohols proceeded successfully at the 4-position under neat conditions to give the corresponding *N*-*O* exchanged products, 2-methoxy-3-trifluoroacetyl-4-quinolyl ethers (**10a-c**) solely in good to high yields (Entries 1-3). Similarly, **7** underwent the dimethylamino-alkoxy exchange reaction with phenethyl and 2-phenoxyethyl alcohols in refluxing mesitylene to afford the corresponding ethers (**10d** and **10e**) in good yields (Entries 4 and 5). Even in the case of more bulky *i*-butyl alcohol, the reaction of **7** was proceeded chemoselectively to convert the corresponding ether (**10f**) in excellent yield (Entry 6). Exchange reaction of **7** with secondary alcohol (cyclohexyl alcohol) was also selective to give *N*-*O* exchanged product (**10g**) in sufficient yield (Entry 7).[9] In all cases in Table 3, no *O*-*O* exchange reaction at 2-position of **7** was observed.

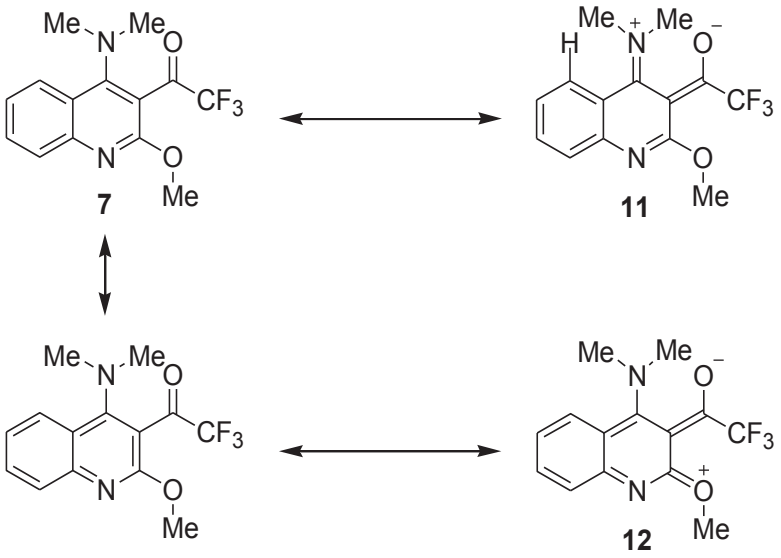
The present unexpected chemoselectivity can be explained as followings. If the dimethylamino group at the 4-position of **7** is conjugated with the trifluoroacetyl group at the 3-position of **7**, it takes a resonance structure **11** (Scheme 4). On the other hand, if the methoxy group at the 2-position of **7** is conjugated

Table 3. Aromatic nucleophilic substitution of **7** with Alcohols (R^4OH)

Entry	R^4	a (eq)	Temp. (°C)	Solvent	Time (h)	Product	Yield (%)[a]
1	*n*-Pr	-[b]	180[c]	*n*-PrOH	72	**10a**	62
2	*n*-Bu	-[b]	reflux	*n*-BuOH	240	**10b**	89
3	*n*-Pentyl	-[b]	reflux	*n*-PentylOH	120	**10c**	77
4	$PhCH_2CH_2$	30	reflux	mesitylene	48	**10d**	77
5	$PhOCH_2CH_2$	30	reflux	mesitylene	96	**10e**	77
6	*i*-Bu	-[b]	180[c]	*i*-BuOH	72	**10f**	92
7	Cyclohexyl	-[b]	reflux	CyclohexylOH	168	**10g**	60

