EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Mechanochemical synthesis of 7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxides via tandem Michael addition-1,3-dipolar cycloaddition and their antibacterial properties

Authors: Zigmee T. Bhutia, Avijit Das, Malabika Biswas, Amrita Chatterjee, and Mainak Banerjee

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701511

Link to VoR: http://dx.doi.org/10.1002/ejoc.201701511

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

Mechanochemical synthesis of 7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxides via tandem Michael addition-1,3-dipolar cycloaddition of aldoximes and evaluation of their antibacterial activities

Zigmee T. Bhutia,[a] Avijit Das,[b] Malabika Biswas,[b] Amrita Chatterjee*[a] and Mainak Banerjee*[a]

Abstract: A solvent-free, green and efficient mechanochemical method for the synthesis of a series of bridged bicyclo aza-sulfone derivatives viz. 7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxides via tandem Michael addition-1,3-dipolar cycloaddition of aldoximes was developed. Mechanochemical grinding/milling facilitates quick formation of aldoximes from corresponding aldehydes and hydroxylamine which upon reaction with divinyl sulfone in a mixer-mill affords 7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide derivatives in good overall yields. The newly synthesized bicyclo aza-sulfone derivatives (**4**) were screened for antibacterial activities. It was found that mostly bicyclo aza-sulfones derived from electron rich aromatic aldehydes inhibit the growth of *Mycobacterium smegmatis* (mc^2-155) and that of aliphatic aldehydes inhibit the growth of *Escherichia coli* (DH5α) in moderate to good effect. However, butyraldehyde derived compound **4r** was found to be very effective against both *M. smegmatis* and *E. coli*. The key advantages of this mechanochemical method are catalyst- and solvent-free condition, shorter reaction time, and the new series of 7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide derivatives are good antibacterial agents against *M. smegmatis* and *E. coli.*

Introduction

1,4-Thiazine-1,1-dioxide (or 4-aza-sulfones) is a common substructure of many biologically active and pharmaceutically important molecules of natural as well as synthetic origin.[1] Compounds containing this moiety exhibit a wide range of biological activities including anti-inflammatory,[1d] antiviral[1e,f] and antibacterial activities[1g,h] (Figure 1). On the other hand, scaffolds like aza-bicyclo[3.2.1]octane[2] and oxa-aza-bicyclo[3.2.1]octane[3] are ubiquitous among various bioactive compounds.[2,3] Of our interest, somewhat complex bridged bicyclic sulfone derivatives, viz. 7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxides are known in the literature[4] but not much is known about their bioactivities. These sulfone derivatives are mainly constructed by tandem Michael addition-1,3-dipolar cycloaddition of oximes, a method separately reported by Griggs[4a-d] and Padwa[4e,f]. While these conventional methods are disadvantageous in terms of use of toxic solvents and high temperature, only one “green method” is available involving reaction in aqueous micellar media.[5]

In the present scenario, most of the large-scale chemical processes use toxic organic solvents for various transformations which account for 80–90% of the waste generated in a typical pharmaceutical/fine chemical processes.[6] In order to achieve

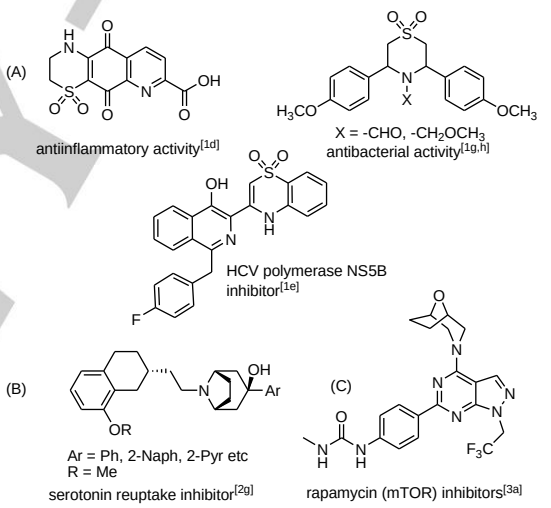
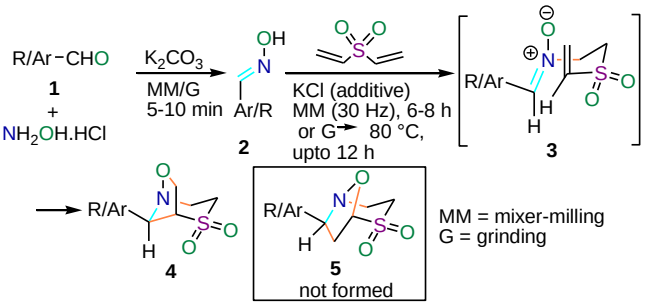


Figure 1. Chemical structures of few relevant bioactive compounds: (A) 1,4-thiazine-1,1-dioxides, (B) one with axa-bicyclo[3,2,1]octane skeleton and (C) one with oxa-axa-bicyclo[3,2,1]octane skeleton.

sustainable and eco-friendly chemical processes, a significant research effort is focused on solvent-free (or solvent-*less*) reactions.[7] In this direction, mechanochemical techniques have gradually become a powerful tool in the paradigm of synthetic organic chemistry.[8] In mechanochemical-organosynthesis the chemical transformations are achieved either by milling in a ball-mill[9,10] or by manual grinding[11,12] in a mortar-pestle. Both methods have gained significant research interests for organic transformations not only for solvent-free conditions but also for time efficiency, cleaner and safer reaction profile, easy handling etc. As a part of our ongoing interests in mechanochemical reactions[13] and nitrone cycloaddition chemistry,[13b,14] we assumed that it is worthwhile to investigate the scope of mechanochemical grinding/milling for the formation of somewhat complex bridged heterobicyclic compounds via tandem Michael

[a] Department of Chemistry, BITS, Pilani, Goa Campus, Goa-403726, India.
[b] Department of Biological Sciences, BITS, Pilani, Goa Campus, Goa- 403726, India.
[*] Fax: +91-832-255-7031; Tel.: +91-832-2580-347 (M.B.), +91-832-2580-320 (A.C.); Email: mainak@goa.bits-pilani.ac.in (M.B.); amrita@goa.bits-pilani.ac.in (A.C.).
Supporting information for this article is given via a link at the end of the document.

addition-1,3-dipolar cycloadditions. We, herein, report an environmentally benign synthetic route to 7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxides (**4**) from various aldehydes and hydroxylamine via in situ formation of aldoximes followed by Michael addition-1,3-dipolar cycloaddition. These compounds were examined for antibacterial activities against acid-fast *Mycobacterium smegmatis*, Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus*.



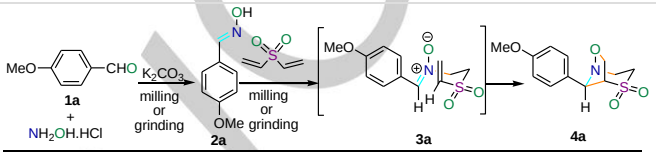
Ar = aromatic: Ph, 4-MeOPh, 4-NO_2Ph etc.
R = alkyl: n-propyl, n-hexyl, n-heptyl etc.

Scheme 1. General scheme for the of synthesis of 7-oxa-4-thia-1-aza bicyclo[3.2.1]octane-4,4-dioxide derivatives (**4**).

Results and Discussion

At the beginning of our studies, the focus was on the optimization of reaction conditions either by grinding in an electrical mortar-pestle (Agate made) or by milling in a mixer-mill (MM400) using 4-methoxybenzaldehyde (**1a**), hydroxylamine hydrochloride and divinyl sulfone in a model reaction. K_2CO_3 was used for the liberation of hydroxylamine from its HCl salt during formation of aldoximes. It was observed that formation of oxime is very fast for both methods. However, electrical grinding under neat condition was not good enough for complete conversion of oxime (**2a**) to intermediate nitrone (**3a**) even after 12 h (Table 1, entry 1). Only presence of a very little amount of product (**4a**) was observed in the reaction mixture after 12 h. Next, liquid-assisted grinding (LAG)[13c,15] by addition of EtOH (0.5 mL per 1 mmol of **1a**) was attempted for the same reaction (Table 1, entry 2). However, no significant change was observed in the course of the reaction. Notably, the addition of solid additives (such as SiO_2, Al_2O_3, KCl etc.) was partly effective in order to get the final compound (**4a**) only in low yields under grinding condition (Table 1, entries 4, 6, 8, 10). In these cases, oximes get converted to nitrones approximately after 6 h but 1,3-dippolar cycloaddition remains sluggish (Table 1, entries 4, 6, 8, 10). On the other hand, milling with a solid additive was found more suitable (Table 1, entry 5, 7, 9, 11) than milling under neat condition (Table 1, entry 3). In case of silica gel (60-120 mesh) as the additive, some amount of aldehyde (**1a**) was isolated. Presumably, acidic silica gel initiates partial hydrolytic decomposition of the aldoxime **2a**, which is the reason for the lower yield of the final product. Although no significant difference was observed in terms of yield of **4a** in the presence of neutral alumina or simple salts like KCl or NaCl, KCl was consider as the additive of choice for further reactions because of easy separation of additive from the product by water wash and for affording marginally better yields than other additives apart from being a side product of the first step. In a separate study, the milling condition was standardized by changing milling frequency, the number of balls and amount of reaction mixture. The best results were obtained by carrying out reactions in a 5 mL jar (stainless steel) with two 7 mm balls for a quantity of 2 mmol of an aldehyde with 5 times w/w of additive and milled at 30 Hz.

