Article

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Citric Acid-catalyzed Synthesis of 2,4-Disubstituted Thiazoles from Ketones via C–Br, C–S, and C–N Bond Formations in One Pot: A Green Approach

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An improved and greener protocol has been developed for the synthesis of 2,4-disubstituted thiazoles via C–Br, C–S, and, C–N bond formations in a single step from readily available ketones, *N*-bromosuccinimide (NBS), and thiourea catalyzed by citric acid in a mixture of ethanol and water (3:1) under reflux conditions. This method has the advantages of freedom from the isolation of lachrymatory α-bromoketones, ease of carrying out, cleaner reaction profile, broad substrate scope, freedom from chromatographic purification, and suitability for large-scale synthesis.

Keywords: Citric acid; Alkyl aryl ketones; α-bromination; Heterocyclization; 2,4-Disubstituted thiazoles.

INTRODUCTION

Thiazole-based heterocycles are important structural motifs in many naturally occurring products as well as in synthetic compounds of pharmaceutical interest.[1] These are valuable building blocks[2] in the development of lead molecules and drug candidates. Among them, 2-aminothiazoles exhibit a wide range of pharmacological activities.[3–10] In addition, these derivatives are also useful in catalysis,[11] fluorescence,[12]diagnoses,[13] dyes,[14] solar cells,[15] photovoltaics,[16] organic semiconductors,[17] etc. Recently, 2-amino-4-arylthiazoles were explored in detail as "prodrugs" for the treatment of type-2 diabetes,[18] tuberculosis,[19] and Parkinson's disease.[20] A variety of methods have been reported for the synthesis of thiazole derivatives from α-bromoketones,[21] simple ketones,[22] and other substrates.[23–29] Most of them suffer from the use of lacrymatory α-bromoketones and their availability, narrow substrate scope, use of volatile and toxic solvents, low yields, tedious work-up procedures, and identification/preparation of a suitable catalyst. Hence, the development of green and sustainable methodologies for the synthesis thiazole derivatives remains an active area of research.

Very recently, we reported a lactic acid-mediated, tandem, one-pot synthesis of 2-aminothiazoles.[22a] Unfortunately, the method is not suitable for strong electron-donating groups such as –OH and $-NH_2$ present on the aromatic ring of ketones. In addition, a series of compounds synthesized in this study require high temperature. However, the use of high temperature affects the thermal and chemical stability of lactic acid, which is due to the possibility of its polymerization at reflux temperatures. Further, it may not be suitable for solid–liquid separation because of the high viscosity of lactic acid.[30] With the objective of finding a solution to the above problems, we identified citric acid as an efficient and green catalyst for the synthesis of 2-amino-4-aryl/naphthyl/coumaryl thiazoles from readily available ketones, *N*-bromosuccinimide (NBS), and thiourea in a one-pot process. Usually, α-bromination of ketone with NBS proceeds by acid catalysis. Compared to that of lactic acid, the p*K*a of citric acid is smaller, which means that citric acid protonates ketones very easily when compared to the lactic acid. Furthermore, citric acid is a nontoxic, low-cost, biodegradable, and environmentally benign catalyst, which is also employed in many organic transformations.[31]

In this work, we employed a biodegradable citric acid catalyst for the synthesis of 2-amino-4-aryl/naphthyl/coumaryl thiazoles (**5**) via C–Br (α-bromination), C–S, and C–N bond formations (heterocyclization) in a one-pot operation from readily available aryl alkyl ketones (**1**) NBS (**2**), and thiourea (**4**) in a mixture of ethanol and water (3:1) under reflux conditions (Scheme 1).

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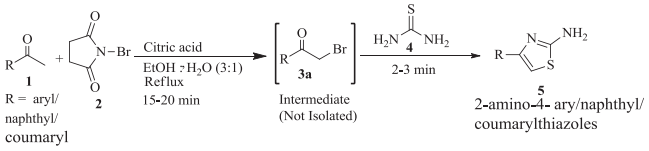


Scheme 1. Synthesis of 2,4-disubstituted thiazoles in one pot.