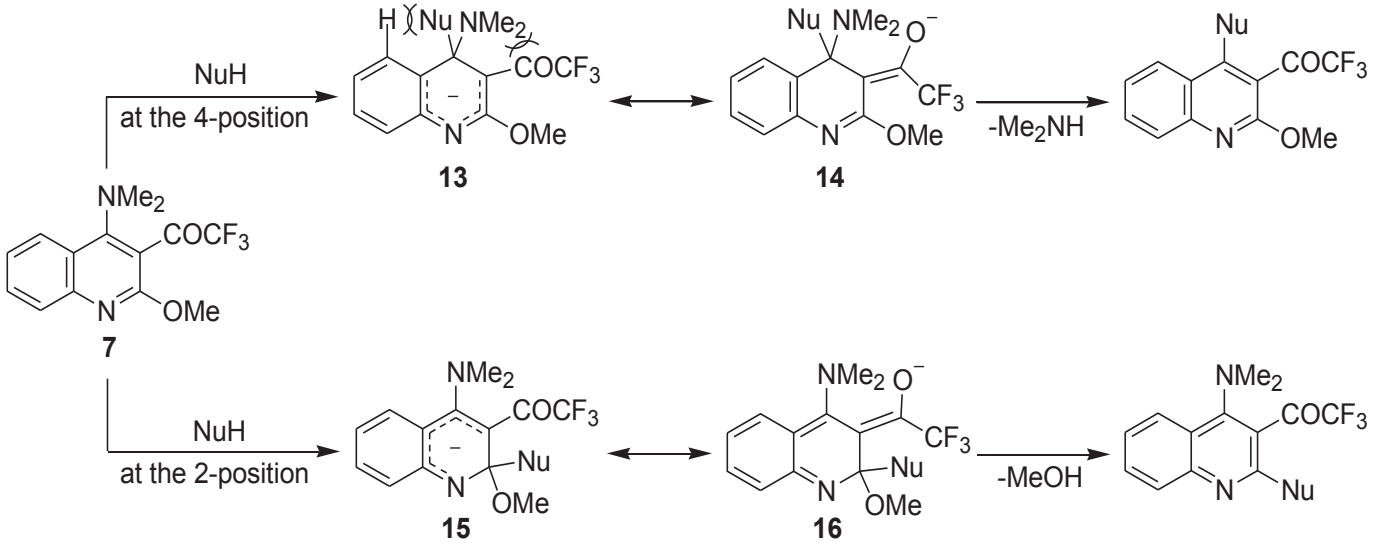
[a] Isolated yields. [b] Under solvolysis conditions. [c] In a sealed tube.

with the trifluoroacetyl group at the 3-position of **7**, it takes a resonance structure **12**. Although the aromaticity of benzene ring in the resonance structure **11** is retained, the aromaticity of benzene ring in the resonance structure **12** is not retained. Therefore, the resonance structure **11** is considered to be stable than the resonance structure **12**. In the resonance structure **11**, dimethylamino group has steric repulsion between trifluoroacetyl group and hydrogen atom at the peri-position, but the resonance contribution of **11** is larger than it of **12**. Therefore, it is considered that nucleophiles easily attack the iminiumu carbon at the 4-position compared to the oxonium carbon at the 2-position.



Scheme 4

Moreover, when nucleophiles (NuH) attack the 4-position of **7**, the Meisenheimer complexes (**13**) are formed (Scheme 5). Meanwhile, the complexes (**15**) are resulted when nucleophiles reacted at the 2-position of **7**. Strong electron-withdrawing trifluoroacetyl group at the 3-position of **7** causes predominant contribution of the canonical form of **14** in **13** and the canonical form **16** in **15**. Benzene unit maintains aromatic structure (aromaticity) in the form **14**, whereas that is destroyed in the form **16**. Consequently, the Meisenheimer complexes (**13**) are more stabilized than **15**. This difference of stability between **13** and **15** results the exclusive formation of **13**, and, consequently, the *Me_2N-Nu* exchanged products (**8**-**10**) from **7**. In addition, the significant steric repulsions around the 4-position between peri-hydrogen and 3-trifluoroacetyl group in **13** that are released by elimination of dimethylamino group accelerates the step from **13** to **8**-**10** (steric acceleration). In the complex **15** in which methoxy group is less bulky than dimethylamino group and no presence of peri-hydrogen around the 2-position, the effect of steric acceleration for the elimination process to *MeO-Nu* exchanged products is decreased. Such difference of steric factors between **13** and **15** may also one of the reasons for the present unexpected chemoselectivity.



Scheme 5

In summary, we have presented unexpected highly chemoselective nucleophilic substitution reactions of 4-dimethylamino-2-methoxy-3-trifluoroacetylquinoline with various amines, thiols, and alcohols giving the corresponding 2-methoxy-3-trifluoroacetyl-4-quinolylamines, sulfides, and ethers, which are not easily accessible by other methods. It is also worth of noting that the present nucleophilic substitution occurs at 4-position which is less active than 2-position in quinoline ring system in general. Quinoline derivatives are one of the most important heterocyclic compounds expecting interesting biological activities,[10-13] and fluorine-containing heterocycles are now widely recognized as important organic materials having potential use in medicinal and agricultural scientific fields.[14] Application of the present highly chemoselective substitution reaction to the syntheses of various fluorine-containing quinoline-fused heterocycles is now under investigation together with the mechanistic study to explain the present interesting chemoselectivity.