Table 1. Optimization of reaction condition for 7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxides.



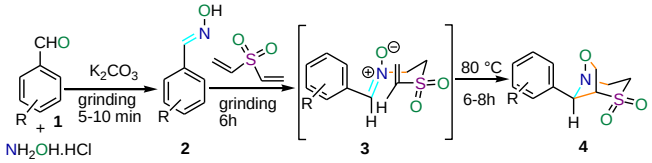
Entry[a]	Solvent/ Additive[b]	Method[c,d]	Time of oxime formation (min)	Time of cycloaddition (h)	% of **3a** isolated[e]	% Yield of **4a**
1	neat	grinding	05	12	55	15
2	EtOH	grinding	05	12	51	20
3	neat	milling	05	12	33	30
4	SiO_2	grinding	10	12	40	20
5	SiO_2	milling	05	6	--	42
6	Al_2O_3 (neutral)	grinding	10	12	38	15
7	Al_2O_3 (neutral)	milling	05	5	--	63
8	KCl	grinding	05	12	35	23
9	KCl	milling	05	6	--	71
10	NaCl	grinding	05	12	34	20
11	NaCl	milling	05	6	--	70

[a] 2 mmol of **1a** was taken for reaction. [b] Additive taken was five time of weight of the aldehyde. [c] Electric grinding at 110 rpm. [d] Mixer milling with 2 balls (7 mm) in 5 ml stainless steel jar at 30 Hz. [e] Nitrone (**3a**) was not detected in TLC for entries 5, 7, 9, 11.

Although grinding in a mortar-pestle at ambient temperature was not promising, attempts were made to use this method for the formation of bridged bicyclo aza-sulfones (**4**) by subsequent heating in a sand-bath. Accordingly, selected aldoximes derived from aromatic aldehydes were ground in the presence of KCl in an electrical mortar-pestle upto 6 h for complete formation of nitrones and the mortar was placed in a sand-bath and heated at 80 °C for several hours with intermittent hand-grinding (Table 2). However, the yield of the desired product (**4**) was below satisfactory level. It was observed that open-air heating generates a complex mixture of side products

(along with **4**) which could not be separated in pure form. However, in some cases (e.g. 4-bromo-benzaldehyde, **1k**), a significant amount of the di-nitrone intermediate was also isolated and was confirmed by ^{1}H NMR. Overall, grinding in mortar-pestle was not found very suitable for the formation of bridged sulfones (**4**). Therefore, further studies were carried out in a Retsch MM400 mixer mill.

Table 2. Synthesis of 8-aryl-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide derivatives by grinding followed by heating.

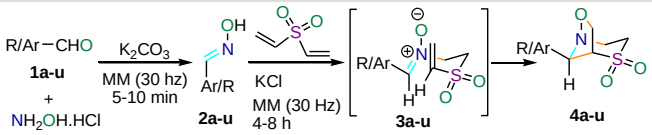


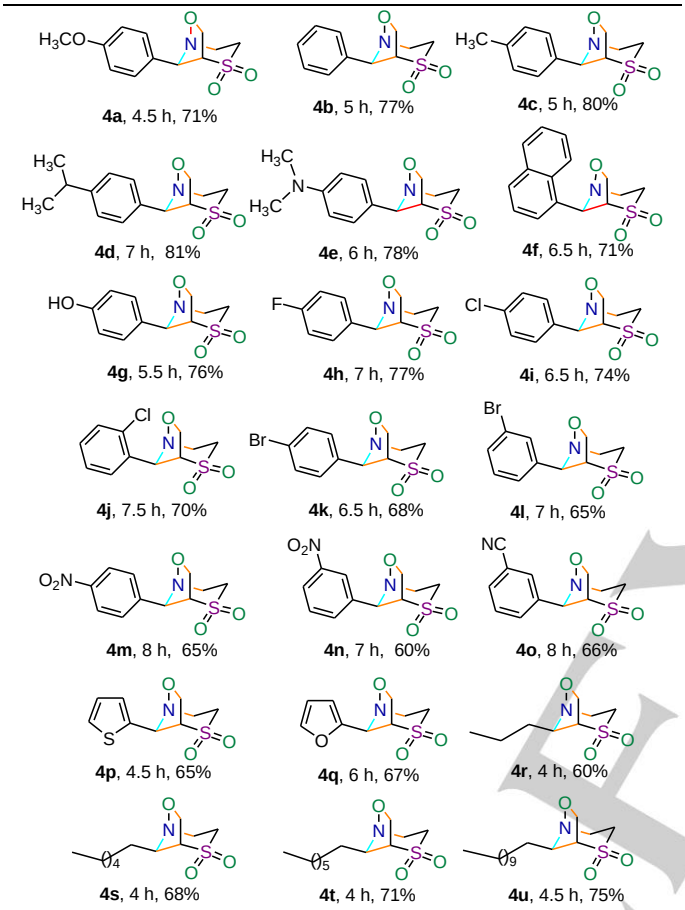
Entry	R (**1**)	Heating time (h)	%Yield[a,b] of **4**
1	**1a**: 4-MeO	6	**4a**: 40
2	**1b**: H	6	**4b**: 38
3	**1h**: 4-F	6	**4h**: 35[c]
4	**1k**: 4-Br	8	**4k**: 35[c]

[a] Grinding in electrical mortar pestle at 110 rpm with KCl (5 times w/w as additive). [b] Isolated yield of **4**. [c] About 15-20 % of dinitrone was also isolated.