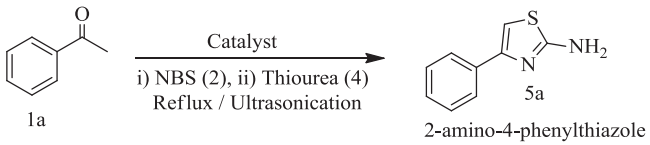
RESULTS AND DISCUSSION

The main objective of this work was to develop a green and sustainable method for the synthesis of analogs of thiazole derivatives (**5**), as depicted in Scheme 1. For this purpose, the regioselective α-bromination of acetophenone (**1a**) with NBS (**2**), followed by heterocyclization with thiourea (**4**) in different solvents under reflux conditions, was used as a model system to optimize the reaction conditions. The obtained results are summarized in Table 1. The α-bromination and hetrocyclization involved in the present process proceeded in the presence of various biodegradable α-hydroxy acidic catalysts such as malic acid, mandelic acid, tartaric acid, and citric acid (5.0% w/w) in water for approximately 120 min. Low yields of product **5a** of 5, 5, 8, and 15% were obtained, respectively. To improve the yield, the same reaction was repeated by employing various solvents such as acetone, isopropanol, ethanol, ethanol/water (1:1, 2:1, and 3:1 ratio), and the results are summarized in Table 1. After the examination of various α-hydroxy acid catalysts and solvents, it was found that citric acid (5.0% w/w) in 3:1 ratio of EtOH/H_2O medium was the best option to obtain good yield (85%) of the product (**5a**) whereas the other α-hydroxy acid catalysts and solvents gave low yields. This may be due to the more acidic nature of citric acid when compared to the other α-hydroxy acids. The same reaction was then carried out under ultrasound irradiation in the presence of various biodegradable α-hydroxy acidic catalysts such as malic acid, mandelic acid, tartaric acid, and citric acid (5.0% w/w) in different solvents for approximately 120 min. The obtained results are presented in Table 1. From this study, we find that citric acid in 3:1 ratio of EtOH/H_2O afforded a moderate yield (55%) of product **5a**, whereas the other catalysts in various solvents provided low yields under ultrasound irradiation. Further, the load of citric acid (5, 10, 15, and 20% w/w) was also varied for optimization of the reaction conditions, and the obtained results are shown in Table 2. We found that a loading of 10% w/w of citric acid in the presence of 3:1 ratio of EtOH/H_2O afforded the maximum yield of product (**5a**) under both conventional stirring (96%) and ultrasound irradiation (70%) in a short period (entry 2, Table 2). However, on further increase in the amount of citric acid to 15 and 20% w/w, the product yield remained the same (entries 3 and 4, Table 2). From the above study, we determined that the conventional method was superior to the ultrasound irradiation method in giving the highest yield of **5a** obtained in a short period.

SCOPE OF THE METHOD

Under optimized reaction conditions, the substrate scope of the present method was examined by using various readily available ketones (**1a–z**), and the obtained results are summarized in Table 3. The parent acetophenone (**1a**) propiophenone (**1b**) provided excellent isolated yields of 95% and 93% of the products **5a** and **5b**, respectively. Ketones with electron-donating groups on the aryl ring, such as 4-methyl (**1c**), 4-ethyl (**1d**), 2-hydroxy (**1e**), 3-hydroxy (**1f**), 4-hydroxy (**1g**), 4-methoxy (**1h**), 3-methoxy (**1i**), and 2,3-methoxy (**1j**) groups afforded excellent isolated yields (90–96%) of the products **5c–5j**, respectively. From the above observation, we found that the electron-donating groups at any position on the aromatic ring of ketones are well tolerated. This is due to the *in situ* formation of α-bromo ketones in high yields. Ketones with electron-withdrawing groups on the aryl ring such as 4-nitro (**1k**) and 3-nitro (**1l**) groups gave low isolated yields (60 and 55%) of the products **5k** and **5l** compared to the ketones with electron-donating groups on the aromatic ring. This may be due to the *in situ* generated α-bromo ketones in moderate yields. Halo groups at different positions on aryl ring of ketones, such as 4-bromo (**1m**), 4-chloro (**1n**), 4-fluoro(**1p**), 3-bromo (**1q**), 2-bromo (**1r**), 2-chloro (**1s**), 3,4-chloro (**1t**), and 2,4-chloro (**1u**) groups afforded good to excellent isolated yields (88–96%) of products **5m**, **5n**, **5p**, **5q**, **5r**, **5s**, **5t**, and **5u**, respectively. In the case of acetonaphthones (**1v** and **1w**), the 2-acetylnaphthalene (**1v**) provided better isolated yield (94%) of product **5v** when compared to 1-acetyl naphthalene (**1w**).This may be due to steric effects. Encouraged by the above results, this methodology was applied for few heterocyclic systems such as 3-acetylcoumarin (**1x**), 2-acetylpyridine (**1y**), and 2-acetylthiophene (**1z**). The study revealed that the 3-acetylcoumarin (**1x**) gave the product **5x** in excellent isolated yield (96%), whereas 2-

Table 1. Optimization of reaction conditions for the preparation of 2-amino-4-phenylthiazole (**5a**)[a]



