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Synthesis and antiproliferative evaluation of 3,5-disubstituted 1,2,4-triazoles containing flurophenyl and trifluoromethanephenyl moieties

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ABSTRACT

An efficient 1,3-dipolar cycloaddition method was performed for the synthesis of a series of monofluoro- and trifluoromethane-3,5-disubstituted 1,2,4-triazoles. This efficient cycloaddition method was to react hydrazonoyl hydrochlorides with a series of aldehydes in the presence of NEt_3 as catalytic basic agent to provide the corresponding product in 28–94%. Their growth inhibitory results against cancer cells indicated that some of the fluorine- and trifluoromethane-containing compounds could effectively inhibit the growth of NCI-H226 and T-cell leukemia (Jurkat) cells. Among the compounds, trifluoromethane-containing 1,2,4-triazoles possessed the five-membered ring groups on the C-5 position of the triazolic ring, including cyclopentyl, 3-furyl, 3-thienyl, and 2-pyrrolyl, possessed the significant inhibitory activity for NCI-H226 cancer cells.

Triazoles are an important class of heterocyclic compounds which show various biological activities including antifungal,[1,2] antimicrobial,[3] antiviral,[4] anti-inflammatory,[5] anti-asthmatic,[6] anticonvulsant activities,[7] antiproliferative,[8] hypotonic activities,[9] antibacterial, antifungal, and antihelmintic activities.[10] Triazole-based agonists or antagonists targeting different receptors were described recently,[11,12] especially the 3,5-disubstituted 1,2,4-triazole scaffold.[13–17]

Fluorine-[18] and trifluoromethane-containing[19] compounds are well known to play an important role in wide fields, including biochemistry and agrochemistry. For example, replacement of hydrogen atoms by fluorines or trifluoromethane groups in pheromones has been shown to produce a variety of effects on the insect response, some of them are a priori unpredictable. As a result, we focused to synthesize a series of fluorine- or trifluoromethane-containing 3,5-disubstituted 1,2,4-triazoles derivatives in this work.

Nitrilimine cycloadditions to ethylenic or ethylynic dipolarophiles are of great interest due to their potential application for the synthesis of various bioactive 5-substituted-4,5-dihydrpyrazole heterocyclic derivatives.[20] Herein, we give an efficient cycloaddition for the conversion of a series of aldehydes to fluorine- or trifluoromethane-containing 3,5-disubstituted 1,2,4-triazoles using hydrazonoyl hydrochlorides and hydroxylamine hydrate in the presence of triethylamine as a catalyst. The reaction mechanism involved the 1,3-dipolar cycloaddition reaction. Furthermore, the cytotoxicities of these 3,5-disubstituted 1,2,4-triazole derivatives were explored for realizing the structure–activity relationship and identifying the structural fragments responsible for the biological activity.

Aldehydes **1**–**12** are the commercially available materials and hydrazonoyl chloride materials **13**–**22** were prepared following the reported procedure.[21] Scheme 1 shows the efficient 1,3-dipolar cycloaddition methodology using nitrilimine as an efficient 1,3-dipolar. The reliable model procedure involved the treatment of a toluene solution of aldehydes **1**–**12** with 1.0 equiv of hydroxylamine hydrochloride with excess amount of triethylamine at room temperature for 30 min. When the aldehydes were completely consumed and converted to the oxime intermediates,[22] hydrazonoyl chloride was then added to the reaction mixture and the solution was heated at reflux for 1–2 h. After aqueous work up and purified by column chromatography on silica gel, the corresponding cycloaddition products **23**–**48** were isolated in moderate to good yields (28–94%, see Table 1 and Chart 1).

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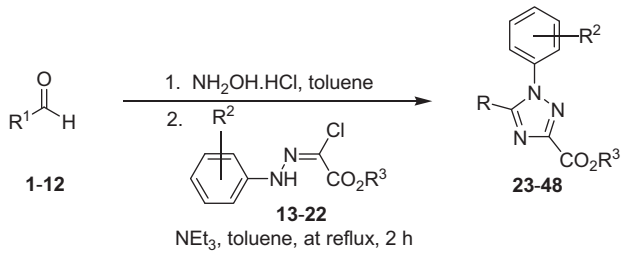


Scheme 1.