The versatility of the mechanochemical method was established by carrying out several reactions under the optimized reaction condition with a series of aromatic and aliphatic aldehydes (**1a-u**) under milling condition (Table 3). Each of the reactions was started by taking an aldehyde, hydroxylamine hydrochloride (1.1 equiv) and K_2CO_3 (1.1 equiv) in a 5 mL stainless steel jar with two stainless steel balls (7 mm dia). The reaction mixture was milled at 30 Hz for 5-10 min. The formation of intermediate aldoximes was monitored by TLC. It often takes just 5 min for quantitative conversion to aldoximes. Subsequently, divinyl sulfone (1.0 equiv) and KCl (5 times w/w of **1**) were added to the reaction mixture and it was further milled at 30 Hz for several hours (Table 3). The reactions afforded 8-aryl/alkyl-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxides (**4**) as the only isolable major product[4a-c] and other possibility i.e. formation of 7-aryl/alkyl-8-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxides (**5**) was not observed. Griggs et al.,[4a-c] Padwa et al.[4e,f] and Hota et al.[5] separately reported that the nitrones (**3**) derived from corresponding aldoximes (**2**) undergo 1,3-dipolar cycloaddition in regio- and stereo-specific manner to afford bridged heterocycles (**4**) only under different reaction conditions (both conventional media and aqueous media). It seems that similar pathway is followed under the mechanochemical condition as well. The progress of the cycloaddition reaction was monitored by TLC at regular intervals. It was observed that the conversion of aldoximes (**2a-u**) to the bridged aza-sulfones (**4a-u**) via formation of intermediate nitrone (**3**) is facile in terms of yields (60-80%) and reaction time (4-8 h). All 8-aryl/alkyl-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxides (**4**) were thoroughly characterized by ^{1}H NMR, ^{13}C NMR, ESI-MS and CHN analysis. The spectra were in good agreement with the reported values of the known compounds.[4a-c,e,f,5] The appearance of a doublet at around δ 4.5 ppm in ^{1}H NMR (peak of exo-H at C-6) and not in the range δ 2.4-2.7 ppm clearly indicates the presence of $–OCH_2–$ (and not aliphatic $–CH_2–$) affirming formation of 7-oxa-bicyclo[3.2.1]octane ring system. In ^{13}C NMR corresponding carbon peak appeared at δ 68-70 ppm and not at the aliphatic zone. Similarly, for aldoximes derived from aromatic aldehydes (e.g. **4a**, **4b**, **4m** and others) the benzylic proton (at C-8) appeared as a sharp singlet at around δ 5.1-5.3 ppm similar to what was observed by Griggs and co-workers[4a,b] during their study which unequivocally confirms the formation of the expected stereoisomer **4**. All the other peaks matched with the structure of **4** (and not **5**). In general, the method worked well with a variety of aliphatic, aromatic and heteroaromatic aldehydes with similar efficacy. It was noticed that the presence of electron donating group (EDG) (**4a**, **4c-f**, Table 3) or electron withdrawing group (EWG) (**4h-n**, Table 3) in the aromatic ring does not have significant effect in the rate of the reaction under mechanochemical condition. While it may be presumed that the presence of EDG is helpful for Michael addition step, 1,3-cycloaddtion determines overall rate of the reaction which is indifferent by the presence of any substituent in the aromatic ring. Even the reactions involving aliphatic aldehydes with not much substituent effect took 4-5 h for completion (**4r-u**, Table 3). However, the results indicated that the yields of the final product may vary based on the substituents present in the aromatic ring of the aldoximes derived from aromatic aldehydes. The aldoximes with greater electron-density produced the final product in higher yield (**4a**, **4c-g**, Table 3) than the aldoximes with lower electron-density (**4k-o**, Table 3). Presumably, the electron donation ability of the substituents in the aromatic ring helps to stabilize the intermediate nitrone (**3**) reducing the possibility of some other side reactions. Noticeably, relatively unstable heteroaromatic aldehydes (such as furfuraldehyde) participated equally to afford final product in good yields. The mechanochemical method was found effective for several aliphatic aldehydes as starting materials producing the desired product in comparable yields in similar time period (**4r-u**, Table 3). From the above results the following mechanistic pathway may be proposed (Figure 2). Mechanochemical grinding/milling allows spontaneous condensation of aldehydes and hydroxylamine. The corresponding aldoximes (**2**) get converted to nitrones by the nucleophilic attack of oxime nitrogen to the Michael receptor, 1,4-diene (here divinyl sulfone). The nitrone may remain in two pre-transition state conformers (**3A** or **3B**). Presumably, kinetic selection prefers conformer **3A** over other with better non-bonded interactions in the transition state(s), which precedes cycloaddition. Moreover, conformer **3B** may experience some torsional strain between $\mathbf{H_A}$ and $\mathbf{H_B}$ (Figure 2). Finally, a comparison was drawn in between the existing methods including (a) conventional reaction media reported by Griggs et al.,[4a] (b) micellar media by Hota et al.[5] and the current

Table 3. Mechanochemical synthesis of 8-aryl/alkyl-7-Oxa-4-thia-1-aza bicyclo[3.2.1]octane-4,4-dioxide derivatives.





All yields refer to isolated product.

Table 4. A comparison of formation of **4b** by various methods

Method	Solvent	Catalyst/ auxiliary	Condition	Yield (%)	Ref.
organic media (Grigg's method)	Xylene	none	140 °C, 6 h	60[a]	4a
micellar media (Hota's method)	water	DBSA (10 mol%)	55 °C,16 h	57[a]	5
mechanochemical (current work)	solvent-free	KCl	MM (30 Hz), 5 h	77[b]	-

[a] Isolated yield of **4b** for the reaction between oxime (**2b**) and divinyl sulfone.
[b] Isolated yield (of **4b**) over two-steps starting from aldehyde (**1b**).

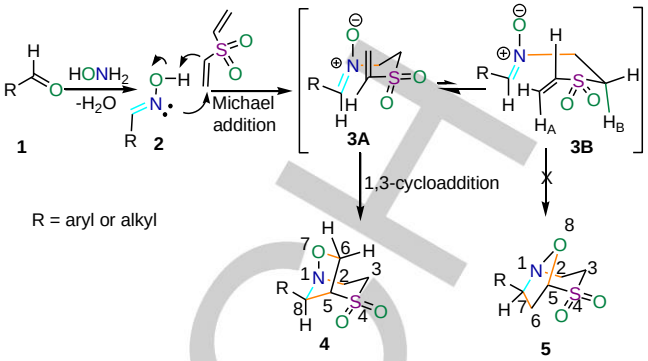


Figure 2. Possible mechanistic pathway for synthesis of 7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxides.

mechanochemical method in terms of reaction condition and yields of a common product, **4b** (Table 4). It is clear from table 4 that the mechanochemical method is far superior to other methods in terms of yield (of **4b**) and the rate of the reaction. However, a direct comparison cannot be drawn as the current method involves in-situ oxime formation followed by cycloaddition, whereas, for other methods the information is based on Michael addition-1,3-dipolar cycloaddition step only.

In vitro antibacterial study

In modern days, bacterial pathogenic diseases like tuberculosis, syphilis and anthrax cause major health problems to the humans. As bacteria develop drug resistance synthesis and screening of new antibacterial agents are essential.[16] At first, for in vitro antibacterial activity study, the synthesized 8-aryl/alkyl-7-Oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide derivatives (**4**) were screened for the inhibition zones against the bacteria by spot plate technique.[17] Selected compounds derived from aromatic, heteroaromatic and aliphatic aldehydes were treated with different categories of bacterial strains viz. acid fast *Mycobacterium smegmatis* (mc^2155), Gram-positive *Staphylococcus aureus* (RN4220) and Gram-negative *Escherichia coli* (DH5α) with Kanamycin as a standard drug. Subsequently, more compounds of similar classes were tested based on the initial results. The compounds which showed strong inhibition zones were tested further for minimum inhibitory concentrations (MICs)[18] by broth microdilution method. The initial spot plate study showed that bridged bicyclo aza-sulfones derived from aromatic aldehydes with electron donating groups such as **4a**, **4g** and heteroaromatic aldehydes such as **4q** showed better inhibition activity against *M. smegmatis* (Table 5). Whereas, compounds (**4**) derived from aromatic aldehydes with strong electron withdrawing groups are not potential inhibitors of *M. smegmatis*. However, this cannot be generalized as some compounds with alkyl chain instead of aromatic rings at C-8 (e.g. **4r**) showed good activities. Notably, only bridged sulfones with alkyl chain at C-8 (**4r-u**) were found to inhibit *E. coli* with the best antibacterial agent being **4s** with MIC 15.6 µg mL-1 (Table 5).

However, these compounds failed to show any appreciable bioactivity against *S aureus*. Based on the initial results, SAR studies may be envisaged on 7-oxa-4-thia-1-aza-bicyclo[3.2.1]-octane-4,4-dioxides in future.

Table 5. MICs of various bicyclo aza-sulfones (**4**) against *Mycobacterium smegmatis* and *Escherichia coli.*

Compounds	M. smegmatis (in µL/mL)	E. coli (in µL/mL)
4a	31.2	-
4b	250	-
4g	62.5	-
4k	250	-
4q	62.5	-
4r	62.5	31.2
4s	-	15.6
4t	-	31.2
4u	-	125

Conclusion

In conclusion, we have developed a catalyst- and solvent-free, cost-effective mechanochemical route for the synthesis of a variety of 7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide derivatives involving tandem Michael addition-1,3-dipolar cycloaddition of aldoximes. Mechanochemical grinding or milling promotes condensation of aldehydes and hydroxylamine within few min. The corresponding aldoximes react with divinyl sulfone in a mixer-mill in-situ to affords 7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide derivatives (**4**) in good overall yields. The methodology works fine with aliphatic, aromatic and heteroaromatic aldehydes. Presence of electron withdrawing and electron donating substituents in the aromatic ring of aldoxime is insignificant in terms of yields and reaction time. However, grinding in an electrical mortar-pestle was found not suitable to get the final product in decent yields. The newly synthesized bridged bicyclo aza sulfone derivatives (**4**) were screened for antibacterial activities against acid-fast *Mycobacterium smegmatis* (mc^2155), Gram-negative *Escherichia coli* (DH5α) and Gram-positive *Staphylococcus aureus* (RN4220). It was found that mostly sulfones derived from aromatic aldehydes with electron donating groups inhibit growth of *M. smegmatis* and that of aliphatic aldehydes inhibit growth of *E. coli* in moderate to good effects. However, these compounds do not show appreciable bioactivity against *S. aureus*. The simplicity of this synthetic process and the use of environmentally benign reaction conditions make this mechanochemical method for bridged bicyclo aza-sulfone derivatives a sustainable alternative to existing synthetic methodologies. Furthermore, several of these 7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxides are reasonably good antibacterial agents against *M. smegmatis* and *E. coli.*

Experimental Section

General information: All reagents were purchased from commercial sources and were used without further purification. All solvents used were of research grade. The milling experiments were performed in Retsch MM-400 and grinding by electrical mortar pestle (Agate made, Scientech instruments, India). The reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel aluminium plates (60F-254) using UV light (254 nm) for visualization. Column chromatography was performed using 60-120 mesh silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance (400 MHz) with tetramethylsilane (TMS) or solvent peak as internal standard. The chemical shifts are reported in parts per million (δ) units. Mass spectra were recorded on Agilent Technologies 6460 triple quard LC/MS using ESI as ion source. IR spectra were recorded in KBr pellets with IR Affinity 1, Shimadzu. CHN data were recorded using Vario MICRO elementar CHNS analyzer.

