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Facile synthesis of 1,3-thiazolidin-4-ones as antitubercular agents

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ABSTRACT

We have developed, highly efficient, one-pot, solvent-free, $[Et_3NH][HSO_4]$ catalyzed multicomponent reaction protocol for the synthesis of 1,3-thiazolidin-4-ones in excellent yields. For the first time, the 1,3-thiazolidin-4-ones were evaluated in vitro for their antimycobacterial activity against *Mycobacterium tuberculosis* dormant *MTB H37Ra* and *Mycobacterium bovis BCG* strains. Among the synthesized basic 1,3-thiazolidin-4-ones, particularly the compounds **4c**, **4d**, **4e**, **4f**, **4h**, **4i** and **4j** displays promising antitubercular activity along with no significant cytotoxicity against the cell lines MCF-7, A549 and HCT-116.

Multicomponent reactions (MCRs) permit rapid access to combinatorial libraries of complex molecules, particularly in drug discovery. Multicomponent reactions and ionic liquids is a perfect synergy for eco-compatible heterocyclic synthesis.[1] 1,3-Thiazolidin-4-ones are important class of compounds due to their biological profiles like antimicrobial,[2] antitubercular,[3] anti-inflammatory,[4] HIV inhibitors,[5] anti-hypertensive,[6] anticonvulsant,[7] anti-hepatitis,[8] anti-hyperglycemic,[9] antioxidant,[10] antifungal[11] and antiproliferative[12] activity. Thiazolones are also display promising biological activities.[13]

Owing to the potential importance of a 1,3-thiazolidin-4-ones as a key moiety in life sciences and pharmaceuticals, various protocols have been developed using various methods and catalysts such as $ZnCl_2$,[14a] DCC,[14b] HBTU,[14c] [bmim][PF_6],[14d] silica gel,[14e] [BmIm]OH,[14f] Hunig's base,[14g] ferrite,[14h] sodium sulfate,[14i] molecular sieves,[14j] nano-Fe_3O_4@SiO_2,[14k] montmorillonite K-10,[14l] baker's yeast,[14m] and DBSA.[14n] However, most of these methods suffer from one or more drawbacks such as low yields, long reaction times, harsh reaction conditions or tedious workup procedures.

Recently, the utility of Acidic Bronsted Ionic Liquid (ABIL), particularly $[Et_3NH][HSO_4]$[15] has received considerable attention because, it is an inexpensive, non-toxic catalyst as well as solvent for many organic transformations in excellent yields. Very recently, we have utilized $[Et_3NH][HSO_4]$ for the synthesis of α-aminophosphonates in excellent yields.[16] To the best of our knowledge and literature survey, there is no report for the antitubercular activity of basic skeletons of 1,3-thiazolidin-4-one derivatives and also use of $[Et_3NH][HSO_4]$ as catalyst for their synthesis.

In view of the diverse therapeutic activity of 1,3-thiazolidin-4-ones and in continuation of our work on efficient synthesis and bioevaluation of highly functionalized heterocyclic compounds,[17] herein, we would like to report a facile synthesis and antitubercular activity of 1,3-thiazolidin-4-ones against dormant *MTB H37Ra* and *Mycobacterium bovis BCG* strains for the first time.

The synthesis of 1,3-thiazolidin-4-ones **4a-u** via cyclocondensation of Schiff's base (obtained in situ from aldehydes and anilines) with thioglycolic acid in the presence of $[Et_3NH][HSO_4]$ as catalyst under solvent free conditions is outlined in Scheme 1.

In our initial endeavour, we have performed the reaction of aniline **1a** (1 mmol), benzaldehyde **2a** (1 mmol) with thioglycolic acid **3** (1 mmol) using 20 mol% of $[Et_3NH][HSO_4]$ at 80 °C in various solvents and solvents-free condition also. According to the study, it has been found that a solvent-free condition is more efficient over using solvents with respect to the reaction time and yield of the desired 1,3-thiazolidin-4-one (Table 1).

Again, we have screened the concentration of $[Et_3NH][HSO_4]$ as a catalyst. In the absence of catalyst, the desired product **4a** was obtained in trace amount (Table S1, Supporting information). After varying the concentration 5, 10, 15, 20 and 25 mol%, the product **4a** was obtained in 40%, 62%, 85%, 94% and 94% yield, respectively (Table S1, supporting information). It indicates that, 20 mol% catalyst is suitable for better yield of product **4a**.