Acetaldehyde **1** was used as the model dipolarophile and allowed to react with various aromatic hydrazonoyl hydrochlorides **13**–**20** bearing various substituents including F, Cl, Br, CF_3, and OMe at the *ortho* or *meta* or *para* position to the nitrilimine group. The reaction gave the corresponding 3,5-disubstituted 1,2,4-triazoles **23**–**30** in good to excellent yields (82–91%, see the entries 1–8 in Table 1 and Chart 1). For realizing the effect of the dipolarophiles' property on the 1,3-dipolar cycloaddition, we applied the same reaction condition to *p*-fluorophenylchlorohydrazone **20** and various aliphatic, cyclic aliphatic, aryl, and heterocyclic aldehyde substrates **2**–**7** to prepare a series of fluorine-containing 3,5-disubstituted 1,2,4-triazoles. The desired fluorine-containing products **31**–**41** were obtained in 28–91% yields (see the entries 8–19 in Table 1 and Chart 1). The poor isolated yields were found for aromatic and heterocyclic aldehyde **8**–**12** as the reactants.

The synthetic strategy was also applicable to *p*-trifluoromethylphenylchlorohydrazone (**17**) as the 1,3-dipole reactant with cyclopentanecarbaldehyde (**6**), cyclohexanecarbaldehyde (**7**), furan-3-carbaldehyde (**8**), thiophene-3-carbaldehyde (**9**), and 1*H*-pyrrole-3-carbaldehyde (**10**) to prepare the trifluormethane-containing desired products (see Table 1). The corresponding 3,5-disubstituted 1,2,4-triazoles **42**–**46** were obtained in good yield (51–94%, see the entries 20–24 in Table 1 and Chart 1). For further investigation of the substituent effect, we extended the same reaction condition toward [(4-trifluoromethylphenyl)-hydrazono]-chloroacetic acid ethyl ester (**21**) and [(4-fluorophenyl)-hydrazono]-chloroacetic acid ethyl ester (**22**), having ethyl carboxylate group at the C-3 position of 1,2,4-triazole ring. The desired products **47** and **48** were produced in 66% and 86% yields, respectively. As a result, this efficient cycloaddition method can be successfully applied to the various aldehydes as a dipolarophile including aliphatic, aryl, and heterocyclic aldehydes and assorted hydrazonoyl hydrochloride compounds as the 1,3-dipole reactants.

The growth inhibitory activity of all methnimidamide compounds is evaluated against a panel of human cancer cell lines in vitro, including lung carcinoma (NCI-H226), nasopharyngeal (NPC-TW01), and T-cell leukemia (Jurkat) cells. The GI_{50} value indicates the concentration of the compound that results in a 50% decrease in the cell growth relative to the vehicle. The results are presented in Table 2 and indicated that trifluoro- and monofluoro-3,5-disubstituted 1,2,4-triazoles **23**–**48** compounds showed the better inhibitory potency against nasopharyngeal (NPC-TW01) and T-cell leukemia (Jurkat) cell.

Methyl 1-(4-fluorophenyl)-5-methyl-1*H*-1,2,4-triazole-3-carboxylate **30** was selected as the compared model for the inhibitory activity study. Their GI_{50} values are 11.7 μM (NCI-H226), 15.2 μM (NPC-TW01), and 8.70 μM (Jurkat), respectively. In comparison with compounds **23**–**29** containing various substituents, including H, *o*-CF_3, *m*-F, *m*-Cl, *p*-Cl, *p*-F, *p*-CF_3, and *p*-OMe, at *N*-1 of the phenyl ring, The results showed that only compound **24**, **26**, and **27** with *o*-, *m*-, and *p*-CF_3Ph substituents on *N*-1 position of triazole ring possessed the better inhibitory activity against NCI-H226 and Jurkat with GI_{50} values between 6.13 μM and 16.6 μM. However, methyl 5-methyl-1-aryl-1*H*-1,2,4-triazole-3-carboxylate **24**–**30** displayed reduced inhibitory activity for NPC-TW01 cell line, expect for compound **28**–**30** (see Table 2).

