An Efficient One-Pot Access to Quinazolinone Derivatives Using TiO_2 Nanoparticles as Catalyst: Synthesis and Vasorelaxant Activity Evaluation

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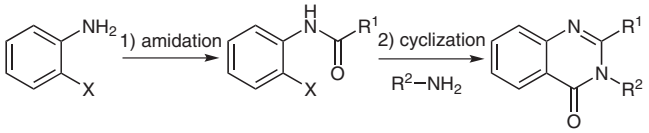
Abstract: A variety of quinazolinone derivatives were successfully synthesized, via a three-component condensation reaction between anthranilic acid, acetic anhydride, and amines. This process was accomplished in the presence of catalytic amount of titanium dioxide nanoparticles (nano-TiO_2), under solvent-free conditions. The synthesized compounds were evaluated for their vasorelaxant activity as they revealed a range of activities on the isolated thoracic rat aorta.

Key words: quinazolinone, multicomponent reaction, TiO_2 nanoparticles, heterogeneous catalyst, vasorelaxant activity

Quinazolinone and quinazoline derivatives are an important source of many natural alkaloids such as luotonin A,[1] tryptanthrin,[2] febrifugine,[3] rutaecarpine,[4] anisotine, and vasicinone.[5] They also have been shown versatile biological activities in medicinal chemistry, including tyrosine kinase inhibitory, antiviral effect, anticancer activity, and antitubercular propertise.[6–10] Additionally, quinazolines have the same basic structure as prazosin,[11] terazosin,[12] and doxazosin,[13] which are used as antihypertensive drugs extensively. There are several methods for the preparation of quinazolinones in the literature with a various range of structural diversities.[14–16] In the most commonly reported methods, quinazolinone derivatives have been produced in a two-step process, initially amidation of anthranilonitrile, anthranilic acid, or anthranilamide and then followed by the cyclization of the resulting intermediate (Scheme 1).



Scheme 1 Two-step process for the synthesis of quinazolinone derivatives

Furthermore, different strategies have been developed for the synthesis of quinazolinone scaffold as the reaction of nitriles with lithiated anthranilamides,[17] thermolysis of 3-arylideneamino-1,2,3-benzotriazin-4-ones,[18] direct condensation of aldehydes and anthranilamide in the presence of $CuCl_2$,[19] and metal-catalyzed synthesis of quinazolinediones.[20] Among many utilized strategies, one of the considerable synthetic tools are the multicomponent approaches, because the complex products are formed in a single step and diversity can be achieved simply by varying the reaction components.[21] The multicomponent reactions (MCR) are considered in medicinal chemistry due to the fact that the functionally substituted starting materials are used to obtain the desired biologically active compounds.[22] There are few methods in the literature for the synthesis of quinazolinone derivatives using multicomponent approaches. However, it is noteworthy that, in each of this methods, different substrates and conditions were used and consequently different category of quinazolinones have been synthesized.[23,24]

In the current study, in continuing of our previous works on the synthesis of biologically active compounds,[25] we would like to report an efficient multicomponent sequence for the one-pot synthesis of 3-substituted 2-methylquinazoline-4(3*H*)-ones using titanium dioxide nanoparticles (nano-TiO_2) as a catalyst. Nano-TiO_2 has been widely used as catalyst support in synthetic chemistry.[26] Also, there are several reactions which are catalyzed by nano-TiO_2 as catalyst due to its unique surface properties.[27] High activity, reusability, strong oxidizing power, easy availability, nontoxicity, and long-term stability are other advantages of nano-TiO_2 as a recyclable catalyst.[28]

Thus, three-component coupling reaction between anthranilic acid (**1**), acetic anhydride (**2**), and aniline (**3a**) as a model reaction was examined under different conditions, and the results are summarized in Table 1.