REFERENCES AND NOTES

1. (a) M. Hojo, R. Masuda, and E. Okada, *Tetrahedron Lett.,*1987, **28**, 6199; (b) M. Hojo, R. Masuda, E. Okada, and H. Miya, *Synthesis*, 1989, 870.
2. (a) E. Okada and N. Tsukushi, *Synlett*, 1999, 210; (b) E. Okada, N. Tsukushi, and N. Shimomura, *Synthesis*, 2000, 237.
3. (a) E. Okada, T. Sakaemura, and N. Shimomura, *Chem. Lett.*, 2000, 50; (b) E. Okada, M. Hatakenaka, T. Sakaemura, N. Shimomura, and T. Ashida, *Heterocycles*, 2012, **86**, 1177; (c) D. Cornut, H. Lemoine, O. Kanishchev, E. Okada, F. Albrieux, A. H. Beavogui, A.-L. Bienvenu, S. Picot, J.-P. Bouillon, and M. Médebielle, *J. Med. Chem*., 2013, **56**, 73; (d) N. Ota, M. Hatakenaka, T. Ashida, and

E. Okada, *Heterocycles*, 2013, **87**, 2641; (e) E. Okada, M. Hatakenaka, M. Kuratani, T. Mori, and T. Ashida, *Heterocycles*, 2014, **88**, 799.

4. (a) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273; (b) J. A. Zoltewicz, *Top. Curr. Chem.*, 1975, **59**, 33.
5. (a) M. L. Belli, G. Illuminati, and G. Marino, *Tetrahedron*, 1963, **19**, 345; (b) A. Šimáček, M. Grepl, L. Hradilová, and P. Hradil, *Synlett*, 2012, **23**, 2205.
6. B. H. Hwang, S. H. Park, E. B. Choi, C. S. Pak, and H. K. Lee, *Tetrahedron*, 2008, **64**, 6698.
7. **A typical procedure for the reaction of 7 with amines to give 2-methoxy-3-trifluoroacetyl-4-quinolylamines (8a-k)**. To a solution of **7** (298 mg, 1 mmol) in MeCN (4 mL) was added *n*-butylamine (219 mg, 3 mmol) and the mixture was stirred under reflux for 4 h. Evaporation of the solvent gave a crude mixture which was subjected to column chromatography on silica gel eluting with *n*-hexane/AcOEt (10:1) to give **8a** (307 mg, 94%); mp 88-89 °C (*n*-hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (br s, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 4.03 (s, 3H), 3.67 (q, J = 4.8 Hz, 2H), 1.72 (quint, J = 7.4 Hz, 2H), 1.47 (sext, J = 7.4 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.3 (q, J_{CF} = 35.7 Hz), 161.1, 158.8, 149.1, 132.3, 128.0, 125.7, 122.7, 117.2, 117.2 (q, J_{CF} = 288.7 Hz), 97.2, 53.1, 48.7, 32.7, 19.9, 13.6; IR (KBr) 3269, 1628, 1197, 1168 cm^{-1}. Anal. Calcd for $C_{16}H_{17}F_3N_2O_2$: C, 58.90; H, 5.25; N, 8.59. Found: C, 58.78; H, 5.44; N, 8.50.
8. **A typical procedure for the reaction of 7 with thiols to give 2-methoxy-3-trifluoroacetyl-4-quinolyl sulfides (9a-g)**. To a solution of **1** (298 mg, 1 mmol) in mesitylene (4 mL) was added phenylmethanethiol (621 mg, 5 mmol) and the mixture was stirred under reflux for 96 h. Evaporation of the solvent gave a crude mixture which was subjected to column chromatography on silica gel eluting with *n*-hexane/AcOEt (10:1) to give **9c** (215 mg, 57%); mp 87-88 °C (*n*-hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 7.7 Hz, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.73 (t, J = 7.7 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.24-7.18 (m, 3H), 7.15-7.09 (m, 2H), 4.10 (s, 3H), 4.04 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.9 (q, J_{CF} = 39.2 Hz), 157.6, 147.2, 144.3, 135.9, 131.6, 128.9, 128.6, 128.0, 127.7, 126.1, 125.7, 125.5, 125.5, 115.2 (q, J_{CF} = 291.4 Hz), 54.1, 42.2; IR (KBr) 1740, 1206, 1167 cm^{-1}. Anal. Calcd for $C_{16}H_{16}F_3NO_2S$: C, 60.50; H, 3.74; N, 3.71. Found: C, 60.81; H, 3.74; N, 3.37.
9. **A typical procedure for the reaction of 7 with alcohols to give 2-methoxy-3-trifluoroacetyl-4-quinolyl ethers (10a-g)**. To a solution of **1** (298 mg, 1 mmol) in *n*-butyl alcohol (8 mL, 88 mmol) was stirred at reflux temperature for 240 h. Evaporation of the solvent gave a crude mixture which was subjected to column chromatography on silica gel eluting with *n*-hexane/AcOEt (20:1) to give **10b** (291 mg, 89%); bp 128 °C/2 torr (oven temperature of