Method for antibacterial activity screening: The agar diffusion method[17] was employed for analysing the antibacterial effect of the synthesized compounds against *Escherichia coli* (DH5α), *Staphylococcus aureus* (RN4220) and *Mycobacterium smegmatis* (mc^2155). 1.5% Agar powder was mixed with the respective selective media, luria bertani broth (Hi-Media) for *Escherichia coli*, BACTO tryptic soy broth (Becton, Dickinson and Company) for *Staphylococcus aureus* and Middlebrook 7H9 broth base (HiMedia) for *Mycobacterium smegmatis*, autoclaved and poured onto sterile Petri dishes. The respective media were finally inoculated with freshly grown bacterial cultures. Meanwhile, all the synthesized compounds were dissolved in DMSO and 5 µL solution of each compound was spotted on the inoculated plates. The spot tested plates were incubated at 37 °C for 18 h for *E. coli* and *S. aureus* and 48 h for *M. smegmatis*. DMSO was also screened for anti-bacterial effect in the same way. The compounds which were found to produce a zone of inhibition were further screened for their antibacterial activity by Broth Micro dilution method for the determination of minimum inhibitory concentrations (MICs).[18] 0.1 mL of the respective liquid media was added to each of the 96 wells of a sterile microtiter plate. Two columns were kept as negative controls: (a) broth only and (b) broth and compound. Two fold dilutions of each compound were made in the wells, thus a plate contained 0.98–500 µg/mL of different compounds and of kanamycin (positive control). The inoculum was adjusted to McFarland 0.1 turbidity standard, and further diluted to the ratio of 1:20. Each well was inoculated with 10 µL of the prepared inoculum and the plates were incubated at 37 °C for respective incubation time. Resazurin was added to the wells at the end of the respective incubation period and incubated for another 3 h to visualise the viability of the bacterial cells. All the experiment was repeated thrice for better reproducibility of the data.

General procedure for the mechanosynthesis of bicyclo aza-sulfones: synthesis of 8-(4-methoxyphenyl)-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4a)[4a]

A 5 mL stainless steel milling vessel was charged with two steel balls (7 mm dia.), **1a** (212 mg, 2 mmol), hydroxylammonium chloride (139 mg, 2.2 mmol) and K_2CO_3 (276 mg, 2.2 mmol). The vessel was closed and milled at 30 Hz for 5 min for aldoximes formation. Divinyl sulfone (236 mg,

2 mmol) and KCl (1.06 gm) were added and the reaction mixture was milled further for the time given in Table 3. The crude product was triturated with a biphasic solution of EtOAc (10 mL) and water (20 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (2 x 10 mL). The organic fractions were combined, washed with brine solution and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography (silica gel, 60-120 mesh). Light yellow solid; yield 71% (eluent 5% MeOH in $CHCl_3$); m.p. 152-153 °C (lit. m.p. 155-156 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.06-3.16 (m, 1H), 3.39-3.49 (m, 2H), 3.77-3.93 (m, 3H), 3.83 (s, 3H), 4.52 (d, *J* = 9.2 Hz, 1H), 5.13 (s, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 45.9, 53.5, 55.3, 68.2, 69.3, 70.2, 114.3, 126.8, 128.5, 159.4; IR (KBr): 3072, 2994, 2886, 2839, 1614, 1516, 1313, 1177, 1121, 970 cm^{-1}; ESI-MS: *m/z* 270 $[M + H]^+$; Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20; S, 11.91. Found: C, 53.75; H, 5.64; N, 5.16; S, 11.92.

8-Phenyl-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4b):[4a,5] White solid; yield 77% (eluent 5% MeOH in $CHCl_3$); m.p. 166-168 °C (lit. m.p. 170 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.06-3.17 (m, 1H), 3.44 (ABq, J_{AB} = 13.2 Hz, 2H), 3.77-3.91 (m, 3H), 4.51 (d, *J* = 8.8 Hz, 1H), 5.16 (s, 1H), 7.30-7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 46.0, 53.5, 68.2, 69.2, 70.6, 125.6, 128.2, 128.9, 136.4; IR (KBr): 3063, 2994, 2887, 1605, 1452, 1313, 1211, 1166, 1121, 970 cm^{-1}; ESI-MS: *m/z* 240 $[M + H]^+$; Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85; S, 13.40. Found: C, 55.32; H, 5.45; N, 5.79; S, 13.47.

8-(4-Methylphenyl)-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4c): Off white solid; yield 80% (eluent 5% MeOH in $CHCl_3$); m.p. 180-182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.35 (s, 3H), 3.05-3.14 (m, 1H), 3.43 (ABq, J_{AB} = 12.8 Hz, 2H), 3.76-3.91 (m, 3H), 4.48-4.52 (m, 1H), 5.15 (s, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.1, 46.0, 53.5, 68.2, 69.3, 70.5, 125.5, 129.6, 133.5, 138.0; IR (KBr): 3042, 2941, 2897, 1516, 1409, 1319, 1290, 1221, 1117, 974 cm^{-1}; ESI-MS: *m/z* 254 $[M + H]^+$; Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53; S, 12.66. Found: C, 57.18; H, 6.04; N, 5.48; S, 12.59.

8-(4-Isopropylphenyl)-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4d): White solid, yield 81% (eluent 4% MeOH in $CHCl_3$); m.p. 232-234 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.26 (d, *J* = 7.2 Hz, 6H), 2.92 (sep, *J* = 7.2 Hz, 1H), 3.06-3.16 (m, 1H), 3.39-3.49 (m, 2H), 3.77-3.86 (m, 1H), 3.91-3.94 (m, 2H), 4.50-4.54 (m, 1H), 5.13 (s, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 23.93, 23.94, 33.8, 46.0, 53.6, 68.2, 69.2, 70.5, 125.5, 127.0, 133.8, 148.9; IR (KBr): 3035, 2957, 2887, 1514, 1418, 1312, 1240, 1123, 972 cm^{-1}; ESI-MS: *m/z* 282 $[M + H]^+$; Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98; S, 11.40. Found: C, 59.89; H, 6.84; N, 4.95; S, 11.34.

8-(4-Dimethylaminophenyl)-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4e): White solid, yield 78% (eluent 5% MeOH in $CHCl_3$); m.p. 208-210 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.95 (s, 6H), 2.99-3.11 (m, 1H), 3.36-3.45 (m, 2H), 3.74-3.86 (m, 2H), 3.93 (dd, J_1 = 5.6 Hz, J_2 = 9.6 Hz, 1H), 4.48 (d, *J* = 9.6 Hz, 1H), 5.07 (s, 1H), 6.69-6.72 (m, 2H), 7.23-7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 40.5, 45.9, 53.6, 68.2, 69.2, 70.4, 112.5, 123.8, 126.3, 150.2; IR (KBr): 3011, 2953, 2803, 1616, 1526. 1358, 1221, 1123, 972 cm^{-1}; ESI-MS: *m/z* 283 $[M + H]^+$; Anal. Calcd for $C_{13}H_{18}N_2O_3S$: C, 55.30; H, 6.43; N, 9.92; S, 11.36. Found: C, 55.36; H, 6.48; N, 9.86; S, 11.44.