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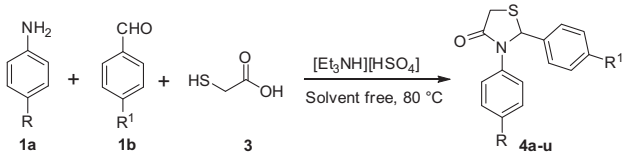


4a, R = H, R^1 = H **4b**, R = Me, R^1 = H **4c**, R = OMe, R^1 = H
4d, R = Cl, R^1 = H **4e**, R = F, R^1 = H **4f**, R = H, R^1 = Cl
4g, R = H, R^1 = Me **4h**, R = H, R^1 = OMe **4i**, R = H, R^1 = F
4j, R = H, R^1 = Br **4k**, R = H, R^1 = NO_2 **4l**, R = Me, R^1 = Me
4m, R = Me, R^1 = Cl **4n**, R = Cl, R^1 = OMe **4o**, R = Me, R^1 = NO_2
4p, R = Cl, R^1 = Cl **4q**, R = Cl, R^1 = OH **4r**, R = Br, R^1 = H
4s, R = Cl, R^1 = F **4t**, R = F, R^1 = Cl **4u**, R = F, R^1 = Me

Scheme 1. [Et_3NH][HSO_4]-catalyzed synthesis of 1,3-thiazolidin-4-ones **4a**–**u**.

Table 1
Screening of solvents[a]

Entry	Solvent	Yield[b] (%)
1	EtOH	57
2	MeOH	60
3	H_2O	47
4	CH_2Cl_2	52
5	CH_3CN	62
6	THF	50
7	DMF	53[c]
8	PhMe	66[c]
9	Solvent-free	94[d]

[a] Reaction conditions: aniline **1a** (1 mmol), benzaldehyde **2a** (1 mmol), thioglycolic acid **3** (1 mmol) and 20 mol% [Et_3NH][HSO_4] at reflux temperature of solvents after 30 min.
[b] Isolated yields.
[c,d] Reaction were performed at 120 and 80 °C, respectively.

Table 2
Comparison of our results with previously reported data for the synthesis of (**4a**)

Entry	Catalyst	Reaction condition	Time (h)	Yield[a] (%)	Ref.
1	DCC	THF/rt	1	91	14b
2	SiO_2	DCM/rt	7	78	14e
3	MCM-41	110 °C	12	97	14f
4	$HClO_4$–SiO_2	PhMe/100 °C	5	85	18a
5	H_2SO_4–SiO_2	PhMe/100 °C	5	55	18a
6	TfOH–SiO_2	PhMe/100 °C	5	72	18a
7	Bi $(SCH_2COOH)_3$	70 °C	2	75	18b
8	[Et_3NH][HSO_4]	80 °C	30 min	94	This work

[a] Isolated yield.

We have also studied the recyclability and reuse of catalyst [Et_3NH][HSO_4] for the subsequent experiments under similar reaction conditions. After completion of the reaction, the reaction mixture was poured on ice cold water and the product was extracted using ethylacetate solvent. The filtrate was subjected for evaporation of water to get viscous liquid, which on cooling afforded ionic liquid. It was then reused at least five consecutive cycles without much appreciable loss in its catalytic activity. The recyclability data demonstrates the high stability of the catalyst under the reaction conditions (Table S2, Supporting information).

In addition to this, we have also compared the present protocol for the synthesis of 1,3-thiazolidin-4-ones is better than earlier reported methods (Table 2).

With this optimized reaction condition, that is, 20 mol % [Et_3NH][HSO_4] catalyst at 80 °C for 30 min, we have utilized[19] this protocol for the synthesis of highly functionalized 1,3-thiazolidin-4-ones **4a**–**u** from corresponding aniline **1a**–**e**, aromatic aldehyde **2a**–**h** and thioglycolic acid **3** in excellent yield (Scheme 1). We have also described the plausible mechanism for the formation of 1,3-thiazolidin-4-ones **4a**–**u** (Scheme S1, Supporting information). This method offers several advantages like milder reaction condition, shorter reaction time, cleaner reaction, high yield and simple experimental and isolation procedures, making it an useful route for the synthesis of 1,3-thiazolidin-4-ones.

Antitubercular activity evaluation of the synthesized 1,3-thiazolidin-4-ones, **4a**–**u** were determined by measuring growth of inhibition against avirulant strain of dormant *MTB H37Ra* (ATCC 25177) and *M. bovis BCG* (ATCC 35743) in liquid *Mycobacterium phlei* medium.