First, titanium chloride ($TiCl_4$) was used as catalyst to promote this reaction, and no product was detected even after 24 hours (Table 1, entry 1). The reaction was also checked in the presence of titanium isopropoxide [Ti(O*i*-Pr)$_4$][29] as catalyst, but no reactivity differences were observed (Table 1, entry 2). Also, in the presence of titanium dioxide (TiO_2, bulk) as catalyst no reaction performed (Table 1, entries 3 and 4). When nano-TiO_2 was used as catalyst for this reaction, compound **4a** was obtained with 32% isolated yield (Table 1, entry 5). By varying the type of solvent the yield of the desired product did not change significantly (Table 1, entries 6, 8, and 9). In water, no product has been observed, probably because the bezoxazine intermediate was destroyed in the vicinity of water

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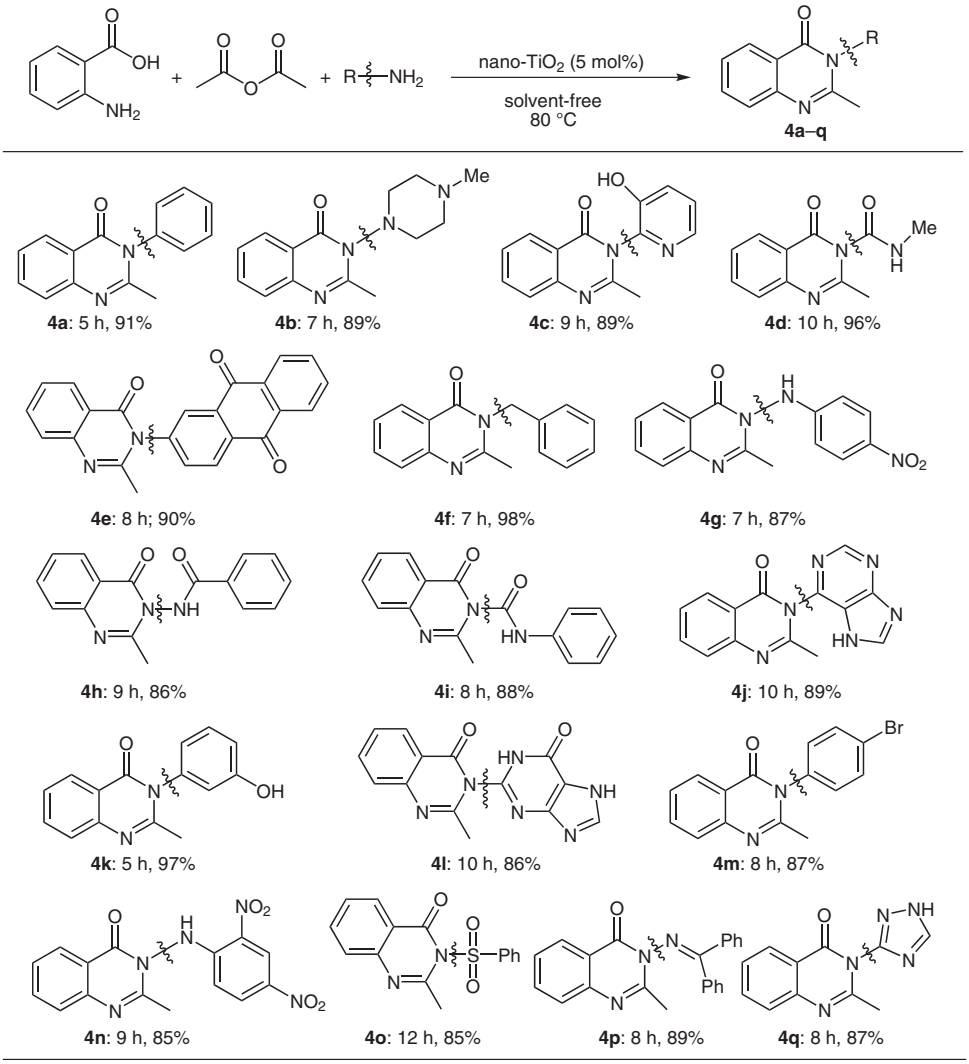
molecules (Table 1, entry 7).[30] Interestingly, under solvent-less conditions and at 80 °C the yield of product was increased to 91% (Table 1, entry 11). Then, the catalyst quantity was also optimized, and 5.0 mol% of catalyst was selected as optimum amount (Table 1, entries 14–16). Thus, the simple system, nano-TiO_2 (5.0 mol%), solvent-free conditions, and 80 °C as reaction temperature, was chosen as the optimized reaction conditions.

To determine the scope of this protocol, various quinazoline-4(3*H*)-one derivatives were synthesized under the normalized conditions, and the results are summarized in Scheme 2.