1a

2-amino-4-phenylthiazole

Entry	Catalyst (5.0% w/w)	Solvent	Product	Conventional stirring		Ultrasonic irradiation	
				Time (min)	Yield (%)[b]	Time (min)	Yield (%)[b]
1	Malic acid	H_2O	**5a**	120	5	120	—
		Acetone		60	10	120	—
		Isopropanol		60	20	120	10
		EtOH		60	30	120	15
		EtOH: H_2O (1:1 ratio)		60	35	120	18
		EtOH: H_2O (2:1 ratio)		60	40	120	20
		EtOH: H2O (3:1 ratio)		60	45	120	25
2	Mandelic acid	H_2O	**5a**	120	5	120	—
		Acetone		60	15	120	—
		Isopropanol		60	25	120	12
		EtOH		60	35	120	20
		EtOH: H_2O (1:1 ratio)		60	40	120	22
		EtOH: H_2O (2:1 ratio)		60	45	120	25
		EtOH: H2O (3:1 ratio)		60	50	120	28
3	Tartaric acid	H_2O	**5a**	120	8	120	5
		Acetone		60	15	120	5
		Isopropanol		60	30	120	20
		EtOH		60	45	120	35
		EtOH: H_2O (1:1 ratio)		60	50	120	42
		EtOH: H_2O (2:1 ratio)		60	55	120	48
		EtOH: H_2O (3:1 ratio)		60	60	120	56
4	Citric acid	H_2O	**5a**	120	15	120	15
		Acetone		60	20	120	18
		Isopropanol		60	45	120	36
		EtOH		60	60	120	41
		EtOH: H_2O (1:1 ratio)		60	70	120	50
		EtOH: H_2O (2:1 ratio)		60	75	120	52
		EtOH: H_2O (3:1 ratio)		60	85	120	55

[a] Reaction conditions: Acetophenone (**1a**) (10.0 mmol), *N*-bromosuccinimide (**2**) (12.0 mmol), catalyst (5.0%, w/w), thiourea (**4**) (12.0 mmol) in solvents at reflux temperature.
[b] Isolated yield.

acetylpyridine (**1y**) and 2-acetylthiophene (**1z**) did not form the desired products **5y** and **5z** because they might be undergoing ring bromination instead of α-bromination. From the above observations, it is found that the isolated yields of the thiazoles depend on the percentage of *in situ* generated α-bromoketones.

Further, to test the scalability of the procedure, the reaction was carried out with 3-acetylcoumarin (**1x**), NBS (**2**), and thiourea (**4**) in the presence of citric acid in different gram-scale reactions (1, 5, 10, 15, 20, and 25 g) in a mixture of ethanol and water (3:1) under reflux conditions, which resulted in 96, 96, 96, 95, 94, and 94%, yields of product **5x**, respectively. From this investigation, it was found that the developed synthetic route is an alternative for the preparation of 2-amino-4-arylthiazoles in gram-scale production.

Table 2. Screening for loading of catalyst[a]

Entry	Catalyst (% w/w)	Solvent	Product	Conventional stirring		Ultrasonic irradiation	
				Time (min)	Yield (%)[b]	Time (min)	Yield (%)[b]
1	5.0	EtOH: H_2O (3:1 ratio)	**5a**	20	85	120	55
2	10.0	EtOH: H_2O (3:1 ratio)	**5a**	20	96	60	70
3	15.0	EtOH: H_2O (3:1 ratio)	**5a**	20	96	60	70
4	20.0	EtOH: H_2O (3:1 ratio)	**5a**	20	94	60	66

[a] Reaction conditions: Acetophenone (**1a**) (10.0 mmol), *N*-bromosuccinimide (**2**) (12.0 mmol), catalyst (5.0%, w/w), thiourea (**4**) (12.0 mmol) in in EtOH/H_2O (3:1 ratio) at reflux temperature.
[b] Isolated yield.

EXPERIMENTAL

Materials and methods

Melting points were determined on an MR-Vis+ instrument (Labindia) and are uncorrected. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Varian 400 MHz spectrometer with $CDCl_3$ as a solvent and tetramethylsilane (TMS) as the internal reference compound. Mass spectral data were acquired on a Exactive Orbitrap mass spectrometer (Thermo Scientific, Waltham, MA, USA). All the reactions were monitored by TLC. All chemicals and solvents were procured from Acros organics Ltd., Merck, or Sigma-Aldrich and were used as received. Millipore double-distilled water was used for the work-up. Supporting information (Supporting Information) contains the ^1H, ^{13}C NMR, and HRMS spectra of newly synthesized compounds (**5**).