In a preliminary screening (Tables S3 and S4, Supporting information), the antimycobacterial activity of compounds was assessed at concentrations of 30, 10 and 3 μg/mL using an established XTT Reduction Menadione assay (XRMA) antitubercular screening protocol[20] using first-line antitubercular drugs rifampicin and isoniazid as reference standards and the results are presented in Table 3.

The diversely functionalized 1,3-thiazolidin-4-one **4a**–**u**, in particular the compounds **4c**, **4f**, **4h**, **4i** and **4j** exhibited IC_{50} values of 2.2, 5.6, 4.2, 6.8 and 8.9 μg/mL, respectively, against dormant *MTB H37Ra*, which indicates that, these may be promising antitubercular agents. However, the only compound **4h** active against *M. bovis BCG* strain with IC_{50} value 8.7 μg/mL. These findings inspired us to evaluate their cytotoxicity. Hence, all of the 1,3-thiazolidin-4-one derivatives **4a**–**u** were evaluated for their cytotoxicity against MCF-7, A549 and HCT-116 cell lines using in vitro MTT assay[21] (primary screening data, Tables S5–S7, Supporting information). Particularly, the selected compounds **4a**, **4c**, **4d**, **4e**, **4f**, **4h**, **4i**, **4j** and **4u** were found to be non toxic against cell lines at the maximum concentration evaluated (Table S8, Supporting information).

Again, the most active antitubercular compounds **4a**, **4c**, **4d**, **4e**, **4f**, **4h**, **4i** and **4j**, were also evaluated for antibacterial activity against Gram-negative and Gram-positive bacteria. These compounds does not displays promising antibacterial activity against the tested strains, (Table S9, Supporting information).

In conclusion, highly efficient and safer protocol has been developed for the synthesis of 1,3-thiazolidin-4-ones via one-pot three-component cyclocondensation of anilines, aryl aldehydes, thioglycolic acid using 20 mol% of [Et_3NH][HSO_4] as a catalyst in excellent yields. The synthesized 1,3-thiazolidin-4-ones were evaluated in vitro for their antimycobacterial activity, cytotoxicity and antimicrobial activity, shows that these compounds are highly selective towards dormant *MTB H37Ra* and *M. bovis BCG* strains.

Table 3
In vitro antitubercular activity against dormant *MTB H37Ra* and *M. bovis BCG*

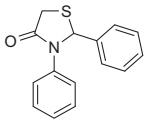
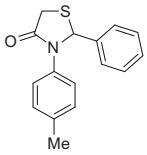
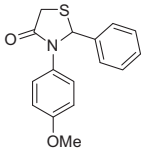
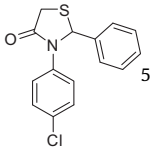
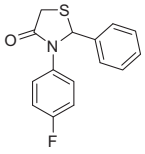
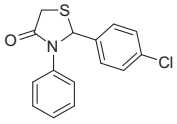
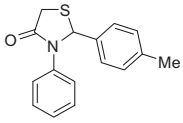
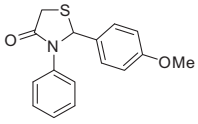
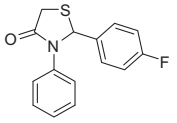
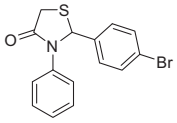
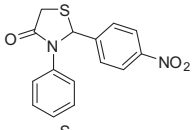
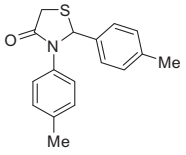
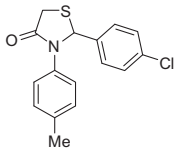
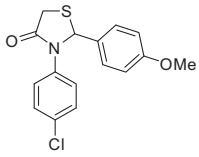
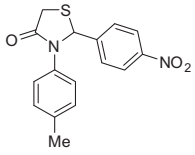
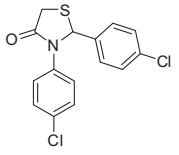
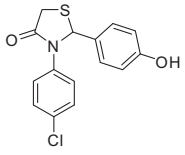
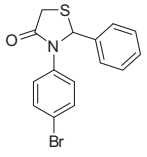
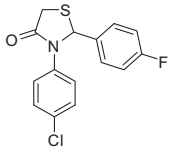
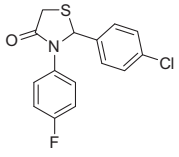
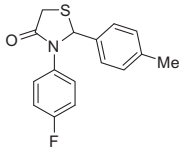
Compounds	Structures	*MTB H37Ra*		*M. bovis BCG*	
		Anti TB IC_{90} (μg/mL)	Anti TB IC_{50} (μg/mL)	Anti TB IC_{90} (μg/mL)	Anti TB IC_{50} (μg/mL)
4a		>30	>30	>30	20.7
4b		>30	>30	>30	>30
4c		24.0	2.2	>30	>30
4d		28.7	17.3	>30	>30
4e		>30	19.8	>30	>30
4f		>30	5.6	>30	>30
4g		>30	>30	>30	>30
4h		>30	4.2	>30	8.7
4i		27.5	6.8	>30	20.9
4j		25.2	8.9	>30	>30
4k		>30	>30	>30	>30
4l		>30	>30	>30	>30

