RSC Advances

This article can be cited before page numbers have been issued, to do this please use: S. SHANMUGAM, B. biguvu, M. Thillaichidambaram and R. Muthiah, *RSC Adv.*, 2015, DOI: 10.1039/C5RA11094G.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

View Article Online
DOI: 10.1039/C5RA11094G

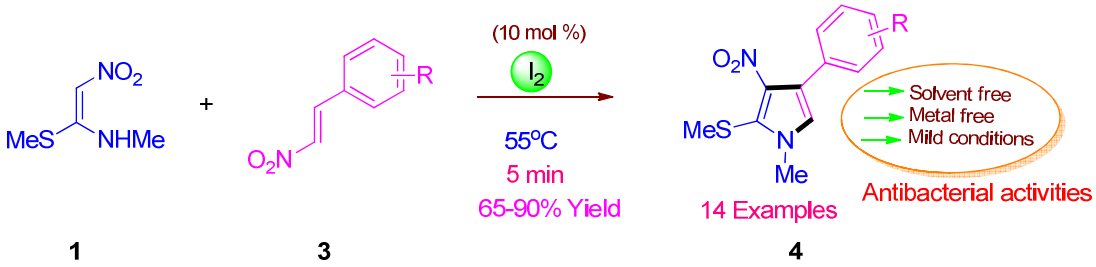
Iodine catalyzed one-pot synthesis of highly substituted *N*-methyl pyrrole *via* [3+2] annulation and their *in vitro* evaluation as antibacterial agents

Biguvu Balachandra[a], *Sivakumar Shanmugam,*[a]* *Thillaichidambaram Muneeswaran*[b], *Muthiah Ramakritinan*[b]

[a]Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai - 625 021, Tamil Nadu, India

[b]Department of Marine and Coastal Studies, School of Energy, Environment and Natural Resorurces, Madurai Kamaraj University, Madurai - 625 021, Tamil Nadu, India

*Email: shivazzen@mkuniversity.org



Dynamic Article Links ▶
View Article Online
DOI: 10.1039/C5RA11094G

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Iodine catalyzed one-pot synthesis of highly substituted *N*-methyl pyrrole *via* [3+2] annulation and their *in vitro* evaluation as antibacterial agents

Biguvu Balachandra[a], Sivakumar Shanmugam[a]*, Thillaichidambaram Muneeswaran[b], Muthiah Ramakritinan[b]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Abstract: A new class of highly substituted pyrroles have been synthesized *via* simple, fast, and efficient, method by environmental friendly iodine catalyzed *via* [3+2] annulation. *N*-methyl-*N*-[(*E*)-1-(methylsulfanyl)-2-nitro-1-ethenyl]amine (NMSM) **1** and *β*-nitro styrene **3** underwent cycloaddition to afford desired product **4** in excellent yields under solvent and metal free conditions. All the pyrrole derivatives were evaluated for their *in vitro* anti-bacterial activity. Among the synthesized pyrrole derivatives, **4b**, **4c**, **4e**, **4g**, **4i**, **4j**, **4l**, **4m** and **4n** displayed good inhibitory properties against a panel of gram positive and negative infectious pathogens.

Introduction

Over the decades, the design and synthesis of substituted pyrroles are important building blocks in organic synthesis. This key heterocyclic core is found in a large number of natural and unnatural compounds, which has significant importance in pharmacology and material science. Besides the natural products and their analogues, unnatural pyrroles show attractive biological activities, which are present in many of bioactive compounds like HIV fusion inhibitors,[1a] antitubercular compounds,[1b-c] including non-steroidal anti-inflammatory compound tolmetin and cholesterol-lowering agent atorvastatin, which is one of the top selling drug worldwide (Figure 1).[1d-e] The Substituted pyrrole derivatives show more biological activities[2] like antioxidant,[3] anti-inflammatory,[4] antibacterial,[5] antifungal agents[6] and antitumor[7] etc. The *N*-methyl substituted heterocycles are significant synthetic targets owing to their wide range of applications as medicinal compounds and also they can modulate physical and biological properties of the molecule. Methyl homologation increases the inhibitory potency of HMG-COA$_R$ inhibitors.[8a-d] The *S*-methyl substituted pyrrole derivatives and its analogue are useful precursors for synthesizing H_2 Receptor Histamine Antagonists.[8e-g] As a result; methods for the preparation of *N*- & *S*-methyl substituted heterocycles containing structural scaffolds are in high demand.

In general, the standard methods to synthesis of pyrrole are Hantzsch,[9] Knorr & Paal-Knorr[10] and multi-component synthesis,[11] tandem reactions,[21] transition-metal-catalyzed cyclization reactions[13] etc. These methods put forward the efficient construction of pyrroles with various substitution pattern, atom economy and regioselectivity. Despite a number of available synthetic strategies and advantages, the modern methodologies are focused on solvent and metal free synthesis of substituted pyrrole due to their lower energy consumption, increased selectivity, minimized waste, hazards, toxicity and cost.[14]Recently, iodine catalyzed reactions have been considerable interest in various organic transformations due to its low toxicity to environment, ready availability and inexpensive. Therefore, it is worth contribute to the creation of environmentally benign processes.[15] In light of literature precedent[1-15], it would be interested to develop an useful and efficient approach to synthesis of *N*- and *S*-methyl substituted pyrrole derivatives, which have a major effect on partitioning into biological membranes[16a-b] for example, methyl thio-ethers and its sulfoxides, sulfones are commonly occurring component in biological active molecules.[16c-d] The *N*-methyl-*N*-[*(E)*-1-(methylsulfanyl)-2-nitro-1-ethenyl]amine (NMSM) **1** is using in the industrial scale for the manufacture of *anti-ulcer* (Histamine H_2 receptor antagonists) bulk drugs ranitidine,[17] nizatidine.[18a] NMSM **1**[18b-c] is a multi-faceted building block in organic synthesis.

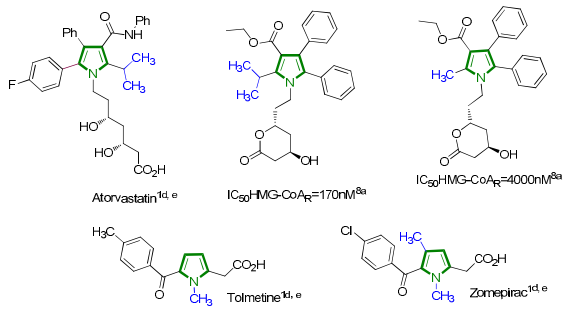


Figure1. Pyrrole based biologically important compounds

The methyl sulfanyl group is an electron donor as well as good

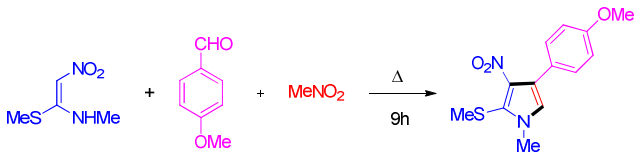
View Article Online
DOI: 10.1039/C5RA11094G

leaving group and it could be replaced with a variety of nucleophiles following the substitution nucleophilic vinyl (S_NV) mechanism.[19] In the current protocol, we reported highly functionalized *N*-methyl substituted pyrrole derivatives **4** *via* one-pot [3+2] cycloaddition of NMSM **1** and *β*-nitrostyrene **3** under solvent free condition.