Table 1
Synthesis of 3,5-disubstituted 1,2,4-triazoles using aldehydes with hydrazonoyl hydrochlorides

Entry	Aldehydes		Hydrazones			1,2,4-Triazoles	Yield (%)
	No.	R^1	No.	R^2	R^3		
1	**1**	Methyl	**13**	H	Me	**23**	88
2	**1**	Methyl	**14**	*o*-CF_3	Me	**24**	87
3	**1**	Methyl	**15**	*m*-Br	Me	**25**	86
4	**1**	Methyl	**16**	*m*-CF_3	Me	**26**	85
5	**1**	Methyl	**17**	*p*-CF_3	Me	**27**	87
6	**1**	Methyl	**18**	*p*-OMe	Me	**28**	82
7	**1**	Methyl	**19**	*p*-Cl	Me	**29**	86
8	**1**	Methyl	**20**	*p*-F	Me	**30**	91
9	**2**	Ethyl	**20**	*p*-F	Me	**31**	91
10	**3**	*i*-Propyl	**20**	*p*-F	Me	**32**	90
11	**4**	*n*-Butyl	**20**	*p*-F	Me	**33**	89
12	**5**	Cyclopropyl	**20**	*p*-F	Me	**34**	91
13	**6**	Cyclopentyl	**20**	*p*-F	Me	**35**	88
14	**7**	Cyclohexyl	**20**	*p*-F	Me	**36**	86
15	**8**	3-Furyl	**20**	*p*-F	Me	**37**	62
16	**9**	3-Thienyl	**20**	*p*-F	Me	**38**	57
17	**10**	2-pyrrolyl	**20**	*p*-F	Me	**39**	41
18	**11**	Phenyl	**20**	*p*-F	Me	**40**	33
19	**12**	2-Naphthyl	**20**	*p*-F	Me	**41**	28
20	**6**	Cyclopentyl	**17**	*p*-CF_3	Me	**42**	94
21	**7**	Cyclohexyl	**17**	*p*-CF_3	Me	**43**	91
22	**8**	3-Furyl	**17**	*p*-CF_3	Me	**44**	64
23	**9**	3-Thienyl	**17**	*p*-CF_3	Me	**45**	62
24	**10**	2-Pyrrolyl	**17**	*p*-CF_3	Me	**46**	51
25	**10**	2-Pyrrolyl	**21**	*p*-CF_3	Et	**47**	66
26	**10**	2-Pyrrolyl	**22**	*p*-F	Et	**48**	86