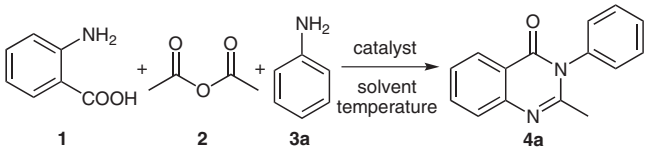
The wide scope capability of this protocol was highlighted by the application of both amines with electron-withdrawing and electron-donating groups under the same reaction conditions. Also, the functional-group compatibility of this reaction was highlighted using amine components, which are attached to other functional groups (Scheme 2, compounds **4b**,**d**,**h**,**i**,**o**). The structural diversity of this reaction was further increased using adenine[31] and guanine[32] as amine component, leading to the formation of new nucleobase derivatives with quinazoline moiety (Scheme 2, compounds **4j**,**l**). According to Scheme 2, in all cases the reactions were accomplished in relatively short reaction time, and the products were obtained with good to excellent yields (more than 85%). In general, the one-pot synthesis of quinazoline-4(3*H*)-ones using nano-TiO_2 as catalyst has some advantages including: i) the reaction was carried out under solvent-free conditions; ii) the reaction was accomplished in a single-step process, and diversity can be achieved by varying the amine component; iii) this protocol avoids the use of corrosive and toxic reagents such as $TiCl_4$; iv) a catalytic amount of nano-TiO_2 was used. The mechanism shown in Scheme 3 is proposed for the three-component condensation reaction between anthranilic acid, acetic anhydride, and amine in the presence of nano-TiO_2.

The possibility of recycling the nano-TiO_2 catalyst for this reaction was tested using the reaction of anthranilic acid and acetic anhydride with aniline under optimized condi-



Scheme 2 Products of three-component condensation reaction between anthranilic acid, Ac_2O, and primary amines in the presence of nano-TiO_2 as catalyst under solvent-free conditions. *Reagents and conditions*: anthranilic acid (1 mmol), Ac_2O (1.5 mmol), amine (1 mmol), catalyst (0.04 g, 5 mol%), 80 °C. All yields are isolated yields.

Table 1 Study of Different Conditions for One-Pot Synthesis of 3-Substituted 2-Methyl Quinazoline-4(3*H*)-one Derivatives[a]



1 2 3a 4a

Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	$TiCl_4$ (10)	$CHCl_3$	reflux	24	n.r.
2	$Ti(Oi\text{-}Pr)_4$ (10)	EtOH	reflux	24	n.r.
3	TiO_2 (10)	EtOH	reflux	24	n.r.
4	TiO_2 (20)	none	100	24	n.r.
5	nano-TiO_2 (5)	EtOH	reflux	24	32
6	nano-TiO_2 (5)	$CHCl_3$	reflux	24	41
7	nano-TiO_2 (5)	H_2O	reflux	24	n.r.
8	nano-TiO_2 (5)	MeCN	reflux	24	53
9	nano-TiO_2 (5)	DMF	100	24	55
10	nano-TiO_2 (5)	none	r.t.	24	48
11	nano-TiO_2 (5)	none	80	5 24	91 92
12	nano-TiO_2 (5)	none	100	5	91
13	nano-TiO_2 (5)	none	120	5	84
14	nano-TiO_2 (3)	none	80	5	81
15	nano-TiO_2 (2)	none	80	5	77
16	nano-TiO_2 (7)	none	80	5	92

[a] Reaction conditions: aniline (1 mmol), anthranilic acid (1 mmol), Ac_2O (1.5 mmol), solvent (5 mL), catalyst.
[b] Isolated yield.

Table 2 Comparison between Four of the Best Vasorelaxant-Active Synthesized Quinazolinones and Acetylcholine Chloride on Isolated Thoracic Rat Aorta

Entry	Compounds	IC_{50} (M)	E_{max}
1	Ach	–7.13 ± 0.14	85.31 ± 5.3
2	**4a**	–6.00 ± 0.55	91.1 ± 5.5
3	**4g**	–7.31 ± 0.94	86.4 ± 4.0
4	**4n**	–7.15 ± 0.81	86.1 ± 8.9
5	**4p**	–7.77 ± 0.31	90.7 ± 3.9

[a] Calculated as logarithm of the concentration.