Table 3 (*continued*)

Compounds	Structures	*MTB H37Ra*		*M. bovis BCG*	
		Anti TB IC_{90} (μg/mL)	Anti TB IC_{50} (μg/mL)	Anti TB IC_{90} (μg/mL)	Anti TB IC_{50} (μg/mL)
4m		>30	>30	>30	>30
4n		>30	>30	>30	>30
4o		>30	>30	>30	>30
4p		>30	>30	>30	>30
4q		>30	>30	>30	>30
4r		>30	>30	>30	>30
4s		>30	>30	>30	>30
4t		>30	>30	>30	>30
4u		>30	29.8	>30	>30
RP	–	0.043 ± 0.15	0.0018 ± 0.009	0.041 ± 0.01	0.0016 ± 0.002
INH	–	0.075 ± 0.25	0.0025 ± 0.0007	0.045 ± 0.02	0.0023 ± 0.001

RP: rifampicin; INH: isoniazid.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2016.02.056.

References and notes

1. Isambert, N.; Duque, M. M. S.; Plaquevent, J. C.; Genisson, Y.; Rodriguez, J.; Constantieux, T. *Chem. Soc. Rev.* **2011**, *40*, 1347.
2. Pansare, D. N.; Mulla, N. A.; Pawar, C. D.; Shende, V. R.; Shinde, D. B. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3569.
3. (a) Patel, N. B.; Patel, H. R.; Shaikh, F. M.; Rajani, D. *Med. Chem. Res.* **2014**, *23*, 1360; (b) Tripathi, A. C.; Gupta, S. J.; Fatima, G. N.; Sonar, P. K.; Verma, A.; Saraf, S. K. *Eur. J. Med. Chem.* **2014**, *72*, 52. and references cited therein.
4. Suthar, S. K.; Jaiswal, V.; Lohan, S.; Bansal, S.; Chaudhary, A.; Tiwari, A.; Alex, A. T.; Joesph, A. *Eur. J. Med. Chem.* **2013**, *63*, 589.
5. Murugesan, V.; Tiwari, V. S.; Saxena, R.; Tripathi, R.; Paranjape, R.; Kulkarni, S.; Makwana, N.; Suryawanshi, R.; Katti, S. B. *Bioorg. Med. Chem.* **2011**, *19*, 6919.
6. Bhalgat, C. M.; Darda, P. V.; Bothara, K. G.; Bhandari, S. V.; Gandhi, J.; Ramesh, B. *Eur. J. Med. Chem.* **2014**, *76*, 580.
7. Nikalje, A. P. G.; Shaikh, A. N.; Shaikh, S. I.; Khan, F. A. K.; Sangshetti, J. N.; Shinde, D. B. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5558.
8. Cakir, G.; Kucukguzel, I.; Guhamazumder, R.; Tatar, E.; Manvar, D.; Basu, A.; Patel, B. A.; Zia, J.; Talele, T. T.; Kaushik-Basu, N. *Arch. Pharm. Chem. Life Sci.* **2015**, *348*, 10.
9. Raza, S.; Srivastava, S. P.; Srivastava, D. S.; Srivastava, A. K.; Haq, W.; Katti, S. B. *Eur. J. Med. Chem.* **2013**, *63*, 611.
10. Isloor, A. M.; Sunil, D.; Shetty, P.; Malladi, S.; Pai, K. S. R.; Maliyakkl, N. *Med. Chem. Res.* **2013**, *22*, 758.
11. Jain, A. K.; Vaidya, A.; Ravichandran, V.; Kashaw, S. K.; Agrawal, R. K. *Bioorg. Med. Chem.* **2012**, *20*, 3378. and references cited therein.
12. Kumar, K. S. S.; Hanumappa, A.; Vetrivel, M.; Hegde, M.; Girish, Y. R.; Byregowda, T. R.; Rao, S.; Raghavan, S. C.; Rangappa, K. S. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3616.