Kugelrohr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.7 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 4.08 (s, 3H), 4.04 (t, *J* = 6.9 Hz, 2H), 1.87-1.82 (m, 2H), 1.56-1.50 (m, 2H), 0.98 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.0 (q, J_{CF} = 38.3 Hz), 163.6, 159.6, 147.9, 131.9, 127.4, 124.5, 123.2, 120.0, 115.4 (q, J_{CF} = 292.0 Hz), 106.4, 75.9, 54.0, 32.0, 19.0, 13.7; IR (KBr) 1744, 1204, 1161 cm^{-1}. Anal. Calcd for $C_{16}H_{16}F_3NO_3$: C, 58.71; H, 4.93; N, 4.28. Found: C, 58.79; H, 4.95; N, 4.46.

10. (a) D. J. Krogstad, I. Y. Gluzman, D. E. Kyle, A. M. J. Oduola, S. K. Martin, W. K. Milhous, and P. H. Schlesinger, *Science*, 1987, **238**, 1283; (b) D. De, J. T. Mague, L. D. Byers, and D. J. Krogstad, *Tetrahedron Lett.*, 1995, **36**, 205; (c) J. K. Natarajan, J. N. Alumasa, K. Yearick, K. A. Ekoue-Kovi, L. B. Casabianca, A. C. de Dios, C. Wolf, and P. D. Roepe, *J. Med. Chem.*, 2008, **51**, 3466; (d) K. Kaur, M. Jain, R. P. Reddy, and R. Jain, *Eur. J. Med. Chem.*, 2010, **45**, 3245.
11. (a) H. Jiang, J. E. Taggart, X. Zhang, D. M. Benbrook, E. E. Lind, and W.-Q. Ding, *Cancer Lett.*, 2011, **312**, 11; (b) M. Yamato, K. Hashigaki, Y. Yasumoto, J. Sakai, S. Tsukagoshi, T. Tashiro, and T. Tsuruo, *Chem. Pharm. Bull.*, 1986, **34**, 3496; (c) V. Moret, Y. Laras, T. Cresteil, G. Aubert, D. Q. Ping, C. Di, M. Barthélémy-Requin, C. Béclin, V. Peyrot, D. Allegro, A. Rolland, F. de Angelis, E. Gatti, P. Pierre, L. Pasquini, E. Petrucci, U. Testa, and J.-L. Kraus, *Eur. J. Med. Chem.*, 2009, **44**, 558.
12. K. Kaur, M. Jain, S. I. Khan, M. R. Jacob, B. L. Tekwani, S. Singh, P. P. Singh, and R. Jain, *Med. Chem. Commun.*, 2011, **2**, 300.
13. J. Jampilek, M. Dolezal, J. Kunes, V. Buchta, and K. Kralova, *Med. Chem.*, 2005, **1**, 591.
14. (a) A. S. Dey and M. M. Joullié, *J. Heterocycl. Chem.*, 1965, **2**, 120; (b) E. B. Nyquist and M. M. Joullié, *J. Heterocycl. Chem.*, 1967, **4**, 539; (c) M. Loy and M. M. Joullié, *J. Med. Chem.*, 1973, **16**, 549; (d) R. Filler, 'Organofluorine Chemicals and Their Industrial Applications', Ellis Horwood, London, 1979; (e) R. Filler and Y. Kobayashi, 'Biomedicinal Aspects of Fluorine Chemistry', Kodansha & Elsevier Biomedical, Tokyo, 1982; (f) J. T. Welch, *Tetrahedron*, 1987, **43**, 3123; (g) R. Filler, Y. Kobayashi, and L. M. Yagupolskii, 'Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications', Elsevier, Amsterdam, 1993; (h) K. Burger, U. Wucherpfennig, and E. Brunner, *Adv. Heterocycl. Chem.*, 1994, **60**, 1.