tions. The recycled catalyst could be reused at least for four times without any treatment.[33] After characterization of new synthesized quinazolinones, their vasorelaxant activity were studied directly on isolated thoracic aorta of rats.[33] According to the results, which are presented in Table 2, IC_{50} (concentration necessary for 50% reduction

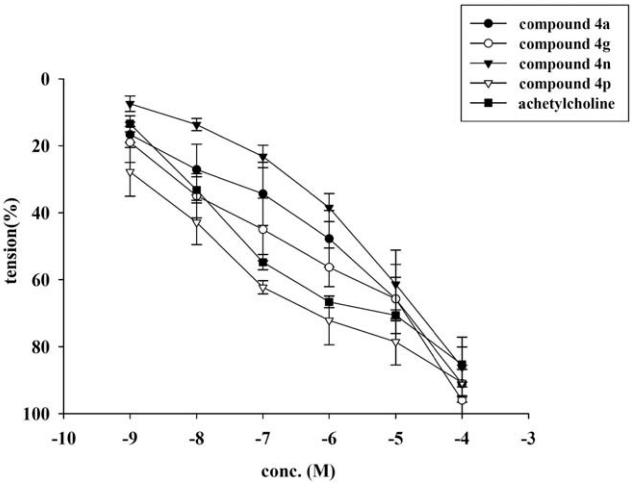


Figure 1 The comparison between four of the best vasorelaxant-active synthesized quinazolinones and acetylcholine

of maximal phenylephrine-induced contracture) of compounds **4a**,**g**,**n**,**p** were comparable with acetylcholine[34] (Ach, as a reference standard for vasodilating activity), but the IC_{50} value of other compounds were significantly lower compared to Ach IC_{50}. Interestingly, these results show that efficacy or maximal responses (E_{max}) of these compounds are comparable with Ach.

These results suggest that in spite of the shift to the right translocation of the dose-response curve of new quinazolinone compounds compared to Ach ones, the relaxation efficacy is as high as for Ach (Figure 1).

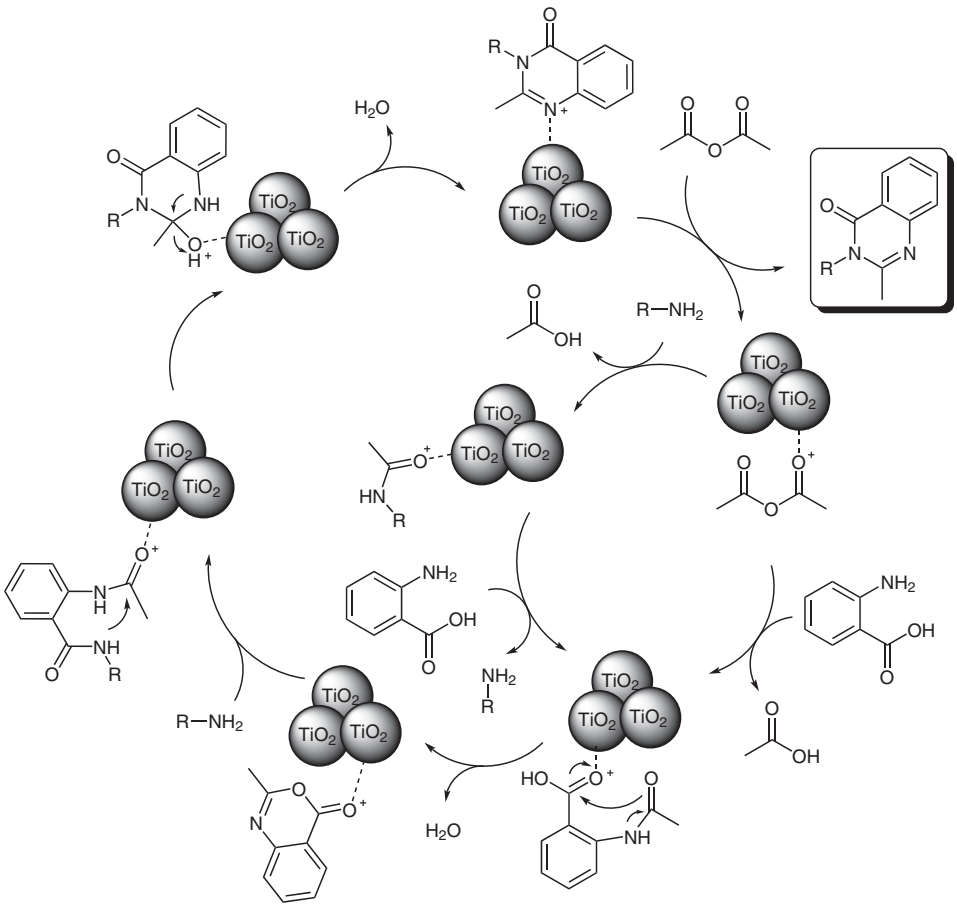
In conclusion, some new 3-substituted 2-methylquinazoline-4(3*H*)-ones were synthesized in a one-step process using TiO_2 nanoparticles as catalyst under mild conditions. TiO_2 nanoparticles efficiently promoted the one-pot, three-component condensation reaction between anthranilic acid, acetic anhydride, and amine derivatives in solvent-free conditions. The target products **4a**–**q** were obtained in excellent isolated yields with a green procedure. The vasorelaxant activity of the synthesized quinazolinones was evaluated on isolated thoracic aorta of rats. The results show that the IC_{50} of compounds **4a**,**g**,**n**,**p** are comparable with acetylcholine in vasorelaxant activity.