13. (a) Pansare, D. N.; Shinde, D. B. *J. Saudi Chem. Soc.*, http://dx.doi.org/10.1016/j.jscs.2015.10.005; (b) Lill, A. P.; Rodl, C. B.; Steinhilber, D.; Stark, H.; Hofmann, B. *Eur. J. Med. Chem.* **2015**, *89*, 503; (c) Chauhan, K.; Sharma, M.; Trivedi, P.; Chaturvedi, V.; Chauhan, P. M. S. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4166; (d) Pansare, D. N.; Shinde, D. B. *Tetrahedron Lett.* **2014**, *55*, 1107; (e) Pansare, D. N.; Shinde, D. B. *Open Chem. J.* **2015**, *2*, 40.
14. (a) Srivastava, S. K.; Srivastava, S. L.; Srivastava, S. D. *J. Indian Chem. Soc.* **2000**, *77*, 104; (b) Srivastava, T.; Haq, W.; Katti, S. B. *Tetrahedron* **2002**, *58*, 7619; (c) Rawal, R. K.; Srivastava, T.; Haq, W.; Katti, S. B. *J. Chem. Res.* **2004**, *5*, 368; (d) Yadav, A. K.; Kumar, M.; Yadav, T.; Jain, R. *Tetrahedron Lett.* **2009**, *50*, 5031; (e) Thakare, M. P.; Kumar, P.; Kumar, N.; Pandey, S. K. *Tetrahedron Lett.* **2014**, *55*, 2463; (f) Pang, H. X.; Hui, Y. H.; Fan, K.; Xing, X. J.; Wu, Y.; Yang, J. H.; Shi, W.; Xie, Z. F. *Chin. Chem. Lett.* **2012**. http://dx.doi.org/10.1016/j.cclet.2015.10.029; (g) Gudurudu, V.; Nguyen, V.; Dalton, J. T.; Miller, D. D. *Synlett* **2004**, 2357; (h) Sadashiva, C. T.; Narendr, J. N.; Chandra, S.; Kavitha, C. V.; Thimmegowda, A.; Subhash, M. N.; Rangappa, K. S. *Eur. J. Med. Chem.* **2009**, *44*, 4848; (i) Kumar, R. C.; Kumar, D. *J. Indian Chem. Soc.* **2002**, *77*, 492; (j) Holmes, C. P.; Chinn, J. P.; Look, G. C.; Gorden, E. M.; Gallop, M. A. *J. Org. Chem.* **1995**, *60*, 7328; (k) Azgomi, N.; Mokhtary, M. *J. Mol. Catal. A: Chem.* **2015**, *398*, 58; (l) Sharma, R.; Veera, G.; Devi, B.; Reddy, K. S.; Reddy, M. V.; Kondapi, A. K.; Bhaskar, C. *Heterocycl. Commun.* **2015**, *21*, 187; (m) Pratap, U. R.; Jawale, D. V.; Bhosle, M. R.; Mane, R. A. *Tetrahedron Lett.* **2011**, *52*, 1689; (n) Prasad, D.; Preetam, A.; Nath, M. *RSC Adv.* **2012**, *2*, 3133.
15. (a) Malla, A. M.; Parveen, M.; Ahmad, F.; Azaz, S.; Alam, M. *RSC Adv.* **2015**, *5*, 19552; (b) Zhou, Z.; Deng, X. *J. Mol. Catal. A: Chem.* **2013**, *367*, 99; (c) Khabazzadeh, H.; Kermani, E. T.; Jazinizadeh, T. *Arab. J. Chem.* **2012**, *5*, 485; (d) Suryawanshi, N. S.; Jain, P.; Singhal, M.; Khan, I. *J. Appl. Chem.* **2012**, *1*, 18; (e) Kermani, E. T.; Khabazzadeh, H.; Jazinizadeh, T. *J. Heterocycl. Chem.* **2011**, *48*, 1192; (f) Rajendran, A.; Raghupathy, D.; Priyadarshini, M. *Int. J. Chem. Technol. Res.* **2011**, *3*, 298; (g) Wang, C.; Zhao, W.; Li, H.; Guo, L. *Green Chem.* **2009**, *11*, 843; (h) Ganeshpure, P. A.; George, G.; Das, J. *J. Mol. Catal. A: Chem.* **2008**, *279*, 182; (i) Jiang, H.; Wang, C.; Li, H.; Wang, Y. *Green Chem.* **2006**, *8*, 1076; (j) Wang, C.; Guo, L.; Li, H.; Wang, Y.; Weng, J.; Wu, L. *Green Chem.* **2006**, *8*, 603; (k) Weng, J.; Wang, C.; Li, H.; Wang, Y. *Green Chem.* **2006**, *8*, 96.