8-Naphthayl-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4f):[4e] Off white solid; yield 71% (eluent 5% MeOH in $CHCl_3$); m.p. 146-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.22-3.29 (m, 1H), 3.52-3.64 (m, 2H), 3.88-4.03 (m, 3H), 4.57 (d, *J* = 9.6 Hz, 1H), 5.81 (s, 1H), 7.50-7.67 (m, 3H), 7.82-7.94 (m, 3H), 8.10 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 46.4, 54.2, 68.3, 68.7, 69.1, 122.4, 124.1, 125.6, 126.0, 127.2, 128.9, 129.2, 129.3, 131.1, 133.8; IR (KBr): 3057, 2945, 2891, 1597, 1510, 1398, 1321, 1213, 1121, 972 cm^{-1}; ESI-MS: *m/z* 290 $[M + H]^+$; Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84; S, 11.08. Found: C, 62.29; H, 5.21; N, 4.79; S, 11.09.

8-(4-Hydroxyphenyl)-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4g): White solid; yield 76% (eluent 5% MeOH in $CHCl_3$); m.p. 210-212 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.26-3.46 (m, 4H), 3.52-3.61 (m, 1H), 3.74 (dd, J_1 = 6.0 Hz, J_2 = 9.6 Hz, 1H), 4.42 (d, *J* = 9.6 Hz, 1H), 5.00 (s, 1H), 6.74 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 9.41 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 45.7, 53.4, 68.1, 68.4, 70.0, 115.6, 127.5, 128.0, 157.2; IR (KBr): 3391, 2951, 2895, 1614, 1520, 1454, 1317, 1290, 1233, 1119, 970 cm^{-1}; ESI-MS: *m/z* 256 $[M + H]^+$; Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49; S, 12.56. Found: C, 51.66; H, 5.18; N, 5.54; S, 12.48.

8-(4-Fluorophenyl)-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4h): Off white solid; yield 77% (eluent 5% MeOH in $CHCl_3$); m.p. 206-208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.06-3.15 (m, 1H), 3.38-3.47 (m, 2H), 3.76-3.89 (m, 3H), 4.50 (d, *J* = 9.2 Hz, 1H), 5.13 (s, 1H), 7.05-7.11 (m, 2H), 7.36-7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 45.9, 53.5, 68.2, 69.2, 70.1, 115.9 (d, *J* = 21.6 Hz), 127.5 (d, *J* = 8.1 Hz), 132.2 (d, *J* = 3.2 Hz), 162.5 (d, *J* = 245.7 Hz); IR (KBr): 3053, 2968, 2887, 1611, 1512, 1404, 1315, 1238, 1121, 972 cm^{-1}; ESI-MS: *m/z* 258 $[M + H]^+$; Anal. Calcd for $C_{11}H_{12}FNO_3S$: C, 51.35; H, 4.70; N, 5.44; S, 12.46. Found: C, 51.45; H, 4.67; N, 5.41; S, 12.38.

8-(4-Chlorophenyl)-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4i): Off white solid; yield 74% (eluent 5% MeOH in $CHCl_3$); m.p. 168-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.07-3.17 (m, 1H), 3.43 (ABq, J_{AB} = 13.0 Hz, 2H), 3.77-3.90 (m, 3H), 4.52 (d, *J* = 9.6 Hz, 1H), 5.13 (s, 1H), 7.35-7.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 45.9, 53.4, 68.2, 69.1, 70.1, 127.1, 129.1, 134.2, 134.9; IR (KBr): 3061, 2949, 2887, 1493, 1404, 1315, 1296, 1221, 1123, 972 cm^{-1}; ESI-MS: *m/z* 274 $[M + H]^+$; Anal. Calcd for $C_{11}H_{12}ClNO_3S$: C, 48.26; H, 4.42; N, 5.12; S, 11.71. Found: C, 48.32; H, 4.39; N, 5.11; S, 11.69.

8-(2-Chlorophenyl)-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4j): Light brown solid; yield 70% (eluent 5% MeOH in $CHCl_3$); m.p. 140-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.10-3.20 (m, 1H), 3.43-3.52 (m, 2H), 3.77-3.89 (m, 2H), 4.02 (dd, J_1 = 2.8 Hz, J_2 = 5.6 Hz, 1H), 4.53 (d, *J* = 9.6 Hz, 1H), 5.35 (s, 1H), 7.28-7.42 (m, 3H), 7.65-7.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 46.3, 53.7, 67.8, 68.1, 69.2, 127.4, 128.1, 129.7, 129.8, 131.7, 133.8; IR (KBr): 3067, 2945, 2893, 1474, 1441, 1319, 1207, 1123, 974 cm^{-1}; ESI-MS: *m/z* 274 $[M + H]^+$; Anal. Calcd for $C_{11}H_{12}ClNO_3S$: C, 48.26; H, 4.42; N, 5.12; S, 11.71. Found: C, 48.34; H, 4.47; N, 5.09; S, 11.80.

8-(4-Bromophenyl)-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4k): Off white solid; yield 68% (eluent 5% MeOH in $CHCl_3$); m.p. 206-208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.08-3.17 (m, 1H), 3.44 (ABq, J_{AB} = 13.2 Hz, 2H), 3.78-3.90 (m, 3H), 4.53 (d, *J* = 8.8 Hz, 1H), 5.12 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 45.9, 53.4, 68.2, 69.0, 70.1, 122.3, 127.5, 132.1, 135.4; IR (KBr): 3051, 2988, 2897, 1498, 1400, 1317, 1294, 1211, 1123, 974 cm^{-1}; ESI-MS: *m/z* 318 $[M + H]^+$ (for ^{79}Br), 320 $[M + H]^+$ (for ^{81}Br); Anal. Calcd for $C_{11}H_{12}BrNO_3S$: C, 41.52; H, 3.80; N, 4.40; S, 10.08. Found: C, 41.53; H, 3.76; N, 4.36; S, 10.06.

8-(3-Bromophenyl)-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4l): Off white solid; yield 65% (eluent 5 % MeOH in $CHCl_3$) m.p. 200-202 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.09-3.19 (m, 1H), 3.38-3.49 (m, 2H), 3.76-3.91 (m, 3H), 4.51 (d, *J* = 9.6 Hz, 1H), 5.12 (s, 1H), 7.24-7.28 (m, 1H), 7.36-7.38 (m, 1H), 7.46 (d, *J* = 8.0 Hz, 1 H), 7.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 45.9, 53.4, 68.2, 69.0, 70.0, 123.1, 124.2, 128.9, 130.5, 131.4, 138.5; IR (KBr): 3082, 2965, 2895, 1566, 1474, 1317, 1223, 1123, 972 cm^{-1}; ESI-MS: *m/z* 318 $[M + H]^+$ (for ^{79}Br), 320 $[M + H]^+$ (for ^{81}Br); Anal. Calcd for $C_{11}H_{12}BrNO_3S$: C, 41.52; H, 3.80; N, 4.40; 10.08. Found: C, 41.43; H, 3.84; N, 4.36; 10.14.

8-(4-Nitrophenyl)-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4m):[4a,5] Pale yellow solid; yield 65% (eluent 5% MeOH in $CHCl_3$); m.p. 236-238 °C (lit. m.p. 240 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.35-3.37 (m, 1H), 3.43-3.53 (m, 2H), 3.62-3.69 (m, 2H), 4.48 (d, *J* = 10.0 Hz, 1H), 4.72 (dd, J_1 = 2.8 Hz, J_2 = 5.6 Hz, 1H), 5.34 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 8.22-8.25 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 45.6, 53.2, 67.6, 68.4, 69.8, 124.0, 128.0, 145.1, 147.4; IR (KBr): 3111, 2972, 2845, 1604, 1516, 1419, 1350, 1231, 1123, 974 cm^{-1}; ESI-MS: *m/z* 285 $[M + H]^+$; Anal. Calcd for $C_{11}H_{12}N_2O_5S$: C, 46.47; H, 4.25; N, 9.85; S, 11.28. Found: C, 46.56; H, 4.19; N, 9.78; S, 11.19.

8-(3-Nitrophenyl)-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4n): Pale yellow solid; yield 60% (eluent 5% MeOH in $CHCl_3$); m.p. 184-186 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.35-3.37 (m, 1H), 3.44-3.53 (m, 2H), 3.63-3.72 (m, 2H), 4.48 (d, *J* = 10 Hz, 1H), 4.79 (dd, J_1 = 2.8 Hz, J_2 = 5.6 Hz, 1H), 5.34 (s, 1H), 7.67-7.71 (m, 1H), 7.91-7.94 (m, 1H), 8.17-8.19 (m, 1H), 8.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 45.6, 53.2, 67.6, 68.5, 69.5, 121.6, 123.1, 130.5, 133.3, 139.9, 148.4; IR (KBr): 3071, 2990, 2897, 1528, 1354, 1313, 1223, 1123, 927 cm^{-1}; ESI-MS: *m/z* 285 $[M + H]^+$; Anal. Calcd for $C_{11}H_{12}N_2O_5S$: C, 46.47; H, 4.25; N, 9.85; S, 11.28. Found: C, 46.37; H, 4.30; N, 9.90; S, 11.19.