General Procedure for the Synthesis of 3-Substituted 2-Methylquinazoline-4(3*H*)-one Derivatives

Into a canonical flask (25 mL) a mixture of anthranilic acid (1 mmol), Ac_2O (1.5 mmol), amine (1 mmol), and nano-TiO_2 (0.04 g, 5 mol%) were stirred at 80 °C for an appropriate time which is specified in Scheme 2. After completion of the reaction, as indicated by TLC and GC, the reaction mixture was washed with CH_2Cl_2 (3 × 10 mL) and catalyst separated by simple filtration. Pure product was obtained by its recrystallization in CH_2Cl_2–*n*-hexane solvent system.[33]

2-Methyl-3-(4-methylpiperazin-1-yl)quinazolin-4(3*H*)-one (4b)

Yield 89%; yellow solid; mp 80 °C. IR (KBr): ν = 3100 (s), 3001 (w), 2931 (s), 1674 (s), 1589 (s), 1458 (m), 779 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS): δ = 1.98 (s, 3 H), 2.53 (s, 3 H), 2.76–



Scheme 3 Proposed mechanism for the three-component condensation reaction between anthranilic acid, Ac_2O, and amine in the presence of nano-TiO_2

2.81 (m, 8 H), 7.30 (t, *J* = 1.0 Hz, 1 H), 7.51 (dd, *J* = 7.5 Hz, 1 H), 7.6 (dd, *J* = 7.5, 2.5 Hz, 1 H), 8.09 (d, *J* = 1.0 Hz, 1 H). ^{13}C NMR (62.9 MHz, DMSO-d_6/TMS): δ = 22.6, 45.1, 49.6, 54.9, 120.9, 122.4, 126.2, 126.3, 134.3, 146.6, 157.6, 161.8. MS: *m/z* (%) = 258 [M^+], 236 (7.4), 201 (4.6), 185 (3.1), 166 (4.8), 137 (7.2), 99 (18.4), 83 (55.7), 57 (base peak, 100). Anal. Calcd for $C_{14}H_{18}N_4O$ (258.32): C, 65.09; H, 7.02; N, 21.69. Found: C, 65.01; H, 6.94; N, 21.61.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References