Results and Discussion

To commencement of our study, the model reaction of NMSM **1** benzaldehyde **2a** and nitromethane was performed in the absence of catalyst in multi-component fashion. Eventually, we ended up with very less conversion of **4a** in 5% yield (Table 1, entry1). Then, reaction was carried out in the presence of solvents like DMSO and DMF which was found to be counterproductive under catalyst free at reflux conditions (Table 1, entry 2&3). To further optimization of reaction condition the reaction was employed in the presence of iodine catalyst in DMF solvent and the results showed that compound obtained were in trace amounts (Table 1, entry 4).To improve the yield of **4a**, different Lewis acids such as $FeCl_3$, Yb $(OTf)_3$ and CuI were used as catalysts to afford **4a** with 15-25% yield (Table 1, entries 6-9). However, when molecular iodine was used as catalyst (10 mol %), the target product **4a** was obtained in 30% yield (Table 1 entry.5). Unfortunately, there was no significant improvement in the cycloaddition after increasing the temperature and amount of catalyst.

Table 1: Optimization of the reaction conditions for three component synthesis of **4a**[a]



1 **2a** **4a**

Entry	Catalyst	Temp (°C)	Solvent	Time (h)	Yield[b] (%)
1	-	90		9	5[c]
2	-	180	DMSO	12	Traces
3	-	145	DMF	12	Traces
4	Iodine	145	DMF	12	Traces
5	Iodine	90	-	9	30[b]
6	$FeCl_3$	90	-	9	20[c]
7	Yb$(OTf)_3$	90	-	9	25[b]
8	AcOH	95	-	9	15[c]
9	CuI	90	-	9	17[c]

[a]Reaction conditions: **1** (1.0 mmol), **2a** (1.0 mmol), Nitromethane (1ml) Catalyst (10mol %).[b] Isolated yields after column chromatography [c]Starting material **1** was recovered.

In order to improve the yield of **4a**, nitrostyrene[20a] was prepared separately and subjected to cycloaddition with NMSM **1** by manual grinding using mortar and pestle at room temperature**.** Initially, we tried catalytic amount of anhydrous $FeCl_3$ with **1** and **3a** in a grinding method to afford **4a** in 63% yield (Table 2, entry 1). We repeated the cycloaddition by using metal catalyst such as $AlCl_3$, CuI, $ZnCl_2$, $CuCl_2.2H_2O$, and Yb$(OTf)_3$ by grinding method at RT, however, there was not much improvement in the yield of **4a** (Table 2, entries 2-6).

Table 2: Optimization reaction condition to the synthesis of **4a** by manual grinding method (Solvent free condition)[a]

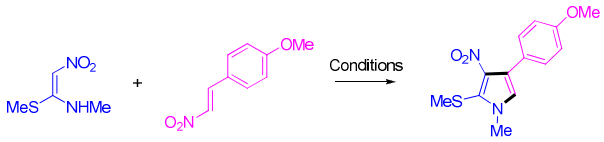
1 **3a** **4a**

Entry	Catalyst	Time (min)	Yield[b] (%)
1	$FeCl_3$	30	63
2	$AlCl_3$	30	52
3	CuI	30	50[c]
4	$ZnCl_2$	30	53
5	$CuCl_2.2H_2O$	30	49[c]
6	Yb$(OTf)_3$	30	65
7	**Iodine**	**30**	**70**
8	Acetic acid	30	65

[a]Reaction conditions: **1** (1 mmol), **3a** (1 mmol), Catalyst (10 mol %), [b]Isolated yields after column chromatography, [c]starting material **1** was recovered

Interestingly, the cycloaddition was obtained in 70% yield of **4a** in the presence of iodine catalyst (Table 2, entry 7). In acetic acid, the conversion of **4a** was obtained in moderate yield (Table 2, entry 8).

Table 3: Optimization of the reaction conditions for two component synthesis of **4a**[a]



1 **3a** **4a**

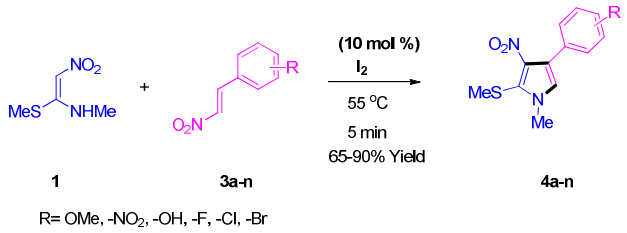
Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	-	-	65	6	32[c]
2	-	-	90	5	25[c]
3	-	MeOH	RT	48	10[c]
4	-	H_2O	Reflux	9	54
5	-	MeOH	Reflux	8	59
6	-	EtOH	Reflux	8	60
7	$FeCl_3$	EtOH	Reflux	8	60
8	$FeCl_3$	MeOH	Reflux	8	62
9	$FeCl_3$	-	50	30 min	67
10	$AlCl_3$	-	55	30 min	60
11	CuI	-	55	30 min	61
12	$ZnCl_2$	-	55	30 min	65
13	$CuCl_2.2H_2O$	-	55	30 min	55
14	Yb$(OTf)_3$	-	55	45	72
15	AcOH	-	55	30 min	50
16	**Iodine**	**-**	**55**	**5 min**	**82**
17	Iodine	-	90	5 min	67
18	Iodine	MeOH	Reflux	6	66

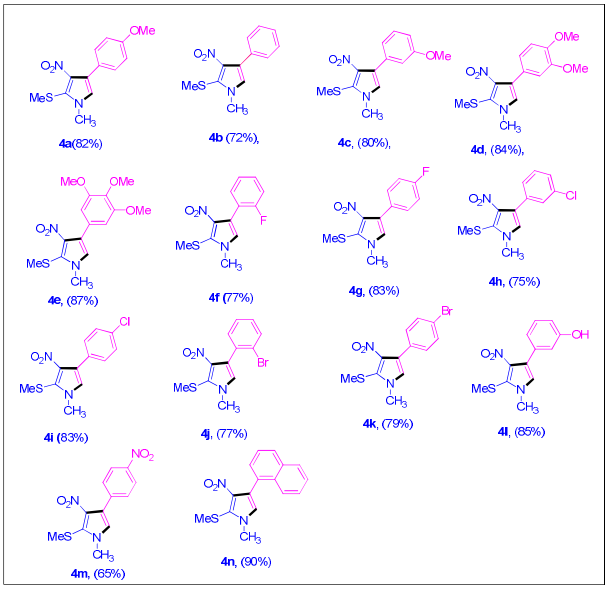
[a]Reaction conditions: **1** (1 mmol), **3a** (1 mmol), Catalyst (10 mol %). [b]Isolated yields after column chromatography, [c]starting material **1** was recovered