8-(3-Cyanophenyl)-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4o): Light yellow solid; yield 66% (eluent 5% MeOH in $CHCl_3$); m.p. 234-236 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.10-3.19 (m, 1H), 3.40-3.52 (m, 3H), 3.73-3.85 (m, 2H), 4.53 (d, *J* = 8.8 Hz, 1H), 5.19 (s, 1H), 7.60-7.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 45.9, 53.4, 68.2, 68.9, 70.2, 112.4, 118.3, 126.7, 132.8, 141.4; IR (KBr): 3048, 2953, 2893, 2228, 1609, 1406, 1314, 1220, 1121, 974 cm^{-1}; ESI-MS: *m/z* 265 $[M + H]^+$; Anal. Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60; S, 12.13. Found: C, 54.44; H, 4.59; N, 10.51; S, 12.05.

8-Thiophene-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4p): Off white solid; yield 65% (eluent 5% MeOH in $CHCl_3$); m.p. 202-204°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.08-3.16 (m, 1H), 3.41-3.53 (m, 2H), 3.76-3.84 (m, 1H), 4.03 (dd, J_1 = 2.8 Hz, J_2 = 5.6 Hz, 1H), 4.17 (dd, J_1 = 5.6 Hz, J_2 = 9.6 Hz 1H), 4.57 (d, *J* = 9.6 Hz, 1H), 5.38 (s, 1H), 7.00-7.06 (m, 2H), 7.31 (*J* = 4.4 Hz, 1H); ^{13}C NMR [100 MHz, DMSO-d_6 in $CDCl_3$ (1:1)]: δ (ppm) 50.5, 58.1, 72.8, 73.2, 73.5, 129.1, 130.5, 131.8, 144.8; IR (KBr): 3096, 2953, 2891, 1474, 1445, 1310, 1238, 1219, 1123, 970 cm^{-1}; ESI-MS: *m/z* 246 $[M + H]^+$; Anal. Calcd for $C_9H_{11}NO_3S_2$: C, 44.06; H, 4.52; N, 5.71; S, 26.14. Found: C, 44.14; H, 4.47; N, 5.68; S, 26.05.

8-Furan-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4q): Pale yellow solid; yield 67% (eluent 5% MeOH in $CHCl_3$); m.p. 152-154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.07-3.18 (m, 1H), 3.41-3.50 (m, 2H), 3.72-3.81 (m, 1H), 4.13 (dd, J_1 = 2.8 Hz, J_2 = 6.0 Hz, 1H), 4.25 (dd, J_1 = 6.0 Hz, J_2 = 9.6 Hz, 1H), 4.59 (d, *J* = 9.6 Hz, 1H), 5.19 (s, 1H), 6.39-6.41 (m, 2H) 7.40 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 46.0, 53.5, 66.38, 66.44, 69.3, 108.0, 110.8, 142.7, 149.1; IR (KBr): 3136, 2980, 2899, 1601, 1508, 1400, 1325, 1227, 1126, 970 cm^{-1}; ESI-MS: *m/z* 230 $[M + H]^+$; Anal. Calcd for $C_9H_{11}NO_4S$: C, 47.15; H, 4.84; N, 6.11; S, 13.99. Found: C, 47.08; H, 4.86; N, 6.07; S, 13.89.

8-Propyl-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4r):[5] White solid; yield 60% (eluent 3% MeOH in $CHCl_3$); m.p. 109-111 °C (lit. m.p. 115 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.98 (t, *J* = 7.2 Hz, 3H), 1.27-1.59 (m, 4H), 3.00-3.05 (m, 1H), 3.27-3.36 (m, 2H), 3.62-3.69 (m, 2H), 3.92-3.95 (m, 1H), 4.17 (dd, J_1 = 5.6 Hz, J_2 = 9.6 Hz, 1H), 4.52 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.6, 19.3, 33.8, 45.9, 53.6, 67.0, 68.8, 68.9; IR (KBr): 2972, 2866, 1460, 1325, 1217, 1176, 1121, 1082, 964, 821 cm^{-1}; ESI-MS: *m/z* 206 $[M + H]^+$; Anal. Calcd for $C_8H_{15}NO_3S$: C, 46.81; H, 7.37; N, 6.82; S, 15.62. Found: C, 46.92; H, 7.39; N, 6.88; S, 15.56.

8-Hexyl-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4s): Off white solid; yield 68% (eluent 3% MeOH in $CHCl_3$); m.p. 89-91 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.88 (t, *J* = 6.8 Hz, 3H), 1.28-1.40 (m, 8H), 1.50-1.54 (m, 2H), 2.98-3.02 (m, 1H), 3.20-3.36 (m, 2H), 3.61-3.66 (m, 2H), 3.86-3.89 (m, 1H), 4.13 (dd, J_1 = 6.0 Hz, J_2 = 9.6 Hz, 1H), 4.48 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.0, 22.5, 26.0, 28.8, 31.6, 31.9, 45.9, 53.6, 67.0, 68.8, 69.1; IR (KBr): 2954, 2928, 2857, 1466, 1329, 1278, 1121, 959 cm^{-1}; ESI-MS: *m/z* 248 $[M + H]^+$; Anal. Calcd for $C_{11}H_{21}NO_3S$: C, 53.41; H, 8.56; N, 5.66; S, 12.96. Found: C, 53.29; H, 8.60; N, 5.61; S, 12.88.

8-Heptyl-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4t): Off white solid; yield 71% (eluent 3% MeOH in $CHCl_3$); m.p. 85-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.88 (t, *J* = 6.4 Hz, 3H), 1.23-1.38 (m, 10H), 1.52-1.57 (m, 2H), 2.97-3.02 (m, 1H), 3.20-3.36 (m, 2H), 3.60-3.65 (m, 2H), 3.86-3.89 (m, 1H), 4.14 (dd, J_1 = 6.0 Hz, J_2 = 10.0 Hz, 1H), 4.82 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.1, 22.6, 26.1, 29.08, 31.7, 31,9, 45.9, 53.6, 66.9, 68.8, 69.1; IR (KBr): 2961, 2922, 2857, 1466, 1331, 1277, 1122, 961 cm^{-1}; ESI-MS: *m/z* 262 $[M + H]^+$; Anal. Calcd for $C_{12}H_{23}NO_3S$: C, 55.14; H, 8.87; N, 5.36; S, 12.27. Found: C, 55.25; H, 8.92; N, 5.38; S, 12.20.

8-Undecanyl-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxide (4u): Off white solid; yield 75% (eluent 3% MeOH in $CHCl_3$); m.p. 90-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.89 (t, *J* = 7.2 Hz, 3H), 1.20-1.42 (m, 18H), 1.50-1.58 (m, 2H), 2.99-3.06 (m, 1H), 3.21-3.38 (m, 2H), 3.61-3.67 (m, 2H), 3.89 (dd, J_1 = 5.6 Hz, J_2 = 8.4 Hz, 1H), 4.15 (dd, J_1 = 5.8 Hz, J_2 = 9.6 Hz, 1H), 4.49 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.1, 22.7, 26.1, 29.1, 29.27, 29.33, 29.43, 29.48, 29.55, 29.60, 31.9, 45.9, 53.6, 67.0, 68.8, 69.2; IR (KBr): 2955, 2920, 2851, 1472, 1327, 1287, 1119, 961 cm^{-1}; ESI-MS: *m/z* 318 $[M + H]^+$; Anal. Calcd for $C_{16}H_{31}NO_3S$: C, 60.53; H, 9.84; N, 4.41; S, 10.10. Found: C, 60.43; H, 9.86; N, 4.40; S, 10.05.

Acknowledgments

M. B. thanks DST-SERB (project No. EMR/2016/002253) for financial support and Z. T. B thanks DST-INSPIRE for INSPIRE Fellowship.

Keywords: Mechanochemistry, Solvent-free synthesis, Tandem reaction, Regio- and stereo-specific cycloaddition, Antibacterial activity.