General experimental procedure for the synthesis of 2,4-disubstituted thiazole derivatives (5)

A mixture of ketones (**1**) (10.0 mmol), NBS (**2**) (12.0 mmol), and citric acid (10% w/w) was dissolved in 10 mL of 3:1 ethanol/water, and the reaction mixture was either stirred under reflux condition for 15–20 min or under ultrasound irradiation at 60–70 °C for approximately 60 min. After the formation of α-bromoketones (**3**) as monitored by TLC, thiourea (**4**) (12.0 mmol) was to the reaction mixture and stirred for 1–2 min under reflux conditions. After completion of the reaction, as indicated by TLC, the reaction mixture was slowly cooled down to RT and poured into a beaker containing 50 mL of water and stirred well. The obtained crude product (**5**) was filtered, washed thoroughly with double-distilled water, and dried. Finally, the crude product (**5**) was recrystallized from hot ethanol. Most of the synthesized compounds are already characterized in the literature.[21,22] Spectroscopic data of these compounds are consistent with those reported previously. Some of the compounds (**5e**, **5f**, **5g**, **5i**, **5j**, **5r**, and **5x**) were characterized by spectroscopic data (^1H and^{13}C NMR and HRMS).

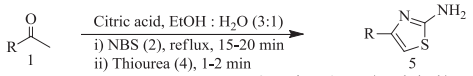
General experimental procedure for gram-scale (25 g) synthesis

A mixture of 3-acetylcoumarin (**1x**) (0.135 mol), NBS (**2**) (0.15 mol), and citric acid (10% w/w) was dissolved in 100 mL of 3:1 ethanol/water and the reaction mixture was refluxed for 20 min. The formation of α-bromoketone (**3x**) was monitored by TLC. After the formation of α-bromoketone (**3x**) as per TLC, thiourea (**4**) (0.15 mol) was to the reaction mixture and stirred for 1–2 min under reflux conditions. After completion of the reaction, as indicated by TLC, the reaction mixture was slowly cooled down to RT and poured into a beaker containing 500 mL water and stirred well. The obtained crude product (**5**) was filtered, washed thoroughly with double-distilled water, and dried. Finally, the crude product (**5x**) was recrystallized from hot ethanol. The isolated yield of the obtained product (**5x**) was 96%.

CONCLUSION

A practical and environmentally friendly process has been demonstrated for the synthesis of 2, 4-disubstituted thiazoles via C–Br, C–S, and C–N bond formations in a single step from readily available various ketones, NBS, and thiourea catalyzed by biodegradable citric acid in a mixture of ethanol and water (3:1) under reflux conditions. Noteworthy features of the catalyst are the environmentally benign nature, regioselectivity, and wide substrate scope. The catalyst is thus a greener alternative to the previously reported

Table 3. Synthesis of a series of 2,4-disubtituted thiazoles from readily available ketones



R = aryl/ naphthyl/coumaryl 2-amino-4- ary/naphthyl/coumarylthiazoles

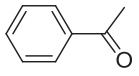
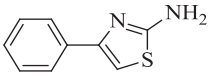
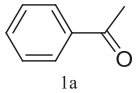
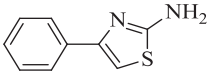
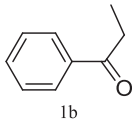
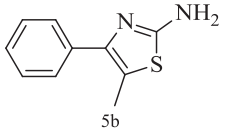
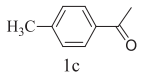
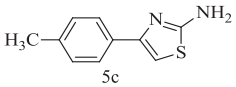
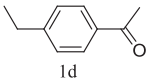
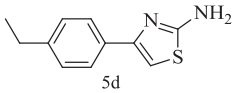
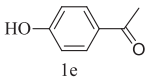
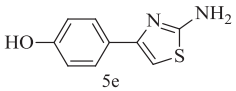
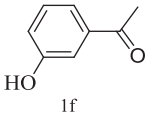
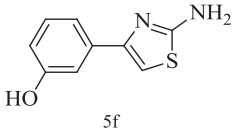
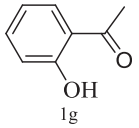
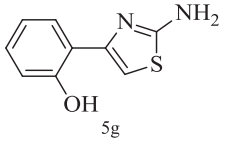
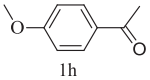
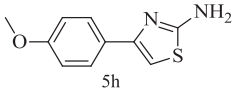
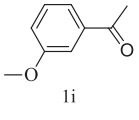
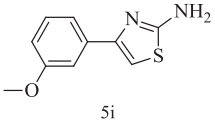
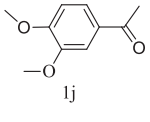
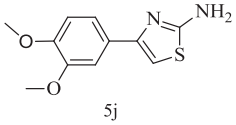
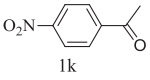
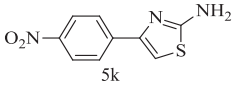
Entry	Substrate	Product	Time (min)	Yield (%)[Ref.]
1	 1a	 5a	20	96[21,22]
2	 1a	 5a	20	93[21,22]
3	 1b	 5b	15	96[21,22]
4	 1c	 5c	20	92[21,22]
5	 1d	 5d	18	96[22]
6	 1e	 5e	16	92[22]
7	 1f	 5f	16	90[22]
8	 1g	 5g	18	94[21,22]
9	 1h	 5h	20	94
10	 1i	 5i	18	94
11	 1j	 5j	25	60[21,22]
12	 1k	 5k	25	55[21,22]