16. Shaikh, M. H.; Subhedar, D. D.; Khan, F. A. K.; Sangshetti, J. N.; Shingate, B. B. *Res. Chem. Inter.*, http://dx.doi.org/10.1007/s11164-015-2348-z.
17. (a) Shaikh M. H.; Subhedar, D. D.; Khan, F. A. K.; Sangshetti, J. N.; Nawale, L.; Arkile, M.; Sarkar, D.; Shingate, B. B. *J. Heterocycl. Chem.*, http://dx.doi.org/10.1002/jhet.2598; (b) Subhedar, D. D.; Shaikh, M. H.; Khan, F. A. K.; Sangshetti, J. N.; Khedkar, V. M.; Shingate, B. B. *New J. Chem.*, http://dx.doi.org/10.1039/c6nj00021e; (c) Shaikh, M. H.; Subhedar, D. D.; Arkile, M.; Khedkar, V. M.; Jadhav, N.; Sarkar, D.; Shingate, B. B. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 561; (d) Shaikh, M. H.; Subhedar, D. D.; Khan, F. A. K.; Sangshetti, J. N.; Shingate, B. B. *Chin. Chem. Lett.* **2016**, *27*, 295; (e) Shaikh, M. H.; Subhedar, D. D.; Nawale, L.; Sarkar, D.; Khan, F. A. K.; Sangshetti, J. N.; Shingate, B. B. *Med. Chem. Commun.* **2015**, *6*, 1104; (f) Shinde, P. V.; Labade, V. B.; Gujar, J. B.; Shingate, B. B.; Shingare, M. S. *Tetrahedron Lett.* **2012**, *53*, 1523; (g) Shinde, P. V.; Labade, V. B.; Shingate, B. B.; Shingare, M. S. *J. Mol. Catal. A: Chem.* **2011**, *336*, 100; (h) Shinde, P. V.; Kategaonkar, A. H.; Shingate, B. B.; Shingare, M. S. *Beilstein J. Org. Chem.* **2011**, *7*, 53; (i) Shinde, P. V.; Kategaonkar, A. H.; Shingate, B. B.; Shingare, M. S. *Tetrahedron Lett.* **2011**, *52*, 2889.
18. (a) Kumar, D.; Sonawane, M.; Pujala, B.; Jain, V. K.; Bhagat, S.; Chakraborti, A. K. *Green Chem.* **2013**, *15*, 2872; (b) Foroughifar, N.; Ebrahimi, S. *Chin. Chem. Lett.* **2013**, *24*, 389.
19. *General procedure for one-pot synthesis of 1,3-thiazolidin-4-ones:* A mixture of anilines (1 mmol), benzaldehydes (1 mmol), thioglycolic acid (1 mmol) and $[Et_3NH][HSO_4]$ 20 mol % was magnetically stirred at 80 °C. The progress of the reaction was monitored by TLC using ethyl acetate/hexane as a solvent system. The reaction mixture was quenched with crushed ice and extracted with ethyl acetate (2 × 25 mL). The organic extracts were washed with brine (2 × 25 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afford the corresponding crude compounds. The obtained crude compounds were recrystallized using ethanol.
20. (a) Khan, A.; Sarkar, S.; Sarkar, D. *Int. J. Antimicrob. Agents* **2008**, *32*, 40; (b) Sarkar, S.; Sarkar, D. *J. Biomol. Screening* **2012**, *17*, 966.
21. Doyen, C. M.; Moshkin, Y. M.; Chalkley, G. E.; Bezstarosti, K.; Demmers, J. A.; Rathke, C.; Renkawitz-Pohl, R.; Verrijzer, C. P. *Cell Rep.* **2003**, *4*, 59.