(1) Zhou, H.-B.; Liu, G.-S.; Yao, Z.-J. *J. Org. Chem.* **2007**, *72*, 6270.
(2) Bandekar, P. P.; Roopnarine, K. A.; Parekh, V. J.; Mitchell, T. R.; Novak, M. J.; Sinden, R. R. *J. Med. Chem.* **2010**, *53*, 3558.
(3) McLaughlin, N. P.; Evans, P. *J. Org. Chem.* **2010**, *75*, 518.
(4) Bergman, J.; Bergman, S. *J. Org. Chem.* **1985**, *50*, 1246.
(5) (a) Kamal, A.; Ramana, K. V.; Rao, M. V. *J. Org. Chem.* **2001**, *66*, 997. (b) Coskun, N.; Etin, M. C. *Tetrahedron Lett.* **2004**, *45*, 8973.
(6) (a) Melvin, J. Y.; Thrasher, J.; McCowan, J. R.; Mason, N. R.; Mendelsohn, L. G. *J. Med. Chem.* **1991**, *34*, 1505. (b) Parmar, S. S.; Kumar, R. *J. Med. Chem.* **1968**, *11*, 635. (c) Bonola, G.; Re, P. D.; Magistretti, M. J.; Massarani, E.; Setnikar, I. *J. Med. Chem.* **1968**, *11*, 1136.
(7) (a) Peet, N. P.; Baugh, L. E.; Sunder, S.; Lewis, J. E.; Matthews, E. H.; Olberding, E. L.; Shah, D. N. *J. Med. Chem.* **1986**, *29*, 2403. (b) Chen, K.; Aowad, A. F.; Adelstein, S. J.; Amin, I.; Kassis, A. I. *J. Med. Chem.* **2007**, *50*, 663.
(8) (a) Tani, J.; Yamada, Y.; Oine, T.; Ochiai, T.; Ishida, R.; Inoue, I. *J. Med. Chem.* **1979**, *22*, 95. (b) Nagase, T.; Mizutani, T.; Sekino, E.; Ishikawa, S.; Ito, S.; Mitobe, Y.; Miyamoto, Y.; Yoshimoto, R.; Tanaka, T.; Ishihara, A.; Takenaga, N.; Tokita, S.; Sato, S. *J. Med. Chem.* **2008**, *51*, 6889. (c) Henderson, E. A.; Bavetsias, V.; Theti, D. S.; Wilson, S. C.; Clauss, R.; Jackman, A. L. *Bioorg. Med. Chem.* **2006**, *14*, 5020.
(9) (a) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Zanatta, N.; Bonacorso, H. G. *Chem. Rev.* **2008**, *108*, 2015. (b) Kim, S. H.; Kim, S. H.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2010**, *51*, 2774. (c) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev.* **2009**, *109*, 4140.
(10) (a) Gopalsamy, A.; Yang, H. *J. Comb. Chem.* **2000**, *2*, 378. (b) Liu, J. F.; Kaselj, M.; Isome, Y.; Ye, P.; Sargent, K.; Sprague, K.; Cherrak, D.; Wilson, C. J.; Si, Y.; Yohannes, D.; Ng, S. C. *J. Comb. Chem.* **2006**, *8*, 7. (c) Hsu, N. M.; Li, C. Y.; Yang, C. M.; Lin, T. S.; Hu, B. H.; Tingare, Y. S.; Chang, W. C.; Srivastava, G. K.; Li, W. R. *J. Comb. Chem.* **2009**, *11*, 943.