Table 3. Continued

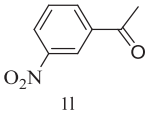
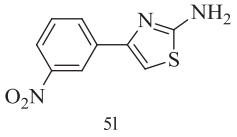
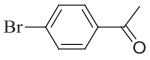
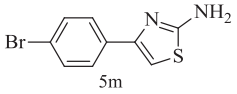
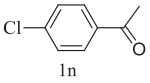
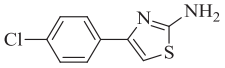
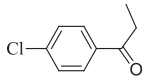
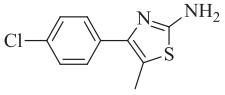
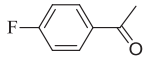
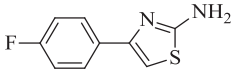
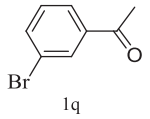
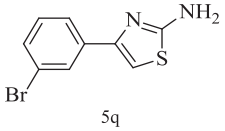
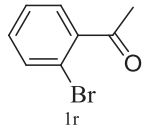
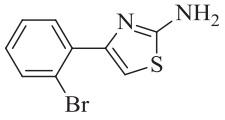
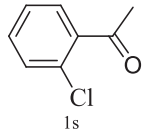
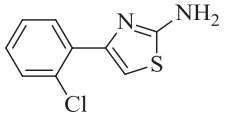
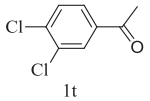
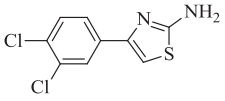
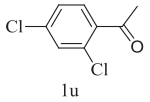
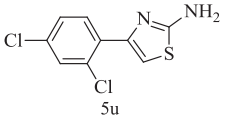
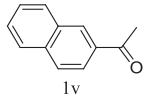
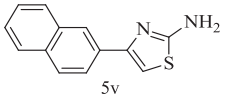
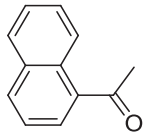
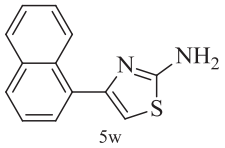
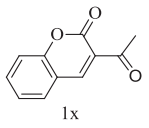
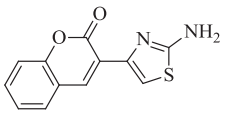
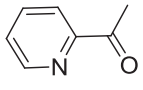
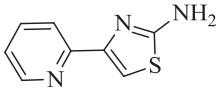
Entry	Substrate	Product	Time (min)	Yield (%)[Ref.]
13	 1l	 5l	16	96[21,22]
14	 1m	 5m	15	95[21,22]
15	 1n	 5n	20	92[21]
16	 1o	 5o	18	94[21,22]
17	 1p	 5p	19	93[21,22]
18	 1q	 5q	20	89
19	 1r	 5r	20	91[22]
20	 1s	 5s	19	90[21,22]
21	 1t	 5t	20	89[21,22]
22	 1u	 5u	18	94[21,22]
23	 1v	 5v	20	90[21,22]
24	 1w	 5w	20	96

Table 3. Continued

Entry	Substrate	Product	Time (min)	Yield (%)[Ref.]
25	 1x	 5x	40	0
26	 1y	 5y	40	0

catalysts. The proposed methodology has several advantages, which include environmentally friendly procedure, ease of operation, simple work-up, freedom from the isolation of highly lachrymatory α-bromoketones, high yields of products, freedom from chromatographic purification, suitability for scale-up, and good tolerance of a wide variety of functional groups present on the aromatic ring of ketone. Further, the synthesized precursors are useful for the preparation of various biologically active, thiazole-based analogs.

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Supporting information

Additional supporting information is available in the online version of this article.