View Article Online
DOI: 10.1039/C5RA11094G

We then tried alternative method to study the tolerance of **3a** and **1** to afford **4a** under optimized reaction conditions with various solvents and catalysts. The cycloaddition was employed with NMSM **1** and **3a** at 65 °C for 6 h under catalyst and solvent free condition (Table 3, entry 1). However the yield was reduced to 25% on increasing the temperature from 65 °C to 90 °C (Table 3, entry 2). The yield of **4a** was considerably increased to (54-62%) yield, when the solvents were varied from water to ethanol under reflux condition (Table 3, entries 4-8). While other Lewis acids were used as catalyst under solvent free conditions, the desire product **4a** was obtained in moderate yields (Table 3, entries 9-14). The compound **4a** was obtained in 50% yield, when catalytic amount of acetic acid was used (Table 3, entry 15).The solvent effect had not much influence to improve the product yield. Further to design an environmentally benign procedure, a model cycloaddition was performed between **1** and **3a** at 55 °C in the presence of iodine as catalyst. Interestingly, the cycloaddition product **4a** was obtained in 82% yield under solvent free conditions in 5 min (Table 3, entry 16). The yield of **4a** was decreased to 67% when reaction was carried out at 90 °C (Table 3 entry17). Similarly, the yield of **4a** was decreased to 66%, when the cycloaddition was performed in MeOH at reflux condition for 6 h (Table 3 entry18) along with iodine catalyst. Overall iodine catalyzed cycloaddition (Table 1, 2 & 3) was found to be better method for the synthesis of **4a**.

Table 4: One-pot two-component synthesis of **4a-n** *via* [3+2] cycloaddition [a]



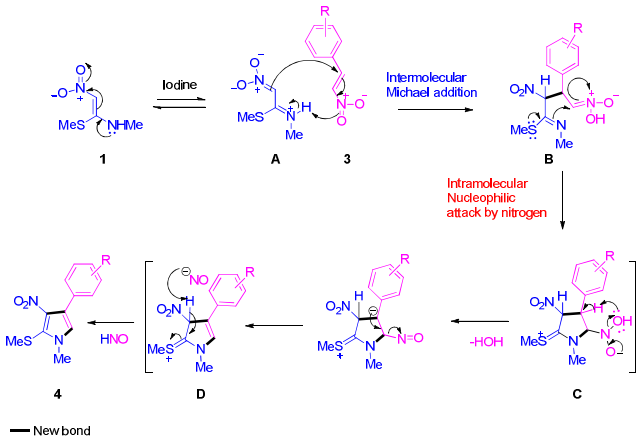


[a] Reaction conditions: **1** (1 mmol), **3** (1 mmol), Catalyst (10 mol %), Isolated yields after column chromatography

Among them, [3+2] cycloaddition under solvent free conditions at 55 °C was found to be the ideal method for the synthesis of tetra substituted pyrrole **4a** in good yield (Table 3, entry 16). The NMR spectral data supports the structure of **4a.**

Following the optimized reaction condition, we have investigated the scope of NMSM **1** and *β*-nitrostyrene **3** *via* [3+2] cycloaddition to afford **4a-n** (Table 4**).** The starting material containing electron–donating and withdrawing groups of *β*-nitrostyrene **3** with **1** were well tolerated under optimized reaction conditions to afford **4a-n** in moderate to good yields (65-90%). Temperature plays significant effect in the reaction because; the yield was improved to 65-90% at 55 °C (Table, 4). In the aryl group of *β*-nitrostyrene **3** contains an electron donating as well as an electron-withdrawing groups present at *ortho* and *meta* positions, which shows little influence to afford **4c, 4f, 4h, 4j** in low yield. Whereas, the *para* substituents **4a**, **4g**, **4i**, and **4k** was obtained in high yield. An electron withdrawing group such as $–NO_2$ was well tolerated under optimized condition and gave a moderate yield of 65% of the desired product **4m** (Table 4). The halogens substituted phenyl group of *β*-nitrostyrene **3** leads to the formation of pyrrole **4g** and **4i** in 83% yield. The naphthyl substituted *β*-nitrostyrene works well for formation of pyrrole **4n** and gave the maximum yield 90% (Table 4).In conclusion all types of *β*-nitrostyrenes could be successfully applied in this reaction providing to *N*-methylated pyrroles **4a-4n** in good yield.

Interestingly, nitro and thioether linkage containing substituted structural scaffolds are allowed to make further coupling reaction.[20b-f] In our present report, the synthesis of tetra substituted pyrrole **4** assumes to get more attention as important an intermediates in organic, biological, as well as material chemistry. All the synthesized compounds **4** were well characterized by IR and NMR (^{1}H, ^{13}C, DEPT-135) spectra. The ^{1}H NMR spectrum of **4a** was explained by taking as an example. The ^{1}H NMR spectrum shows two doublet at δ 7.28 ppm (d, J = 9.0 Hz, 2H), 6.91 ppm (d, J = 8.6 Hz, 2H) for *para* methoxy substituted phenyl group and the aromatic proton of substituted pyrrole (C 5, H) appears as a singlet at 6.67 ppm. The *N*-methyl, *S*-methyl and methoxy protons appear as singlet at 3.83 ppm 2.49 ppm and 3.79 ppm respectively. The singlet at δ = 6.67 ppm (C-5 proton) is the diagnostic signal for **4a.**



Scheme 1: Plausible reaction mechanism to formation of **4**

On the basis of literature reports[21], plausible mechanism was proposed for the iodine catalyzed cycloaddition of **1** and **3** to

View Article Online
DOI: 10.1039/C5RA11094G

yield **4** (Scheme.1). Here, iodine acts as a mild Lewis acid, which increases the nucleophilicity of NMSM **1.** In the first step, due to the polarized push-pull alkene of NMSM **1** undergoes Michael addition of **3** to form new C-C single bond to form **B**. Further, lone pair of sulphur atom of methyl sulfanyl group shifted their electrons towards nitrogen, which makes intramolecular nucleophilic attack of nitrogen through formation of new N-C bond to give **C**. Intermediate **C** undergoes elimination of H_2O to give intermediate **D** which on further elimination of nitrosyl hydride (HNO) leads to the formation of product **4**.