(11) Andrus, M. B.; Mettath, S. N.; Song, C. *J. Org. Chem.* **2002**, *67*, 8284.
(12) Chou, W. C.; Tan, C. W.; Chen, S. F.; Ku, H. *J. Org. Chem.* **1998**, *63*, 10015.
(13) Giardin, D.; Martarelli, D.; Sagratini, G.; Angeli, P.; Ballinari, D.; Gulini, U.; Melchiorre, C.; Poggesi, E.; Pompei, P. *J. Med. Chem.* **2009**, *52*, 4951.
(14) (a) Gopalsamy, A.; Yang, H. *J. Comb. Chem.* **2000**, *2*, 378. (b) Yang, D.; Fu, H.; Hu, L.; Jiang, Y.; Zhao, Y. *J. Comb. Chem.* **2009**, *11*, 653.
(15) (a) Larksarp, C.; Alper, H. *J. Org. Chem.* **2000**, *65*, 2773. (b) Kabri, Y.; Gellis, A.; Vanelle, V. *Green Chem.* **2009**, *11*, 201. (c) Chilin, A.; Marzaro, G.; Zanatta, S.; Guiotto, A. *Tetrahedron Lett.* **2007**, *48*, 3229. (d) Adib, M.; Ansari, S.; Mohammadi, A.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2010**, *51*, 30.
(16) Xue, S.; McKenna, J.; Shieh, W. C.; Repi, O. *J. Org. Chem.* **2004**, *69*, 6474.
(17) Couture, A.; Cornet, H.; Grandclaudon, P. *Synthesis* **1991**, 1009.
(18) Paterson, T. M. C.; Smalley, R. K.; Suschitzky, H. *Synthesis* **1975**, 187.
(19) Li, G.; Kakarla, R.; Gerritz, S. W.; Pendri, A.; Ma, B. *Tetrahedron Lett.* **2009**, *50*, 6048.
(20) (a) Zhang, X.; Ye, D.; Sun, H.; Guo, D.; Wang, J.; Huang, H.; Zhang, X.; Jianga, H.; Liu, H. *Green Chem.* **2009**, *11*, 1881. (b) Huang, C.; Fu, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem. Commun.* **2008**, 6333. (c) Huang, X.; Yang, H.; Fu, H.; Qiao, R.; Zhao, Y. *Synthesis* **2009**, 2679.
(21) Khalafi-Nezhad, A.; Panahi, F. *Synthesis* **2011**, 984.
(22) (a) Mehta, V. P.; Modha, S. G.; Ruijter, E.; Hecke, K. V.; Meervelt, L. V.; Pannecouque, C.; Balzarini, J.; Orru, R. V. A.; Eycken, E. V. *J. Org. Chem.* **2011**, *76*, 2828. (b) Weber, L. *Curr. Med. Chem.* **2002**, *9*, 2085.
(23) (a) Dabiri, M.; Salehi, P.; Khajavi, M. S.; Mohammadi, A. A. *Heterocycles* **2004**, *63*, 1417. (b) Dandia, A.; Singh, R.; Sarawgi, P. *J. Fluorine Chem.* **2005**, *126*, 307. (c) Khosropour, A. R.; Mohammadpoor-Baltork, I.; Ghorbankhani, H. *Tetrahedron Lett.* **2006**, *47*, 3561.
(24) Mossetti, R.; Pirali, T.; Saggiorato, D.; Tron, G. C. *Chem. Commun.* **2011**, *47*, 6966.
(25) (a) Khalafi-Nezhad, A.; Soltani Rad, M. N.; Mohabatkar, H.; Asrari, Z.; Hemmateenejad, B. *Bioorg. Med. Chem.* **2005**, *13*, 1931. (b) Khalafi-Nezhad, A.; Zarea, A.; Soltani Rad, M. N.; Mokhtari, B.; Parhami, A. *Synthesis* **2005**, 419. (c) Khalafi-Nezhad, A.; Soltani Rad, M. N.; Hakimelahi, G. H. *Helv. Chem. Acta* **2003**, *86*, 2396. (d) Oryan, A.; Khalafi-Nezhad, A.; Toloo, N.; Soltani Rad, M. N. *J. Vet. Med. A.* **2007**, *54*, 585.
(26) (a) Hubert, C.; Denicourt-Nowicki, A.; Beaunier, P.; Roucoux, A. *Green Chem.* **2010**, *12*, 1167. (b) Hosseini-Sarvari, M.; Sodagar, E.; Doroodmand, M. M. *J. Org. Chem.* **2011**, *76*, 2853. (c) Seh, Z. W.; Liu, S.; Zhang, S. Y.; Shah, K. W.; Han, M. Y. *Chem. Commun.* **2011**, *47*, 6689.
(27) (a) Huang, H.; Leung, D. Y. C. *ACS Catal.* **2011**, *1*, 348. (b) Hosseini-Sarvari, M. *Tetrahedron* **2008**, *64*, 5459.
(28) (a) Yamazaki, S. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2955. (b) Reich, H. J.; Chow, F.; Peake, S. L. *Synthesis* **1978**, 299. (c) Bortolini, O.; Di Furia, F.; Modena, G.; Seraglia, R. *J. Org. Chem.* **1985**, *50*, 2688.
(29) Ramanjulu, J. M.; DeMartino, M. P.; Lan, Y.; Marquis, R. *Org. Lett.* **2010**, *12*, 2270.
(30) Jatav, V.; Mishra, P.; Kashaw, S.; Stables, J. P. *Eur. J. Med. Chem.* **2008**, 135.
(31) Mane, R. S.; Ghosh, S.; Chopade, B. A.; Reiser, O.; Dhavale, D. D. *J. Org. Chem.* **2011**, *76*, 2892.
(32) Damha, M. J.; Ogilvie, K. K. *J. Org. Chem.* **1986**, *51*, 3559.
(33) See Supporting Information.
(34) Hansen, C. P.; Jensen, A. A.; Christensen, J. K.; Balle, T.; Liljefors, T.; Frølund, B. *J. Med. Chem.* **2008**, *51*, 7380.