1. a) C. Brown, R. M. Davidson, *Advances in Heterocyclic Chemistry,* ed. A. R. Kartrizky, Academic Press, London, **1985**, *38*, 135–176; b) A. Aiello, E. Fattorusso, P. Luciano, M. Menna, M. A. Calzado, E. Muñoz, F. Bonadies, M. Guiso, M. F. Sanasi, G. Cocco, R. Nicoletti, *Bioorg. Med. Chem.* **2010**, *18*, 719–727; c) V. M. Ogurok, S. A. Siry, E. B. Rusanov, Y. G. Vlasenko, Y. G. Shermolovich, *J. Fluorine Chem.* **2015**, *182*, 47–52; d) E. W. Chia, A. N. Pearce, M. V. Berridge, L. Larsen, N. B. Perry, C. E. Sansom, C. A. Godfrey, L. R. Hanton, G.-L. Lu, M. Walton, W. A. Denny, V. L. Webb, B. R. Copp, J. L. Harper, *Bioorg. Med. Chem.* **2008**, *16*, 9432–9442; e) R. T. Hendricks, J. B. Fell, J. F. Blake, J. P. Fischer, J. E. Robinson, P. J. Stengel, A. L. Bernacki, V. J. P. Leveque, S. L. Pogam, I. Najera, J. A. Josey, J. R. Harris, S. Swallow, S. R. Spencer, S. Rajyaguru, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3637–3641; f) J. de Vicente, R. T. Hendricks, D. B. Smith, J. B. Fell, J. Fischer, P. J. Stengel, P. Mohr, J. E. Robinson, J. F. Blake, S. R. Spencer, R. K. Hilgenkamp, G. Adjabeng, T. R. Elworthy, J. Tracy, E. Chin, J. Li, B. Wang, R. Stephenson, C. Oshiro, S. F. Harris, M. Ghate, V. Leveque, S. L. Pogam, M. Brandl, S. Rajyaguru, A. Briggs, G. Ao-Ieong, S. Sukhtankar, L. Alexandrova, R. Farrell, B. Xu, C. Yee, J. T. Bamberg, I. Najera, S . Larrabee, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3642–3646; g) V. Sundari, G. Nagarajan, R. Valliappan, *Med. Chem. Res.* **2007**, *16*, 402–407; h) S. Govindan, R. Valliappan, J. Chakravarthy, P. Vanitha, V. Sundari, *J. Chem. Pharm. Res.* **2013**, *5*, 99–103; i) A. Aiello, E. Fattorusso, P Luciano, A. Macho, M. Menna, E. Muñoz, *J. Med. Chem.* **2005**, *48*, 3410–3416; j) A. N. Pearce, E. W. Chia, M. V. Berridge, G. R. Clark, J. L. Harper, L. Larsen, E. W. Maas, M. J. Page, N. B. Perry, V. L. Webb, B. R. Copp, *J. Nat. Prod.* **2007**, *70*, 936–940; k) A. Aiello, E. Fattorusso, P. Luciano, A. Mangoni, M. Menna, *Eur. J. Org. Chem.* **2005**, *2005*, 5024–5030; l) L. Du, F. Mahdi, S. Datta, M. B. Jekabsons, Y.-D. Zhou, D. G. Nagle, *J. Nat. Prod.* **2012**, *75*, 1553–1559; m) A. Carbone, C. L. Lucas, C. J. Moody, *J. Org. Chem.* **2012**, *77*, 9179−9189.

2. a) D. Peters, B. L. Eriksen, E. O. Nielsen, J. P. Redrobe, G. M. Olsen, *US Pat.* 8110586B2, **2012**; b) A. M. Gilbert, G. P. Stack, R. Nilakantan, J. Kodah, M. Tran, R. Scerni, X. Shi, D. L. Smith, T. H. Andree, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 515–518; c) B. Drewes, W. Sihver, S. Willbold, R. A. Olsson, H. H. Coenen, *Nucl. Med. Biol.* **2007**, *34*, 531–539; d) P. J. Riss, F. Roesch, *Bioorg. Med. Chem.* **2009**, *17*, 7630–7634; e) F. I. Carroll, A. H. Lewin, J. W. Boja, M. J. Kuhar, *J. Med. Chem.* **1992**, *35*, 969–981

3. a) A. Zask, J. Kaplan, J. C. Verheijen, D. J. Richard, K. Curran, N. Brooijmans, E. M. Bennett, L. Toral-Barza, I. Hollander, S. Ayral-Kaloustian, K. Yu, *J. Med. Chem.* **2009**, *52*, 7942–7945; b) D. J. S. Jean, Jr., K. S. Ashton, M. D. Bartberger, J. Chen, S. Chmait, R. Cupples, E. Galbreath, J. Helmering, F.-T. Hong, S. R. Jordan, L. Liu, R. K. Kunz, K. Michelsen, N. Nishimura, L. D. Pennington, S. F. Poon, D. Reid, G. Sivits, M. M. Stec, S. Tadesse, N. Tamayo, G. Van, K. C. Yang, J. Zhang, M. H. Norman, C. Fotsch, D. J. Lloyd, C. Hale, *J. Med. Chem.* **2014**, *57*, 325−338; c) Z. Chen, A. M. Venkatesan, O. D. Santos, E. D. Santos, C. M. Dehnhardt, S. Ayral-Kaloustian, J. Ashcroft, L. A. McDonald, T. S. Mansour, *J. Org. Chem.* **2010**, *75*, 1643–1651; d) A. M. Venkatesan, Z. Chen, O. D. Santos, C. Dehnhardt, E. D. Santos, S. Ayral-Kaloustian, R. Mallon, I. Hollander, L. Feldberg, J. Lucas, K. Yu, I. Chaudhary, T. S. Mansour, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5869–5873.

4. a) R. Grigg, M. J. Dorrity, F. Heaney, J. F. Malone, S. Rajviroongit, V. Sridharan, S. Surendrakumar, *Tetrahedron* **1991**, *41*, 8297–8322; b) R. Grigg, J. F. Malone, M. R. J. Dorrity, F. Heaney, S. Rajvnoongt, V. Sridharan, S. Surendrakumar, *Tetrahedron Lett.* **1988**, *29*, 4323–4324; c) M. Frederickson, R. Grigg, J. Redpath, M. Thornton-Pet, *Tetrahedron* **1994**, *50*, 5495–5552; d) P. Armstrong, R. Grigg, W. J. Warnock, *J. Chem. Soc. Chem. Commun.* **1987**, 1325–1327; e) B. H. Norman, Y. Gareau, A. Padwa, *J. Org. Chem.* **1991**, *56*, 2154–2161; f) A. Padwa, B. H. Norman, *Tetrahedron Lett.* **1988**, *29*, 2417–2420; g) M. J. Uddin, T. Fujimoto, A. Kakehi, H. Shirai, I. Yamamoto, *Heterocycl. Commun.,* **2000**, *6,* 113–118; h) M. T. McKiernan, F. Heaney, *Tetrahedron Lett.* **1996**, *37*, 4597–4600.

5. S. K. Hota, A. Chatterjee, P. K. Bhattacharya, P. Chattopadhyay, *Green Chem.* **2009**, *11*, 169–176

6. a) P. Anastas, L. G. Heine, T. C. Williamson, *Green Chemical Syntheses and Processes,* Oxford University Press: New York, **2000**; b) M. Lancaster, *Green Chemistry: An Introductory Text,* Royal Society of Chemistry: Cambridge, UK, **2002**; c) D. J. C. Constable, C. Jimenez-Gonzalez, R. K. Henderson, *Org. Process Res. Dev.* **2007**, *11*, 133–137; d) J. Andraos, *Org. Process Res. Dev.* **2005**, *9*, 149–163.

7. a) K. Tanaka, F. Toda, *Solvent-free Organic Synthesis*, Wiley-VCH, Weinheim, **2003**; b) J.-L. Do, T. Friščić, *Synlett* **2017**, *28*, 2066–2092; c) T. K. Achar, A. Bose, P. Mal, *Beilstein J. Org. Chem.* **2017**, *13*, 1907–1931; d) A. Sarkar, S. Santra, S. K. Kundu, A. Hajra, G. V. Zyryanov, O. N. Chupakhin, V. N. Charushin, A. Majee, *Green Chem.* **2016**, *18*, 4475–4525; e) S. K. Varma, *Green Chem.* **2014**, *16*, 2027–2041; f) J. G. Hernández, C. G. Avila-Ortiz, E. Juaristi, "*Useful Chemical Activation Alternatives in Solvent-Free Organic Reactions*" in "Comprehensive Organic Synthesis", 2nd Ed. G. A. Molander, P. Knochel, Eds. vol. 9, Oxford: Elsevier, **2014**, 287–314.