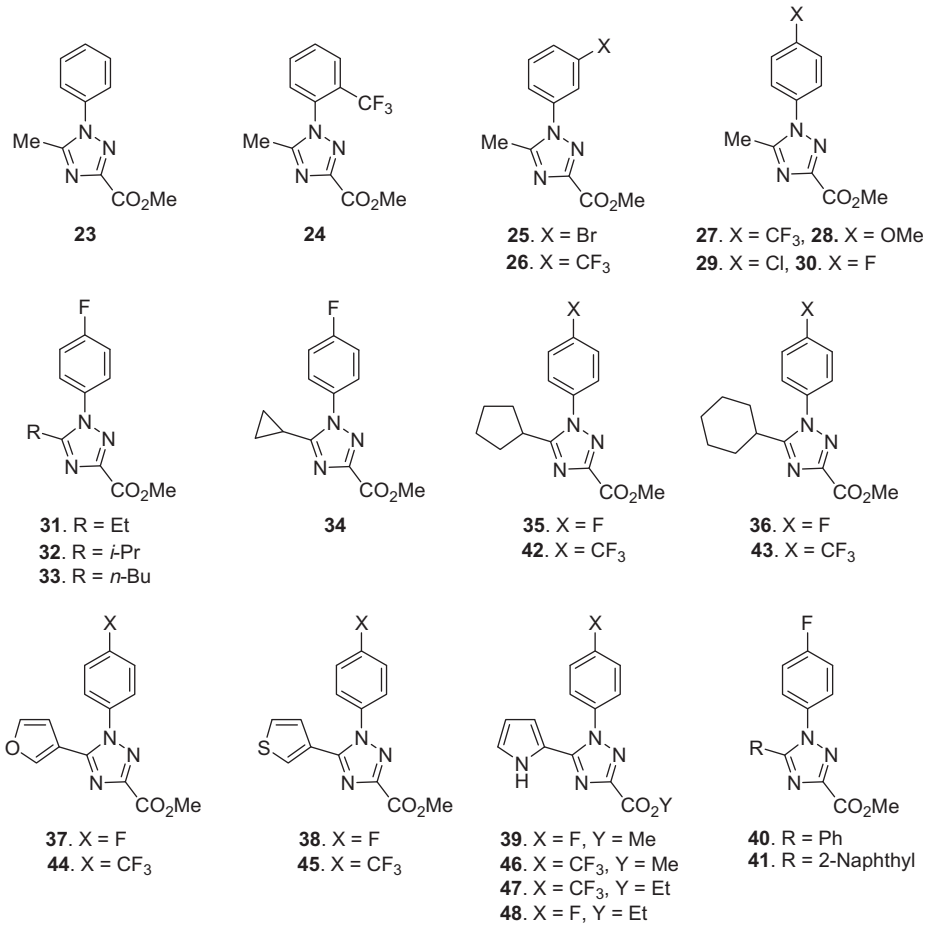


Chart 1.

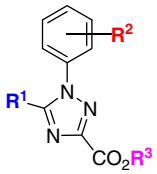
For the further structure–activity relationship study, we modified monofluorine-containing 1,2,4-triazole-3-carboxylate **30** to **31**–**41** with various substituents at C-5 position in 1,2,4-triazole ring, such as ethyl (**31**), *i*-propyl (**32**), *n*-butyl (**33**), cyclopropyl (**34**), cyclopentyl (**35**), cyclohexyl (**36**), 3-furyl (**37**), 3-thienyl (**38**), 2-pyrroyl (**39**), phenyl (**40**), and 2-naphthyl group (**41**). Their antiproliferative activities were presented in Table 2. Most of the modified monofluorine-containing 1,2,4-triazole-3-carboxylates **31**–**41** exhibited significant inhibition against T-cell leukemia cell (Jurkat, <11.0 μM, see Table 2), except for compound **32** (>100 μM), **33** (>100 μM), **36** (>100 μM), **38** (54.0 μM) and **41** (18.5 μM) with bulky groups including *i*-propyl, *t*-butyl, cyclohexyl, 3-thienyl or 2-naphthyl groups at C-5 position on the triazole ring. In addition, compounds **32**–**33**, **36**, and **38** also showed the better antiproliferative activity against NCI-H226 (<6.90 μM, see Table 2), which possess the flexible *i*-propyl, *n*-butyl and cyclohexyl alkyl groups and 3-thienyl at C-5 position on the triazole ring. Finally, monofluoro-containing 1,2,4-triazoles compounds **35** and **37**–**39** having the five-membered ring groups on the C-5 position of triazole ring, including cyclopentyl, 3-furyl, 3-thienyl, and 2-pyrrolyl, possessed the good inhibitory activity for NPC-TW01cell near between 9.58 and 11.7 μM (see Table 2).

Since fluorine-[18] and trifluoromethane-containing[19] compounds are well known to play an important role in wide fields, including biochemistry and agrochemistry, we prepared a series of trifluormethane-containing 1,2,4-triazole-3-carboxylates **42**–**46** possessing five- or six-membered ring at the C-5 position of the triazole ring for further structure–activity relationship study (see Table 2 and Chart 1). Most of the compounds **42**–**46** were more potent than monofluorine-containing 1,2,4-triazole compounds **31**–**41** against NCI-H226 cell line with GI_{50} values between 5.65 μM and 6.01 μM. However, trifluormethane-containing 1,2,4-triazole compounds **42**–**46** provided the less satisfactory antiproliferative activity results against NPC-TW01 (>97.2 μM) and T-cell leukemia cell (Jurkat, >34.9 μM, see Table 2).

On the other hand, compounds **47** and **48** with 2-pyrroyl group at C-5 position in pyrazole ring were modified from methyl carboxylate to ethyl carboxylate group at C-3 position of 1,2,4-triazole ring. We found the ethyl carboxylate group grafted at C-3 position in triazolic ring promoted the inhibitory activity against NCI-H226 cell line from 72.0 to 5.71 μM. Nevertheless, only little change in activity was observed between compound **46** (5.65 μM) and compound **47** (5.61 μM). As a result, monofluoro-containing 3,5-disubstituted 1,2,4-triazole compounds **32**–**33**, **36**, and **48** and trifluormethane-containing 3,5-disubstituted 1,2,4-triazole compounds **42**–**47** may be regarded as the potent leads against NCI-H226 in future investigation.