REFERENCES

1. S. Shweta, T. V. Sravanthi, S. Yuvaraj, S. L. Manju, D. Mukesh, *RSC Adv.* **2016**, *6*, 19271.
2. G. Kaupp, F. A. Amer, M. A. E. A. Metwally Latif, *J. Heterocycl. Chem.* **2003**, *40*, 963.
3. (a) N. M. Parekh, K. V. Juddhawala, B. M. Rawal, *Med. Chem. Res.* **2013**, *22*, 2737. (b) S. K. Bharti, G. Nath, R. Tilak, S. K. Singh, *Eur. J. Med. Chem.* **2010**, *45*, 651–660. (c) Z. Fan, Z. Shi, H. Zhang, X. Liu, L. Bao, L. Ma, X. Zuo, Q. Zheng, N. Mi, *J. Agric. Food Chem.* **2009**, *57*, 4279.
4. B. V. Yang, D. S. Weinstein, L. M. Doweyko, H. Gong, W. Vaccaro, T. Huynh, H. Xiao, A. M. Doweyko, L. Mckay, D. A. Holloway, J. E. Somerville, S. Habte, M. Cunningham, M. McMahon, R. Townsend, D. Shuster, J. H. Dodd, S. G. Nadler, J. C. Barrish, *J. Med. Chem.* **2010**, *53*, 8241.
5. D. G. Cabrera, F. Douelle, T.–S. Feng, A. T. Nchinda, Y. Younis, K. L. White, Q. Wu, E. Ryan, J. N. Burrows, D. Waterson, M. J. Witty, S. Wittlin, S. A. Charman, K. Chibale, *J. Med. Chem.* **2011**, *54*, 7713.
6. (a) R. Romeo, G. B. Pier, K. S. Maria, P. Delia, A. T. Mojgan, B. Andrea, F. Xian-Hua, J. Li, Z. Su-Zhan, H. Ernest, R. Bortolozzi, E. Porcù, G. Basso, G. Viola, *J. Med. Chem.* **2012**, *55*, 5433. (b) S. Ghaemmaghami, B. C. H. May, A. R. Renslo, S. B. Prusiner, *J. Virol.* **2010**, *84*, 3408. (c) N. Siddiqui, W. Ahsan, *Eur. J. Med. Chem.* **2010**, *45*, 1536.
7. (a) S. Singh, N. R. Prasad, E. E. Chufan, B. A. Patel, Y.-J. Wang, Z.–S. Chen, S. V. Ambudkar, T. T. Talele, *J. Med. Chem.* **2014**, *57*, 4058. (b) J. S. de Toledo, P. E. S. Junior, V. Manfrim, C. F. Pinzan, A. S. de Araujo, A. K. Cruz, F. S. Emery, *Chem. Biol. Drug Des.* **2013**, *81*, 749. (c) E. Carosati, A. Tochowicz, G. Marverti, G. Guaitoli, P. Benedetti, S. Ferrari, R. M. Stroud, J. Finer-Moore, R. Luciani, D. Farina, G. Cruciani, M. P. Costi, *J. Med. Chem.* **2012**, *55*, 10272. (d) J. Liu, F. Jiang, Y. Jin, Y. Zhang, J. Liu, W. Liu, L. Fu, *Eur. J. Med. Chem.* **2012**, *57*, 10.
8. (a) H. Shao, S. Shi, S. Huang, A. J. Hole, A. Y. Abbas, S. Baumli, X. Liu, F. Lam, D. W. Foley, P. M. Fischer, M. Noble, J. A. Endicott, C. Pepper, S. Wang, *J. Med. Chem.* **2013**, *56*, 640. (b) A. J. Hole, S. Baumli, H. Shao, S. Shi, S. Huang, C. Pepper, P. M. Fischer, S. Wang, J. A. Endicott, M. E. Noble, *J. Med. Chem.* **2013**, *56*, 660.
9. (a) Z. Shilong, Z. Qiu, X. Yulan, M. Madhusoodanan, Z. Qiang, R. L. Schroeder, S. Jayalakshmi, H. Ling, H. McFerrin, W. Guangdi, *J. Med. Chem.* **2014**, *57*, 6653. (b) M. Johnson, T. Antonio, M. E. A. Reith, A. K. Dutta, *J. Med. Chem.* **2012**, *55*, 5826. (c) M. Biagetti, C. P. Leslie, A. Mazzali, C. Seri, D. A. Pizzi, J. Bentley, T. Genski, R. Di Fabio, L. Zonzini, L. Caberlotto, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4741.
10. (a) H. Mohammad, A. S. Mayhoub, A. Ghafoor, M. Soofi, R. A. Alajlouni, M. Cushman, M. N. Seleem,