Biological data

Disc diffusion method

Based on the biological literature survey, the synthesized compounds (**4a-n**) were evaluated for their anti-bacterial activity against selected gram positive and negative bacteria, which were individually responsible for various infections and disorders by using standard disk diffusion assay[22] described by Murray et al 1995. The gram negative bacteria such as *Salmonella typhi,*

Table 5: Antibacterial activity screening for compounds **4a-4n**

Entry	Compound code	Gram Negative [a]			Gram Positive[a]		
		S. typhi	*E. coli*	*P. aerugionsa*	*S. pneumonia*	*B. subtilis*	*B.cereus*
1	**4a**	-	-	-	-	-	-
2	**4b**	-	-	-	-	6	9
3	**4c**	-	-	-	9	9	-
4	**4d**	-	-	-	-	-	-
5	**4e**	7	8	7	9	9	8
6	**4f**	-	-	-	-	-	-
7	**4g**	-	-	-	8	11	-
8	**4h**	-	-	-	-	-	-
9	**4i**	7	-	-	-	-	-
10	**4j**	8	-	-	-	-	-
11	**4k**	-	-	-	-	-	-
12	**4l**	6	-	9	11	8	8
13	**4m**	9	-	-	-	-	-
14	**4n**	-	-	-	7	7	8
15	**Cont.l**	-	-	-	-	-	-
16	**Std[b]**	14	10	15	14	18	16

[a] Value represents the activity of compounds against the bacteria (with 0.01M solution), Zone of inhibition in diameter (mm). [b] Streptomycin. - No inhibition

Escherichia coli, Pseudomonas aeruginosa cause typhoid fever,[23] haemolytic uremic syndrome,[24] *and* nosocomial infections,[25] respectively. The gram positive *Streptococcus pneumoniae* is responsible for bronchitis, rhinitis, acute sinusitis, otitis media, conjunctivitis, meningitis, bacteraemia, sepsis, osteomyelitis, septic arthritis, endocarditis, peritonitis, pericarditis, cellulitis, and brain abscess.[26] *Bacillus subtilis,* a gram positive model organism causes food poisoning.[27] *Bacillus cereus,* causes food borne illness, causing severe nausea, vomiting, and diarrhoea and are responsible for "fried rice syndrome."[28] The stock solutions of the synthesized compounds were prepared in DMSO and filter sterilized using 0.45µm syringe filter. Briefly overnight grown cultures containing 108 CFU/mL were spread on the Muller Hinton agar plates. The sterile paper discs (Himedia lab) were impregnated with filter sterilized compounds approximately 20 µL per disc. The paper discs were placed on the agar plates and incubated at 30 °C for 24 h. After 24 h of incubation, the zone of inhibition around the discs was observed and measured (Table 5). The values presented in the table were the average of the two independent tests.

The results of the initial antibacterial activity screening revealed that, among the pyrrole derivatives the compounds **4b**, **4c**, **4e**, **4g**, **4i**, **4j**, **4l**, **4m**, **4n** displayed activity against gram-positive bacteria and gram-negative bacteria, inhibitory zone (6-11mm) shown in Table 5. The compounds **4e** and **4l** showed good activity against almost all bacteria. Whereas the compound **4g** displayed good activity against gram-positive bacteria (Table 5 entry 7). These results showed considerable interest to find minimum inhibitory concentration (MIC).

Minimum inhibitory concentration (MIC)

The compounds which showed sensitivity to the bacteria was selected for the determination of MIC.[29]

Table 6: MIC Values (µg /mL) against infectious Pathogens

Entry	Compound code	Gram Negative [a]			Gram Positive[a]		
		S. typhi	*E. coli*	*P. aerugionsa*	*S. pneumonia*	*B. subtilis*	*B. cereus*
1	**4b**	-	-			5.0	5.0
2	**4c**	-	-	-	5.5	5.5	-
3	**4e**	33.8	6.7	6.7	6.7	6.7	6.7
4	**4g**	-	-	-	26.6	5.3	-
5	**4i**	28.2	-	-	-	-	-
6	**4j**	6.5	-	-	-	-	-
7	**4l**	5.3	-	26.4	5.3	26.4	5.3
8	**4m**	5.8	-	-	-	-	-
9	**4n**	-	-	-	-	29.8	5.9
10	**Std[b]**	2.0	5.0	2.0	3.0	1.0	2.0

[a] Values show considerable activity, µg /mL required to confine the bacterial growth, [b] Streptomycin, - No inhibition

The overnight grown cultures were adjusted to OD of 0.1. Stock solutions of synthesized compounds and standard were serially diluted to achieve a concentration between 10mM to 0.001mM and 1to10 µg/mL respectively. MIC values of the compounds were determined by adopting the micro-well dilution method (Zgoda and Porter, 2001). [30] Briefly, each well of the 96 well plates were seeded with the serially diluted compounds and bacterial cultures and nutrient broth to a final volume of 200 µL per well. The well containing cells and nutrient broth serve as negative control. Similarly the well seeded with DMSO, cells and nutrient broth serve as solvent control. The plates were sealed tightly with sterile plate sealer and incubated for 24 h in an orbital shaker at 90 rpm. Bacterial growth was measured by optical density (OD) at 600 nm using 96 well plate readers (ELISA Plate reader) and also by the visual appearance of turbidity. Further confirmation was made by plating 10µL of the samples from the clear wells on nutrient agar.

View Article Online
DOI: 10.1039/C5RA11094G

MIC Values are defined as the lowest concentration that completely inhibited visible growth of microorganism. The compound **4b** displayed activity against *Bacillus cereus*, *Bacillus subtilis* (Gram-positive bacteria) due the presence of phenyl substitution on the pyrrole ring (Table 6, entry 1). Moreover 3-methoxy substituted aryl group of pyrrole **4c** showed considerable activity against *Streptococcus pneumoniae*, *Bacillus subtilis* (Table 6, entry 2). Whereas 3,4,5-trimethoxy compound **4e** displayed activity against both the gram-positive bacteria and gram-negative bacteria (Table 6, entry 3). The halogens substituted phenyl derivatives of **4** showed good antibacterial activities. Among the halogens, 4-flouro derivative (**4g**) was the most effective on *Bacillus subtilis* and has a considerable activity against *Streptococcus pneumoniae* (Table 6, entry 4).Whereas **4i** (4-chloro) and **4j** (2-bromo) showed moderate activities on gram-negative bacteria *Salmonella typhi* (Table 6, entry 5, 6).

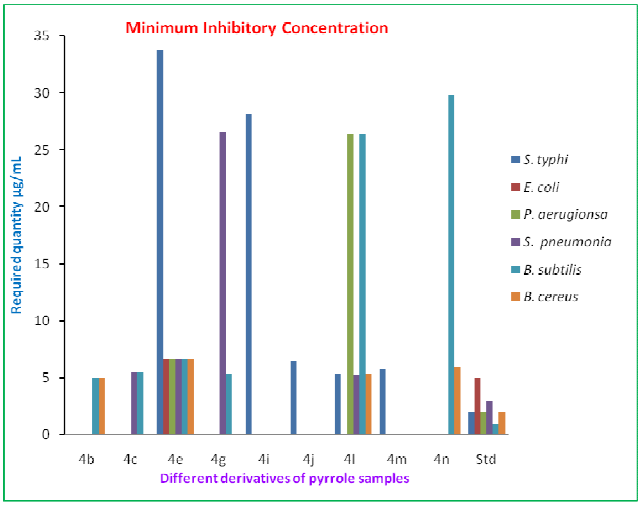


Figure2. Minimum Inhibitory concentration of selected compounds

Interestingly 3-hydroxy substituted aryl group of **4l** showed wide range of activity (Table 6, entry 7), but 4-nitro substituted aryl group of **4m** weakly effective against *Salmonella typhi* (Table 6, entry 8). The compound **4n** with naphthyl substitution displayed activity against *Bacillus cereus*, *Bacillus subtilis* (gram-positive bacteria) (Table 6, entry 9). Due to strong resistant of pathogens towards the anti-bacterial agent, some of the pyrrole derivatives did not show inhibitory properties against gram negative and positive bacteria (Table 5 & 6). The obtained results showed that different substitutions influence the activity of the *N*-methyl substituted pyrrole compounds.