In conclusion, we have performed an efficient 1,3-dipolar cycloaddition method to prepare a series of monofluoro- and trifluoromethane-3,5-disubstituted 1,2,4-triazole compounds by using an efficient 1,3-dipolar cycloaddition from hydrazonoyl hydrochlorides with aldehydes and excess amount of NEt_3. Based on their growth inhibitory activity data on cancer cells, monofluoro- and trifluormethane-containing 1,2,4-triazole compounds were found to effectively inhibit the growth of NCI-H226 cancer cells. Moreover, monofluoro-containing 1,2,4-triazoles possessed phenyl and

Table 2
The inhibitory activity of the 3,5-disubstituted 1,2,4-triazoles derivatives in NCI-H226, NPC-TW01, and Jurkat



Compounds	1,2,4-Triazoles (**23**–**48**)			GI_{50}[a,b] (μM)		
	R^1 (C-5)	R^2 (*N*-1)	R^3 (C-3)	NCI-H226	NPC-TW01	Jurkat
Reference	Methotrexate			10.25	0.10	1.25
23	Me	H	Me	>100	>100	>100
24	Me	*o*-CF_3	Me	6.13	>100	>100
25	Me	*m*-Br	Me	7.35	>100	>100
26	Me	*m*-CF_3	Me	14.3	>100	10.6
27	Me	*p*-CF_3	Me	16.6	>100	9.10
28	Me	*p*-OMe	Me	>100	9.92	>100
29	Me	*p*-Cl	Me	84.0	17.5	65.9
30	Me	*p*-F	Me	11.7	15.2	8.70
31	Et	*p*-F	Me	71.3	15.8	11.0
32	*i*-Pr	*p*-F	Me	6.17	>100	>100
33	*n*-Bu	*p*-F	Me	6.40	>100	>100
34	Cyclopropyl	*p*-F	Me	16.3	95.9	9.42
35	Cyclopentyl	*p*-F	Me	70.5	10.4	9.55
36	Cyclohexyl	*p*-F	Me	6.26	30.5	>100
37	3-Furyl	*p*-F	Me	91.6	11.7	9.32
38	3-Thienyl	*p*-F	Me	6.94	10.7	54.0
39	2-Pyrrolyl	*p*-F	Me	72.0	9.58	9.01
40	Phenyl	*p*-F	Me	89.3	15.6	10.0
41	2-Naphthyl	*p*-F	Me	79.3	>100	18.5
42	Cyclopentyl	*p*-CF_3	Me	5.71	56.4	>100
43	Cyclohexyl	*p*-CF_3	Me	5.76	>100	>100
44	3-Furyl	*p*-CF_3	Me	6.01	>100	97.2
45	3-Thienyl	*p*-CF_3	Me	5.74	34.9	>100
46	2-Pyrrolyl	*p*-CF_3	Me	5.65	>100	>100
47	2-Pyrroryl	*p*-CF_3	Et	5.61	76.4	>100
48	2-Pyrroryl	*p*-F	Et	5.71	64.3	>100

[a] NCI-H226: human lung carcinoma; NPC-TW01: human nasopharyngeal carcinoma; Jurkat: human T-cell leukemia.
[b] All tested compounds were dissolved in 100% DMSO at a concentration of 20 mM as the stock solution. Cells were cultured without or in the presence of the methnimidamide derivatives at different concentrations for 72 h. Cell survival was determined by MTT assay. Drug molar concentration causing 50% cell growth inhibition (GI_{50}) was calculated. Each value represents the mean ± SD of three independent experiments.

the five-membered ring groups at the C-5 position of the triazolic ring, incuding cyclohyl, 3-furyl, 2-pyrrolyl, and 3-thienyl, possessed the significant inhibitory activity for NPC-TW01.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.07.009.