J. Med. Chem. **2014**, *57*, 1609. (b) S. S. Pravin, M. Prashanti, M. Naik, K. Murugan, V. Shinde, N. Radha, B. Jyothi, K. Anupriya, S. Hameed, G. Holdgate, G. Davies, H. McMiken, N. Hegde, A. Anisha, V. Janani, M. Panda, B. Balachandra, V. K. Sambandamurthy, J. A. Read, *J. Med. Chem.* **2013**, *56*, 8533.
11. Q.-L. Luo, J.–P. Tan, Z.–F. Li, W.–H. Nan, D.–R. Xiao, *J. Org. Chem.* **2012**, *77*, 8332.
12. Y. Kimura, T. Hanami, Y. Tanaka, M. J. L. de Hoon, T. Soma, M. Harbers, A. Lezhava, Y. Hayashizaki, K. Usui, *Biochemistry* **2012**, *51*, 6056.
13. (a) B. Benjamin, *ACS Med. Chem. Lett.* **2014**, *5*, 619. (b) K. K. Roy, S. Singh, S. K. Sharma, R. Srivastava, V. Chaturvedi, A. K. Saxena, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5589.
14. M. Yamaguchi, O. Takiguchi, M. Tsukase, Y. Ishiwata, *PCT Int. Appl. Ther.* **2009**, *2009005139*, 08.
15. J. Kim, H.–S. Shim, H. Lee, M.–S. Choi, J.–J. Kim, Y. Seo, *J. Phys. Chem. C* **2014**, *118*, 11559.
16. S. V. Mierloo, A. Hadipour, M.–J. Spijkman, N. V. Brande, B. Ruttens, J. Kesters, J. D'Haen, G. V. Assche, D. M. de Leeuw, T. Aernouts, J. Manca, L. Lutsen, D. J. Vanderzande, W. Maes, *Chem. Mater.* **2012**, *24*, 587.
17. V. T. T. Huong, T. Ba Tai, M. T. Nguyen, *J. Phys. Chem. A* **2014**, *118*, 3335.
18. (a) M. D. Erion, P. D. van Poelje, Q. Dang, S. R. Kasibhatla, S. C. Potter, M. R. Reddy, K. R. Reddy, T. Jiang, W. N. Lipscomb, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 7970. (b) T. Hasegawa, J. Eiki, M. Chiba, *Drug Metab. Dispos.* **2014**, *42*, 1548.
19. (a) Q. Al-Balas, N. G. Anthony, B. Al-Jaidi, A. Alnimr, G. Abbott, A. K. Brown, R. C. Taylor, G. S. Besra, T. D. McHugh, S. H. Gillespie, B. F. Johnston, S. P. Mackay, G. D. Coxon, *PLoS One* **2009**, *4*, e5617. (b) P. Makam, T. Kannan, *Eur. J. Med. Chem.* **2014**, *87*, 643. (c) A. Meissner, H. I. Boshoff, M. Vasan, B. P. Duckworth, C. E. Barry, C. C. Aldrich, *Bioorg. Med. Chem.* **2013**, *21*, 6385. (d) M. Pieroni, B. Wan, S. Cho, S. G. Franzblau, G. Costantino, *Eur. J. Med. Chem.* **2014**, *72*, 26.
20. (a) K. Y. Chau, J. M. Cooper, A. H. Schapira, *J. Mol. Neurosci.* **2013**, *51*, 573. (b) Y. Izumi, H. Sawada, N. Yamamoto, T. Kume, H. Katsuki, S. Shimohama, A. Akaike, *Eur. J. Pharmacol.* **2007**, *557*, 132.
21. (a) P. M. Khaja Mohinuddin, B. Mohan Reddy, D. K. Sangita, N. C. Gangi Reddy, *Curr. Green Chem.* **2015**, *2*, 163. (b) H. M. Meshram, P. B. Thakur, B. Madhu Babu, V. M. Bangade, *Tetrahedron Lett.* **2012**, *53*, 5265. (c) P. Praveen Kumar, Y. Dathu Reddy, C. Venkata Ramana Reddy, B. Rama Devi, P. K. Dubey, *J. Sulfur Chem.* **2011**, *32*, 37. (d) M. M. Heravi, N. Poormohammad, Y. S. Beheshtiha, B. Baghernejad, *Synth. Commun.* **2011**, *41*, 579. (e) T. M. Potewar, S. A. Ingale, K. V. Srinivasan, *Tetrahedron* **2008**, *64*, 5019. (f) T. M. Potewar, S. A. Ingale, K. V. Srinivasan, *Tetrahedron* **2007**, *63*, 11066. (g) G. W. Kabalka, A. R. Mereddy, *Tetrahedron Lett.* **2006**, *47*, 5171.
22. (a) B. Mohan Reddy, P. M. D. Khaja Mohinuddin, G. Trivikram Reddy, N. C. Gangi Reddy, *Cogent Chem.* **2016**, *2*, 1154237. (b) T. V. Sravanthi, S. L. Manju, *J. Fluoresc.* **2015**, *25*, 1727. (c) Y.-P. Zhu, J.-J. Yuan, Q. Zhao, M. Lian, Q.-H. Gao, M.-C. Liu, Y. Yang, A.-X. Wu, *Tetrahedron* **2012**, *68*, 173. (d) A. Nitta, H. Fujii, S. Sakami, M. Satoh, J. Nakaki, S. Satoh, H. Kumagai, H. Kawai, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7036. (e) M. M. Kumar, A. Kumar, *J. Heterocyclic Chem.* **2012**, *49*, 959. (f) K. Hitendra, S. Manisha, M. P. Kaushik, *Catal. Commun.* **2007**, *8*, 741. (gX. Huang, Q. Zhu, J.-Z. Zhang, *Chin. J. Chem.* **2002**, *20*, 1411. (h)H. Hirt, R. Haenggi, J. Reyes, M. Seeger-Weibel, F. Gallou, *Org. Process. Res. Dev.* **2008**, *12*, 111. (i) R. M. Dodson, L. C. King, *J. Am. Chem. Soc.* **1946**, *68*, 871. (j) B. S. Jagdale, V. A. Adola, *Int. J. Pharm. Res. Sci.* **2015**, *4*, 46. (k) G. Rajul, K. F. Neeraj, F. Shivkanya, *Turk. J. Pharm Sci.* **2013**, *10*, 425. (l) G. Vinod Kumar, S. Ashok Kumar, K. Lokesh Kumar, *Electrochim. Acta* **2013**, *95*, 132.
23. (a) R.-S. Hou, H.-M. Wang, H.-H. Tsai, L.-C. Chen, *J. Chin. Chem. Soc.* **2006**, *53*, 863. (b) P.-Y. Lin, R.-S. Hou, H.-M. Wang, I.-J. Kang, L.-C. Chen, *J. Chin. Chem. Soc.* **2009**, *56*, 455.
24. A. Shawkat, *J. Chin. Chem. Soc.* **2003**, *50*, 1085.
25. W. W. Wagnat, A. Y. Mohamed, I. H. Faten, A. O. Salama, *J. Chin. Chem. Soc.* **2008**, *55*, 1133.
26. S. Heck, A. Dömling, *Synlett* **2000**, *3*, 424.
27. (a) M. Siva, N. Adel, *ACS Comb. Sci.* **2014**, *16*, 39. (b) C. T. Walsh, S. J. Malcolmson, T. S. Young, *ACS Chem. Biol.* **2012**, *7*, 429.
28. V. Golubev, F. Zubkov, M. Krasavin, *Tetrahedron Lett.* **2013**, *54*, 4844.
29. (a) N. Iravani, M. Keshavarz, T. Haghnegahdara, M. Salehia, *J. Chin. Chem. Soc.* **2014**, *61*, 1259. (b) N. Iravani, M. Keshavarz, M. Monfareda, F. Hosseinia, *J. Chin. Chem. Soc.* **2014**, *61*, 357.
30. J. Yang, J. N. Tana, Y. Gu, *Green Chem.* **2012**, *14*, 3304.
31. (a) S. Rohokale, S. Kote, S. Deshmukh, S. R. Thopate, *Chem. Pap.* **2014**, *68*, 575. (b) A. S. Kabeer, N. C. Uddhav, B. N. Vijaykumar, *IOSR J. Appl. Chem.* **2014**, *7*, 90. (c) S. Sajjadifar, G. M AliZolfigol, S. Chehardoli, P. Miri, Moosavi, *Int. J. Chem. Tech. Res.* **2013**, *5*, 422. (d) A. N. Camilo, A. S. Cesar,