CONCLUSION

Hence we have developed a simple, fast, and efficient method to the synthesis of tetra substituted pyrrole in the presence of catalytic amount of iodine under metal & solvent free conditions. In comparison with reported procedures, the present one affords environmentally benign approach for synthesis of pyrrole derivatives **4a-n**. In this procedure new **C-C** and **C-N** bonds were effectively constructed. The presence of nitro and sulphur groups were opens to further construction of complex derivatives. The synthesized compounds **4a-n** was evaluated for their anti-bacterial activity against selected bacteria. Most of the synthesized compounds have good antibacterial activity.

Experimental Section

General Consideration

Melting points were determined in open capillary tubes and were uncorrected. IR spectra were taken on a Jasco FT-IR instrument in KBr pellets and reported in cm^{-1}. Mass spectra were performed with Agilent mass spectrometer and recorded in positive & negative mode with an ESI source. The ^{1}H and ^{13}C NMR spectra of the new compounds were measured at 300 MHz and 75MHz in $CDCl_3$ and DMSO-d_6 with TMS as the internal standard. Chemical shifts were expressed in ppm, coupling constant (*J* values) were given in Hertz (Hz) and spin multiplicities were indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), td (triplet of doublets). Elemental analyses were carried out with Perkin Elmer 2400 Series II analyzer. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60-80 °C) and ethyl acetate as eluent. All chemicals were purchased and used without further purification. The starting material *β*-nitrostyrene **3** was prepared according to the previous literature methods. Nitroketene-*N,S*-acetal (NMSM) **1** is commercially available and was used without further purification.

General procedure for preparation of *β*-nitrostyrene (3)

Aldehyde (0.05), nitro methane (0.05), and MeOH (10-20 mL) were added to a round –bottom flask and then stirred vigorously. NaOH solution (10.5M, 10 mL) was added drop wise in ice bath; a large amount of yellow solid precipitated, and stirring was continued for 15 min. Distilled H_2O was added until the solution became clear, then the solution was added drop wise to concentrated HCl (30 mL), and a yellow solid precipitated. The yellow solid was filtered and washed with H_2O, then evaporated in a vacuum drying oven. After recrystallization (EtOH), yellow needle-like crystals were obtained. 4-OMe-β-nitrostyrene (**3a**) Isolated yield (93%) Yellow solid; M.P. 86-88 °C; ^{1}H NMR (300 MHz, CDCl3): δ, 7.98 (d, J = 13.6 Hz, 1H), 7.52 (m, 3H), 6.96 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, CDCl3): δ, 162.88, 138.97, 134.91, 131.11, 122.44, 114.84, and 55.45. Other *β*-nitro styrene derivatives were prepared with similar procedure and characterized by ^{1}H, ^{13}C NMR.

General procedure for synthesis of substituted pyrrole (4)

NMSM **1** (1.0mmol), *β*-nitro styrene **3** (1.0mmol) and molecular iodine (10mol %) were charged in a 25 ml glass vial equipped with stirring bar. The reaction mixture was heated on oil bath at 55 °C for 5-10 min (Monitored by TLC). After cooling down to room temperature, the resulting mixture was extracted with ethyl acetate (3×7ml), and then washed with water (2×10ml) followed by brine solution (1×15ml).The organic phases were collected and dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to afford the corresponding products **4**.

Experimental procedure for three component one pot synthesis of substituted pyrrole (Table 1)

Aldehyde (1.0 mmol), nitro methane (1ml), and molecular iodine

View Article Online
DOI: 10.1039/C5RA11094G

(10mol %) were charged in a 25 ml glass vial equipped with stirring bar. The reaction mixture allowed refluxing at 90 °C for 50-60min, after cooling down to room temperature, NMSM **1** (1.0mmol) was added by sequentially and continued to reflux for 9h(Monitored by TLC). The resulting mixture was extracted with ethyl acetate (3×7ml), and then washed with water (2×10ml) followed by brine solution (1×15ml).The organic phases were collected and dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to afford the corresponding products **4a.**

Experimental procedure for one pot synthesis of substituted pyrrole by manual grinding method (Table 2)

NMSM **1** (1.0mmol), *β*-nitro styrene **3** (1.0mmol) and catalyst (10mol %) were allowed to manual grinding for 30 min (Monitored by TLC) at RT by using Mortar and pestle. The resulting mixture was extracted with ethyl acetate (3×7ml), and then washed with water (2×10ml) followed by brine solution (1×15ml).The organic phases were collected and dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to afford the corresponding products **4a.**

4-(4-methoxyphenyl)-1-methyl-2-(methylthio)-3-nitro-1*H*-pyrrole (4a)

Yellow solid; m.p.128-130°C; yield: 0.153g (82%); ^{1}H NMR (300 MHz, $CDCl_3$): δ, 7.28 (d, J = 9.0 Hz, 2H), 6.91 (d, J = 8.6 Hz, 2H), 6.67 (s, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 158.88, 136.99, 129.74, 126.09, 124.47, 122.17, 121.76, 113.55, 55.14, 34.87, 19.38; IR (ATR KBr cell, cm^{-1}): 791, 1327, 1495, 3741, 3840; Anal. Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06 Found: C, 56.01; H, 5.03; N, 10.02; LC-MS (ESI) calcd.m/z: 278, found 279 $[(M+H)]^+$.

1-methyl-2-(methylthio)-3-nitro-4-phenyl-1*H*-pyrrole (4b)

Yellow solid; m.p.129-131°C; yield: 0.120g (72%); ^{1}H NMR (300 MHz, $CDCl_3$): δ, 7.35 (s, 5H), 6.71 (s, 1H), 3.80 (s, 3H), 2.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ, 137.00, 132.06, 128.46, 128.06, 127.20, 126.30,122.32, 122.06, 34.88, 19.38; IR (ATR KBr cell, cm^{-1}): 691, 756, 1322, 1479, 2348, 3728.Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28 Found: C, 58.03; H, 4.86; N, 11.26; LC-MS (ESI) calcd. m/z: 248, found 249 $[(M+H)]^+$.

4-(3-methoxyphenyl)-1-methyl-2-(methylthio)-3-nitro-1*H*-pyrrole (4c)

Yellow solid; m.p.127-129 °C; yield: 0.150g (80%); ^{1}H NMR (300 MHz, $CDCl_3$): δ, 7.27 (s, 1H), 6.91 (m 3H), 6.72 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 159.38, 137.30, 133.46, 129.11, 126.24, 122.41, 121.96, 121.00, 114.25, 113.01, 55.18, 34.89, 19.46; IR (ATR KBr cell, cm^{-1}): 688, 784, 1321, 1477, 2349, 2930; Anal. Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06 Found: C, 56.01; H, 5.03; N, 10.02; LC-MS (ESI) calcd.m/z: 278, found 279 $[(M+H)]^+$.