Reference and notes

1. (a) Collin, X.; Sauleau, A.; Coulon, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2601; (b) Jalilian, A. R.; Sattari, S.; Bineshmarvasti, M.; Shafiee, A.; Daneshtalab, M. *Arch. Pharm. Pharm. Med. Chem.* **2000**, *333*, 347.
2. Lebouvier, N.; Giraud, F.; Corbin, T.; Na, Y. M.; Le Baut, G.; Marchand, P.; Le Borgne, M. *Tetrahedron Lett.* **2006**, *47*, 6479.
3. (a) Papakonstantinou-Garoufalias, S.; Pouli, N.; Marakos, P.; Chytyroglou-Ladas, A. *Farmaco* **2002**, *57*, 973; (b) Shafiee, A.; Sayadi, A.; Roozbahani, M. H.; Foroumadi, A.; Kamal, F. *Arch. Pharm. Pharm. Med. Chem.* **2002**, *10*, 495.
4. De Clercq, E. *J. Clin. Virol.* **2004**, *30*, 115.
5. Navidpour, L.; Shadnia, H.; Shafaroodi, H.; Amini, M.; Dehpour, A. R.; Shafiee, A. *Bioorg. Med. Chem.* **2007**, *15*, 1976.
6. Naito, Y.; Akahoshi, F.; Takeda, S.; Okada, T.; Kajii, M.; Nishimura, H.; Sugiura, M.; Fukaya, C.; Kagitani, Y. *J. Med. Chem.* **1996**, *39*, 3019.
7. (a) Almasirad, A.; Vousooghi, N.; Tabatabai, S. A.; Kebriaeezadeh, A.; Shafiee, A. *Acta Chim. Slov.* **2007**, *54*, 317; (b) Almasirad, A.; Tabatabai, S. A.; Faizi, M.; Kebriaeezadeh, A.; Mehrabi, N.; Dalvandi, A.; Shafiee, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6057.
8. (a) Saha, A. K.; Liu, L.; Simoneaux, R.; DeCorte, B.; Meyer, C.; Skrzat, S.; Breslin, H. J.; Kukla, M. J.; End, D. W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5407; (b) Ouyang, X. H.; Chen, X. L.; Piatnitski, E. L.; Kiselyov, A. S.; He, H. Y.; Mao, Y. Y.; Pattaropong, V.; Yu, Y.; Kim, K. H.; Kincaid, J.; Smith, L.; Wong, W. C.; Lee, S. P.; Milligan, D. L.; Malikzay, A.; Fleming, J.; Gerlak, J.; Deevi, D.; Doody, J. F.; Chiang, H. H.; Patel, S. N.; Wang, Y.; Rolser, R. L.; Kussie, P.; Labelle, M.; Tuma, M. C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5154.
9. Hester, J. B., Jr.; Rudzik, A. D.; Kamdar, B. V. *J. Med. Chem.* **1971**, *14*, 1078.
10. (a) Hardman, J.; Limbird, L.; Gilman, A. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9th ed.; McGraw-Hill: New York, 1996; p 988; (b) Gennaro, A. R.; Remington In *The Science and Practice of Pharmacy*; Mack Easton: PA, 1995; Vol. II, p 1327; (c) Richardson, K.; Whittle, P. *J. Eur. Pat. Appl. EP* **1984**, *115*, 416; Richardson, K.; Whittle, P. J. *Chem. Abstr.* **1984**, *101*, 230544p; (d) Ammermann, E.; Loecher, F.; Lorenz, G.; Janseen, B.; Karbach, S.; Meyer, N. *Brighton Crop Prot. Conf. Pest. Dis.* **1990**, *2*, 407; Ammermann, E.; Loecher, F.; Lorenz, G.; Janseen, B.; Karbach, S.; Meyer, N. *Chem. Abstr.* **1991**, *114*, 223404h; (e) Heindel, N. D.; Reid, J. R. *J. Heterocycl. Chem.* **1980**, *17*, 1087.
11. Contour-Galcera, M. O.; Sidhu, A.; Plas, P.; Roubert, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3555.
12. Jagerovic, N.; Hemandez-Folgado, L.; Alkorta, I.; Goya, P.; Martin, M. I.; Dannert, M. T.; Alsasua, A.; Frigola, J.; Cuberes, M. R.; Dordal, A.; Holenz, J. *Eur. J. Med. Chem.* **2006**, *41*, 114.
13. Alanine, A.; Anselm, L.; Steward, L.; Thomi, S.; Vifian, W.; Groaning, M. D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 817.