O. P. Cristian, *Rev. Colomb. Quim.* **2013**, *42*, 5. (e) Q. S. Ding, J. L. Zhang, J. X. Chen, M. C. Liu, J. C. Ding, H. Y. Wu, *J. Heterocycl. Chem.* **2012**, *49*, 375. (f) A. D. Vasconcelos, P. S. Oliveira, M. Ritter, R. A. Freitag, R. L. Romano, F. H. Quina, L. Pizzuti, C. M. P. Pereira, F. M. Stefanello, A. G. Barschak, *J. Biochem. Mol. Toxicol.* **2012**, *26*, 155. (g) S. R. Thopate, S. R. Kote, S. V. Rohokale, N. M. Thorat, *J. Chem. Res.* **2011**, *35*, 124. (h) A. Ghorbani-Choghamarani, T. Taghipour, *Lett. Org. Chem.* **2011**, *8*, 470. (i) M. Z. Ahmed, N. T. Patel, K. A. Shaikh, M. A. Baseer, S. Shaikh, V. A. Patti, *Elixir. Org. Chem.* **2010**, *43*, 6583. (j) R. Enugala, S. Nuvvula, V. Kotra, R. Varala, S. R. Adapa, *Heterocycles* **2008**, *75*, 2523. (k) E. Ramu, V. Kotra, N. Bansal, R. Varala, S. R. Adapa, *Rasayan J. Chem.* **2008**, *1*, 188. (l) A. G. Choghamarani, T. Taghipour, G. Azadia, *J. Chin. Chem. Soc.* **2013**, *60*, 1202.