8. a) A. Stolle, T. Szuppa, S. E. S. Leonhardt, B. Ondruschka, *Chem. Soc. Rev.* **2011**, *40*, 2317–2329; b) J. G. Hernández, T. Friščić, *Tetrahedron lett.* **2015**, *56*, 4253–4265; c) D. Tan, L. Loots, T. Friščić, *Chem. Commun.* **2016**, *52*, 7760–7781; d) G.-W. Wang, *Chem. Soc. Rev.* **2013**, *42*, 7668–7700; e) J. L. Do, T. Friščić, *ACS Cent. Sci.* **2017**, *3*, 13−19; f) J. G. Hernández, E. Juaristi, *Chem. Commun.* **2012**, *48*, 5396–5409.

9. B. C. Ranu, A. Stolle, *Ball Milling Towards Green Synthesis: Applications, Projects and Challenges*, Ed., Royal Society of Chemistry, Cambridge, UK, **2015**.

10. For recent references of organic synthesis in ball mill, see: a) L. Akelis, C. Rousseau, J. Rousseau, R. Juskenas, J. Dodonova, S. Menuel, D. Prevost, S. Tumkevicius, E. Monflier, F. Hapiot, *Eur. J. Org. Chem.* **2016**, *2016*, 31–35; b) G. N. Hermann, C. L. Junga, C. Bolm, *Green Chem.* **2017**, *19*, 2520–2523; c) J. G. Hernández, K. J. Ardila-Fierro, D. Crawford, S. L. James, C. Bolm , *Green Chem.* **2017**, *19*, 2620–2625; d) G. N. Hermann, C. Bolm, *ACS Catal.* **2017**, *7,* 4592–4596; e) M. Leonardi, M. Villacampa, J. C. Menéndez, *J. Org. Chem.* **2017**, *82*, 2570–2578; f) J.-L. Do, C. Mottillo, D. Tan, V. Štrukil, T. Friščić, *J. Am. Chem. Soc.* **2015**, *137*, 2476–2479; g) D. Tan, C. Mottillo, A. D. Katsenis, V. Štrukil, T. Friščić, *Angew. Chem. Int. Ed.* **2014**, *53*, 9321–9324; h) P. K. Sahoo, C. Giri, T. S. Haldar, R. Puttreddy, K. Rissanen, P. Mal, *Eur. J. Org. Chem.* **2016**, *2016*, 1283–1291; i) P. K. Sahoo, A. Bose, P. Mal, *Eur. J. Org. Chem.* **2015**, *2015*, 6994–6998; j) J. G. Hernández, E. Juaristi, *J. Org. Chem.* **2010**, *75*, 7107–7111; k) L. A. Polindara-García, E. Juaristi, *Eur. J. Org. Chem.* **2016**, *2016*, 1095–1102; l) J. M. Landeros, E. Juaristi, *Eur. J. Org. Chem.* **2017**, *2017*, 687–694.

11. a) K. Tanaka, F. Toda, *Chem. Rev.* **2000**, *100*, 1025–1074; b) F. Toda, *Acc. Chem. Res.* **1995**, *28*, 480–486.

12. For selected examples of organic synthesis by grinding in mortar-pestle, see: a) J. Kaur, A. Kumari, S. S. Chimni, *Tetrahedron* **2017**, *73*, 802–808; b) S. Majumdar, M. Chakraborty, N. Pramanik, D. K. Maiti, *RSC Adv.* **2015**, *5*, 51012–51018; c) A. Khaskel, P. Gogoi, P. Barman, B. Bandyopadhyay, *RSC Adv.* **2014**, *4*, 35559–35567; d) H. Shy, P. Mackin, A. S. Orvieto, D. Gharbharan, G. R. Peterson, N. Bampos, T. D. Hamilton, *Faraday Discuss.* **2014**, *170*, 59–69; e) G. Brahmachari, S. Das, *RSC Adv.* **2014**, *4*, 7380–7388.

13. a) Z. T. Bhutia, P. Geethika, A. Das, M. Biswas, A. Chatterjee, M. Banerjee, *ChemistrySelect* **2017**, *2*, 1183–1187; b) Z. T. Bhutia, P. Geethika, A. Malik, V. Kumar, A. Chatterjee, B. G. Roy, M. Banerjee, *RSC Adv.* **2015**, *5*, 99566–99672; c) M. Banerjee, A. Chatterjee, V. Kumar, Z. T. Bhutia, D. G. Khandare, M. S. Majik, B. G. Roy, *RSC Adv.* **2014**, *4*, 39606–39611.
14. a) V. Kumar, A. Chatterjee, B. G. Roy, M. Banerjee, *Catal. Commun.* **2017**, *94*, 77–81; b) A. Chatterjee, S. K. Hota, M. Banerjee, P. K. Bhattacharya, *Tetrahedron Lett.* **2010**, *51*, 6700–6703.
15. a) G. A. Bowmaker, *Chem. Commun.* **2013**, *49*, 334–348; b) A. Mascitti, M. Lupacchini, R. Guerra, I. Taydakov, L. Tonucci, N. d'Alessandro, F. Lamaty, J. Martinez and E.Colacino, Beilstein *J. Org. Chem.* **2017**, *13*, 19–25; c) J. L. Howard, Y. Sagatov, L. Repusseau, C. Schotten, D. L. Browne, *Green Chem.* **2017**, *19*, 2798–2802.
16. a) C. Dayakar, B. S. Kumar, G. Sneha, G. Sagarika, K. Meghana, S. Ramakrishna, R. S. Prakasham, B. C. Raju, *Bioorg. Med. Chem.* **2017**, *25*, 5678–5691; b) M. F. E. Shehry, M. M. Ghorab, S. Y. Abbas, E. A. Fayed, S. A. Shedid, Y. A. Ammar, *Eur. J. Med. Chem.* DOI: 10.1016/j.ejmech.2017.10.046; c) P. R Modiya, C. N Patel, *Org. Med. Chem. Lett.* **2012**, *2*, 29–39; d) H. Beyzaei, R. Aryan, M. Moghaddam-Manesh, B. Ghasemi, P. Karimi, H. S. Delarami, M. Sanchooli, *J. Mol. Struct.* **2017**, *1144*, 273–279; e) W. He, B. M. Griffiths, W. Wang, X. Wang, *Org. Biomol. Chem.* **2017**, *15*, 4241–4245; f) B. Wang, W. Huang, J. Zhou, X. Tang, Y. Chen, C. Peng, B. Han, *Org. Biomol. Chem.* **2017**, *15*, 6548–6556; g) C. E. Schumacher, P. W. R. Harris, X.-B. Ding, B. Krause, T. H. Wright, G. M. Cook, D. P. Furkert, M. A. Brimble, *Org. Biomol. Chem.* **2017**, *15*, 8755–8760 ; h) A. A. Fadda, M. A. E. Salam, E. H. Tawfik, E. M. Anwar, H. A. Etman, *RSC Adv.* **2017**, *7*, 39773–39785; i) W. R. J. D. Galloway, A. Bender, M. Welch, D. R. Spring, *Chem. Commun.* **2009**, *45*, 2446–2462; j) L. Yang, X.-P. Bao, *RSC Adv.* **2017**, *7*, 34005–34011.
17. a) S. H. Zinner, R. B. Provonchee, K. S. Elias, *Laboratory Aspects of Infections. Chemotherapy,* eds. J. D. Williams and A. M. Geddes, Springer, Boston, MA, **1975**, *2*; b) B. Bonev, J. Hooper, J. l. Parisot, *J. Antimicrob. Chemother*. **2008**, *61*, 1295–1301.
18. a) I. Wiegand, K. Hilpert, R. E. W. Hancock, *Nat. Protoc.* **2008**, *3*, 163–175; b) J. M. Andrews, *J. Antimicrob. Chemother.* **2001**, *48*, 5-16.

10.1002/ejoc.201701511

Key Topic: Synthetic Method, Mechanochemistry

TOC:

An efficient mechanochemical method for the highly regio- and stereo-selective synthesis of bridged bicyclo aza-sulfones viz. 7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane-4,4-dioxides by tandem Michael addition-1,3-dipolar cycloaddition has been developed. Some of these compounds are reasonably good antibacterial agents against *M. smegmatis* and *E. coli.*