14. Dumaître, B.; Dodic, N. *J. Med. Chem.* **1996**, *39*, 1635.
15. Yeung, K.-S.; Farkas, M. E.; Kadow, J. F.; Meanwell, N. A. *Tetrahedron Lett.* **2005**, *46*, 3429.
16. Liu, C.; Iwanowicz, J. *Tetrahedron Lett.* **2003**, *44*, 1409.
17. Abdel-Megeed, A. M.; Abdel-Rahman, H. M.; Alkaramany, G.-E. S.; El-Gendy, M. A. *Eur. J. Med. Chem.* **2009**, *44*, 117.
18. (a) Filler, R. *Chem. Tech.* **1974**, 752; (b) Schlosser, M. F. *Tetrahedron* **1978**, *34*, 3; (c) Patrick, T. B. *J. Chem. Educ.* **1979**, *56*, 228; (d) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123; (e) Liebman, J. F., Greenberg, A., Dolbier, W. R., Eds. Fluorine-containing Molecules. Structure, Reactivity, Synthesis and Applications; VCM Publishers Inc., 1988; (f)*Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991; (g) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991; (h) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Biomedical Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, 1993; (i) Resnati, G. *Tetrahedron* **1993**, *49*, 9385; (j) *Fluoroorganic Chemistry: Synthetic Challenges and Biomedical Rewards*; Resnati, G.; Soloshonok, V. A., Eds.; Tetrahedron Symposium-in-Print no. 58. *Tetrahedron* **1996**, *52*, 1.; (k) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619.
19. (a) Hodge, C. N.; Aldrich, P. E.; Ferna'ndez, C. H.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Erickson-Viitanen, S. *Antiviral Chem. Chemother.* **1994**, *5*, 257; (b) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Smith, S. A.; Petrillo, E. D. *J. Med. Chem.* **1993**, *36*, 2431; (c) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813.
20. (a) Giorgio Molteni, G.; Alessandro Pontib, A.; Orlandi, M. *New J. Chem.* **2002**, *26*, 1346; (b) Ponti, A.; Giorgio Molteni, G. *New J. Chem.* **2002**, *26*, 1340; (c) Caramella, P.; Grünanger, P. In Padwa, A., Ed.; 1,3-Dipolar Cycloaddition Chemistry; Wiley Interscience: New York, USA, 1984; Vol. 1, (d) Broggini, G.; Molteni, G.; Zecchi, G. *Heterocycles* **1998**, *47*, 541; (e) Dalloul, H. M.; Boyle, P. H. *Heterocycl. Commun.* **2007**, *13*, 155.
21. (a) Pfefferkorn, J. A.; Choi, C.; Larsen, S. D.; Auerbach, B.; Hutchings, R.; Park, W.; Askew, V.; Dillon, L.; Hanselman, J. C.; Lin, Z.; Lu, G. H.; Robertson, A.; Sekerke, C.; Harris, c. M. S.; Pavlovsky, A.; Bainbridge, G.; Caspers, N.; Kowala, M.; Tait, B. D. *J. Med. Chem.* **2008**, *51*, 31; (b) Silvestri, R.; Cascio, M. G.; Regina, G. L.; Piscitelli, F.; Lavecchia, A.; Brizzi, A.; Pasquini, S.; Botta, M.; Novellino, E.; Marzo, V. D.; Corelli, F. *J. Med. Chem.* **2008**, *51*, 1560; (c) Pinto, D. J. P.; Orwat, M. J.; Koch, S.; Rossi, K. A.; Alexander, R. S.; Smallwood, A.; Wong, P. C.; Rendina, A. R.; Luettgen, J. M.; Knabb, R. M.; He, K.; Xin, B.; Wexler, R. R.; Lam, P. Y. S. *J. Med. Chem.* **2007**, *50*, 5339.
22. (a) Grigorjeva, A.; Jirgensons, A.; Domracheva, I.; Yashchenko, E.; Shestakova, I.; Andrianov, V.; Kalvinsh, I. *Chem. Heterocycl. Compd.* **2009**, *45*, 161; (b) Ramón, R. S.; Bosson, J.; Díez-González, S.; Marion, N.; Nolan, S. P. *J. Org. Chem.* **2010**, *75*, 1197.