4-(3,4-dimethoxyphenyl)-1-methyl-2-(methylthio)-3-nitro-1*H*-pyrrole (4d)

Yellow solid; m.p.118-120°C; yield: 0.174g (84%); ^{1}H NMR (300 MHz, $CDCl_3$): δ, 6.93 – 6.85 (m, 3H), 6.70 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.80 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 148.63, 137.22, 126.10, 124.91, 122.23, 121.97, 121.02, 112.53, 111.13, 110.89, 55.90, 55.86, 34.85, 19.42; IR (ATR KBr cell, cm^{-1}): 804, 1240, 1504, 3741, 3840; Anal. Calcd for $C_{14}H_{16}N_2O_4S$: C, 54.53; H, 5.23; N, 9.08 Found: C, 54.50; H, 5.21; N, 9.05; LC-MS (ESI) calcd.m/z: 308, found 309 $[(M+H)]^+$.

1-methyl-2-(methylthio)-3-nitro-4-(3,4,5-trimethoxyphenyl)-1*H*-pyrrole (4e)

Yellow solid; m.p.132-134°C; yield: 0.198g (87%); ^{1} H NMR (300 MHz, $CDCl_3$): δ, 6.73 (s, 1H), 6.57 (s, 2H), 3.88 (s, 3H), 3.86 (s, 6H), 3.80 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 152.85, 137.43, 137.04, 127.68, 126.42, 122.44, 122.06, 105.96, 60.77, 56.04, 34.93, 19.44; IR (ATR KBr cell, cm^{-1}): 698, 820, 1105, 1339, 1497, 3741, 3840; Anal. Calcd for $C_{15}H_{18}N_2O_5$ S: C, 53.24; H, 5.36; N, 8.28 Found: C, 53.22; H, 5.34; N, 8.25; LC-MS (ESI) calcd.m/z: 338, found 339 $[(M+H)]^+$.

4-(2-fluorophenyl)-1-methyl-2-(methylthio)-3-nitro-1*H*-pyrrole (4f)

Yellow solid; m.p.218-220°C; yield: 0.138g (77%); ^{1}H NMR (300 MHz, $CDCl_3$): δ, 7.38 – 7.24 (m, 2H), 7.20 – 7.04 (m, 2H), 6.76 (s, 1H), 3.81 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 161.60, 158.32, 130.60, 129.37, 129.26, 126.49, 123.97, 122.98, 120.49, 120.29, 115.64, 115.34, 35.12, 19.48; IR (ATR KBr cell, cm^{-1}): 636, 767, 1329, 1480, 2348, 3728; Anal. Calcd for $C_{12}H_{11}FN_2O_2S$: C, 54.12; H, 4.16; N, 10.52; Found: C, 54.11; H, 4.14; N, 10.51; LC-MS (ESI) calcd.m/z: 266, found 267 $[(M+H)]^+$.

4-(4-fluorophenyl)-1-methyl-2-(methylthio)-3-nitro-1*H*-pyrrole (4g)

Yellow solid; m.p.168-170°C; yield: 0.149g (83%); ^{1}H NMR (300 MHz, $CDCl_3$): δ, 7.32 (d, J = 8.6 Hz, 2H), 7.07 (d, J = 8.7 Hz, 2H), 6.69 (s, 1H), 3.80 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 163.84, 160.58, 130.45, 130.34, 128.24, 126.70, 122.42, 121.27, 115.23, 114.94, 35.03, 19.42; IR (ATR KBr cell, cm^{-1}): 793, 829, 1210, 1322, 1489, 3741, 3840 ; Anal. Calcd for $C_{12}H_{11}FN_2O_2S$: C, 54.12; H, 4.16; N, 10.52 Found: C, 54.10; H, 4.13; N, 10.50; LC-MS (ESI) calcd.m/z: 266, found 267 $[(M+H)]^+$.

4-(3-chlorophenyl)-1-methyl-2-(methylthio)-3-nitro-1*H*-pyrrole (4h)

Yellow solid; m.p.96-98 °C; yield: 0.142g (75%); ^{1}H NMR (300 MHz, $CDCl_3$): δ, 7.33 (s, 1H), 7.27 (m, 3H), 6.72 (s, 1H), 3.80, (s, 3H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 136.64, 133.98, 133.62, 129.21, 128.41, 127.11, 126.94, 126.79, 122.74, 120.47, 34.93, 19.26; IR (ATR KBr cell, cm^{-1}): 778, 1312, 1478, 3741, 3840; Anal. Calcd for $C_{12}H_{11}ClN_2O_2S$: C, 50.97; H, 3.92; N, 9.91 Found: C, 50.95; H, 3.91; N, 9.90; LC-MS (ESI) calcd.m/z: 282, found 283 $[(M+H)]^+$.

4-(4-chlorophenyl)-1-methyl-2-(methylthio)-3-nitro-1*H*-pyrrole (4i)

Yellow solid; m.p.76-78°C; yield: 0.158g (83%); ^{1}H NMR (300 MHz, $CDCl_3$): δ, 7.34 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 7.1 Hz, 2H), 6.70 (s, 1H), 3.80 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (75 MHz,

View Article Online
DOI: 10.1039/C5RA11094G

$CDCl_3$): δ, 136.89, 133.25, 130.72, 129.95, 128.30, 126.94, 122.48, 121.02, 35.05, 19.42; IR (ATR KBr cell, cm^{-1}): 832, 1320, 1487, 3741, 3840; Anal. Calcd for $C_{12}H_{11}ClN_2O_2S$: C, 50.97; H, 3.92; N, 9.91 Found: C, 50.95; H, 3.91; N, 9.90; LC-MS (ESI) calcd.m/z: 282, found 283 $[(M+H)]^+$.

4-(2-bromophenyl)-1-methyl-2-(methylthio)-3-nitro-1*H*-pyrrole (4j)

Yellow solid; m.p.188-190 °C ; yield: 0.170g (77%); ^1H NMR (300 MHz, $CDCl_3$): δ, 7.63 (d, J = 7.9 Hz, 1H), 7.39 – 7.13 (m, 3H), 6.68 (s, 1H), 3.82 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 134.01, 132.46, 131.24, 129.08, 127.05*, 126.45, 124.60, 122.87, 121.15, 35.15, 19.34; IR (ATR KBr cell, cm^{-1}): 764, 1325, 1479, 2347, 3615, 3728; Anal. Calcd for $C_{12}H_{11}BrN_2O_2S$: C, 44.05; H, 3.39; N, 8.56 Found: C, 44.03; H, 3.36; N, 8.55; LC-MS (ESI) calcd.m/z: 327, found 328 $[(M+H)]^+$. [*- Two carbon signals have merged together]

4-(4-bromophenyl)-1-methyl-2-(methylthio)-3-nitro-1*H*-pyrrole (4k)

Yellow solid; m.p.102-104 °C; yield: 0.174g (79%); ^1H NMR (300 MHz, $CDCl_3$): δ, 7.49 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 6.70 (s, 1H), 3.80 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 136.83, 131.23, 131.19, 130.25, 126.99, 122.45, 121.40, 121.00, 35.07, 19.42; IR (ATR KBr cell, cm^{-1}): 617, 781, 1320, 1439, 3741,3839; Anal. Calcd for $C_{12}H_{11}BrN_2O_2S$: C, 44.05; H, 3.39; N, 8.56 Found: C, 44.02; H, 3.37; N, 8.54; LC-MS (ESI) calcd.m/z: 327, found 328 $[(M+H)]^+$.

3-(1-methyl-5-(methylthio)-4-nitro-1*H*-pyrrol-3-yl) phenol (4l)

Yellow solid; m.p.140-142°C; yield: 0.151g (85%); ^1H NMR (300 MHz, $CDCl_3$): δ, 7.33 – 7.15 (m, 1H), 6.90 (d, J = 7.4 Hz, 1H), 6.81 (d, J = 11.8 Hz, 1H), 6.70 (s, 1H), 5.01 (s, 1H), 3.79 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (75 MHz, DMSO): δ, 157.38, 136.71, 133.46, 129.44, 125.70, 123.91, 120.59, 118.98, 115.17, 114.30, 35.11, 19.33; IR (ATR KBr cell, cm^{-1}): 774, 1306, 1472, 3447, 3741, 3840; Anal. Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60 Found: C, 54.51; H, 4.56; N, 10.58; LC-MS (ESI) calcd.m/z: 264, found 265 $[(M+H)]^+$.

1-methyl-2-(methylthio)-3-nitro-4-(4-nitrophenyl)-1*H*-pyrrole (4m)

Yellow solid; m.p.258-260°C; yield: 0.128g (65%); ^1H NMR (300 MHz, $CDCl_3$): δ, 8.23 (d, J = 8.9 Hz, 2H), 7.50 (d, J = 8.9 Hz, 2H), 6.82 (s, 1H), 3.84 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 146.83, 139.15, 136.85, 129.31, 128.23, 123.45, 123.09, 120.09, 35.29, 19.44; IR (ATR KBr cell, cm^{-1}): 807, 1321, 1493, 2348, 3729; Anal. Calcd for $C_{12}H_{11}N_3O_4S$: C, 49.14; H, 3.78; N, 14.33; Found: C, 49.13; H, 3.76; N, 14.34; LC-MS (ESI) calcd.m/z: 293, found 294 $[(M+H)]^+$.

1-methyl-2-(methylthio)-4-(naphthalen-1-yl)-3-nitro-1*H*-pyrrole (4n)

Orange solid; m.p.168-170°C; yield: 0.181g (90%); ^1H NMR (300 MHz, $CDCl_3$): δ, 7.91 – 7.82 (m, 2H), 7.68 (d, J = 8.2 Hz, 1H), 7.52 – 7.34 (m, 4H), 6.74 (s, 1H), 3.86 (s, 3H), 2.56 (s, 3H); ^{13}CNMR (75 MHz, $CDCl_3$): δ, 138.20, 133.35, 132.45, 130.58, 128.25, 128.15, 127.31, 126.28, 126.12, 125.71, 125.29, 125.07, 123.46, 120.24, 35.05, 19.31; IR (ATR KBr cell, cm^{-1}): 780, 1324, 1481, 3741, 3840 Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39 Found: C, 64.40; H, 4.71; N, 9.37; LC-MS (ESI) calcd.m/z: 298, found 299 $[(M+H)]^+$.

Acknowledgements

SS thank DST and UGC-MRP, New Delhi, for financial assistance. We thank DST-IRHPA for funding towards high resolution NMR spectrometer. BBC thanks the University Grants Commission, New Delhi, for the award of Senior Research Fellowship.

Notes and references

[a]*Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai – 625 021. *shivazzen@mkuniversity.org; Tel: Office: + 91 452 245 8471 Ex. 371*
[b]*Department of Marine and Coastal Studies, School of Energy, Environment and Natural Resources, Madurai Kamaraj University, Madurai – 625 021.Tamil Nadu, India.*

† Electronic Supplementary Information (ESI) available: All the ^1H & ^{13}C NMR and Mass spectrums of **4a-n** are available. See DOI: 10.1039/b000000x/

1 (a) C. Teixeira, F. Barbault, J. Rebehmed, K. Liu, L. Xie, H. Lu, S. Jiang, B. Fan and F. Maurel, *Bioorg. Med. Chem*., 2008, **16,** 3039-3048; (b) M. Biava, G. C. Porretta, D. Deidda, R. Pompei, A. Tafic and F. Manettic, *Bioorg. Med. Chem*., 2004, **12**, 1453-1458; (c) M. Protopopova, E. Bogatcheva, B. Nikonenko, S. Hundert, L. Einck and C. A. Nacy, *Med. Chem*., 2007, **3**, 301-316; (d) V. Este´vez, M. Villacampa, and J. C. Mene´ndez, *Chem. Soc. Rev*., 2010, **39**, 4402-4421; (e) V. Este´vez, M. Villacampa and J. C. Mene´ndez, *Chem. Soc. Rev*., 2014, **43**, 4633-4657.

2 (a) J. A. H. Lainton, J. W. Huffman, B. R. Martin and D. R. Compton *Tetrahedron Lett.,* 1995, **36**, 1401-1404; (b) C. Y. DeLeon and B. Ganem, *Tetrahedron,* 1997, **53**, 7731-7752; (c) R. Martín, M. Rodríguez Rivero and S. L. Buchwald, *Angew. Chem. Int. Ed.,* 2006, **45**, 7079-7082; (d) H. S. P. Rao and S. Sivakumar, *Beilstein. J. Org. Chem*., 2007, **3**, 31; (e) H. Fan, J. Peng, M. T. Hamann and J. F. Hu, *Chem. Rev.,* 2008, **108**, 264-287; (f) J. Deblander, S. V. Aeken, J. Jacobs, N. D. Kimpe and K. A. Tehrani, *Eur. J. Org. Chem.,* 2009, 4882-4892; (g) S. Rakshit, F. W. Patureau and F. Glorius, *J. Am. Chem. Soc*., 2010, **132**, 9585-9587; (h) R. J. Billedeau, K. R. Klein, D. Kaplan and Y. Lou, *Org. Lett.,* 2013, **15**, 1421-1423; (i) P. Dhanalakshmi and S. Sivakumar, *RSC Adv*., 2014, **4**, 29493-29501; (j) M. Arun Divakar, V. Sudhamani, S. Sivakumar, T. Muneeswaran, S. Tamilzhalagan, M. Ramakritinan and K. Ganesan, *RSC Adv*., 2015, **5,** 8362-8370.

3 (a) A. S. Demir, I. M. Akhmedov and O. Sesenoglu, *Tetrahedron,* 2002, **58**, 9793-9799; (b) D. Wang, X. Hu and G. Zhao, *Int. J. Food Sci. Technol.,* 2008, **43**, 1880-1886.

4 (a) V. J. Demopoulos and E. J. Rekka, *Pharm. Sci.,* 1995, **84**, 79-82; (b) J. M. Muchowski, *Adv. Med. Chem.,* 1992, **1**, 109-135; (c) B. Khalili, P. Jajarmi, B. Eftekhari-Sis and M. M. Hashemi, *J. Org. Chem.,* 2008, **73**, 2090-2095.

5 (a) R. W. Bürli, D. McMinn, J. A. Kaizerman, W. Hu, Y. Ge, Q. Pack, V. Jiang, M. Gross, M. Garcia, R. Tanaka and H. E. Moser, *Bioorg. Med. Chem. Lett*., 2004, **14**, 1253-1257.

6 (a) H. M. Meshram, B. R. V. Prasad and D. Aravind Kumar, *Tetrahedron Lett.,* 2010, **51**, 3477-3480; (b) M. Z. Wang, H. Xu, T. W. Liu, Q. Feng, S. J. Yu, S. H. Wang and Z. M. Li, *Eur. J. Med. Chem.,* 2011, **46**, 1463-1472; (c) A. K. Verma, S. K. Reddy Kotla, T. Aggarwal, S. Kumar, H. Nimesh and R. K. Tiwari, *J. Org. Chem*., 2013, **78**, 5372-5384.

7 (a) E. Gimenez-Arnau, S. Missailidis and M. F. G. Stevens, *Anti-Cancer Drug. Des.,* 1998, **13**, 431-451; (b) P. Cozzi and N. Mongelli, *Curr. Pharm. Des.,* 1998, **4**, 181-201; (c) Y. R. Torres, T. S. Bugni, R. G. S. Berlinck, C. M. Ireland, A. Magalhaes, A. G. Ferreira, R. M. Rocha, *J. Org. Chem.,* 2002, **67**, 5429-5432; (d) B. Das, N. Bhunia and M. Lingaiah, *Synthesis,* 2011, 3471–3474.

View Article Online
DOI: 10.1039/C5RA11094G

8 (a) E. J. Barreiro, A. E. Kummerle and C. A. M. Fraga, *Chem. Rev.,* 2011, **111**, 5215-5246; (b) H. Schönherr and T. Cernak, *Angew.Chem. Int. Ed.,* 2013, **52**, 12256-12267; (c) H. Schönherr and T. Cernak, *Angew. Chem.,* 2013, **125**, 12480-12492; (d) Z. J. Fu, Z. J. Li, Q. Xiong and H. Cai, *Eur. J. Org. Chem*., 2014, 7798-7802; (e) Roantree, M. Laurence and Y.R. Christopher *Eur.Pat.Appl.,*5985,12 Dec 1979; (f) R.C. Young, G.J. Durant, J.C. Emmett, C. R. Ganellin, M.J. Graham, R.C. Mitchell, H. D. Prain, and M.L. Roantree, *J. Med. Chem.,* 1986, **29**, 44-49; (g) R.C. Young, R.C. Mitchell, T.H. Brown, C. R.Ganellin, R. Griffiths, M.Jones, K.K. Rana, D.Saunders, I.R. Smith, N. E.Sore, and T.J. Wilks, *J. Med. Chem.,* 1988, **31**, 656-671.

9 A. Hantzsch, *Ber. Dtsch. Chem. Ges*., 1890, **23**, 1474-1476.

10 (a) L. Knorr, *Ber. Dtsch. Chem. Ges.,* 1884, **17**, 1635-1642; (b) C. Pall, *Ber. Dtsch. Chem. Ges.,* 1885, **18**, 367-371.

11 (a) F. Benedetti, F. Berti, P. Nitti, G. Pitacco and E. Valentin, *Gazz. Chim. Ital.,* 1990, 120, 25-28; (b) H. Shiraishi, T. Nishitani, S. Sakaguchi and Y. Ishii, *J. Org. Chem.,* 1998, **63**, 6234-6238; (c) G. Dou, C. Shi and D. Shi, *J. Comb. Chem.,* 2008, **10**, 810-813; (d) Y. Lu and B. A. Arndtsen, *Angew. Chem. Int. Ed.,* 2008, **47**, 5430-5433; (e) Y. J. Bian, X. Y. Liu, K. G. Ji, X. Z. Shu, L. N. Guo and Y. M. Liang, *Tetrahedron,* 2009, **65**, 1424-1429; (f) A. Aponick, C. Y. Li, J. Malinge and E. F. Marques, *Org. Lett.,* 2009, **11**, 4624-4627; (g) S. L. A. Langle, M. Abarbri, J. Thibonnet, A. Duchene and J. L. Parrain, *Chem. Commun.,* 2010, **46**, 5157-5159; (h) W. Liu, H. Jiang and L. Huang, *Org. Lett.,* 2010, **12**, 312-315.

12 (a) X. T. Liu, L. Huang, F. J. Zheng, Z. P. Zhana, *Adv. Synth. Catal*., 2008, **350**, 2778-2788; (b) Q. Cai, F. Zhou, T. Xu, L. Fu and K. Ding, *Org. Lett.,* 2011, **13**, 340-343; (c) H. Ueda, M. Kameya, H. Yamaguchi, K. Sugimoto and H. Tokuyama, *Org. Lett.,* 2014, **16**, 4948-4951.

13 (a) M. Sukhendu, B. Srijit and J. Umasish, *J. Org. Chem., 2010*, **75**, 1674-1683; (b) A. Saito, T. Konishi and Y. Hanzawa, *Org. Lett*., 2010, **12**, 372-374; (c) A. Takahashi, S. Kawai, I. Hachiya and M. Shimizu, *Eur. J. Org. Chem*., 2010, 191-200; (d) M. N. Zhao, Z. H. Ren, Y. Y. Wang and Z. H. Guan, *Org. Lett*., 2014, **16**, 608-611.

14 (a) K. Tanaka and F. Toda, *Chem. Rev*., 2000, **100**, 1025-1074; (b) M. S. Singh and S. Chowdhury, *RSC Adv*., 2012, **2**, 4547-4592; (c) I. B. Subrahmanya and D. R. Trivedi, *Tetrahedron Lett*., 2013, **54**, 5577-5582.

15 (a) S. Tang, Y. Wu, W. Q. Liao, R. P. Bai, C. Liu and A. W. Lei, *Chem. Commun.,* 2014, **50**, 4496-4499; (b) A. Sagar, S. Vidyacharan and D. S. Sharada, *RSC Adv*., 2014, **4**, 37047-37050; (c) S. Ko, M. N. V. Sastry, C. Lin and C. F. Yao, *Tetrahedron Lett.*, 2005, **46**, 5771-5774; (d) C. M. Chu, S. Gao, M. N. V. Sastry and C. F. Yao, *Tetrahedron Lett*., 2005, **46**, 4971-4974; (e) B. K. Banik, M. Fernandez and C. Alvarez, *Tetrahedron Lett.,* 2005, **46**, 2479-2482; (f) B. P. Bandgar and K. A. Shaikh, *Tetrahedron Lett.,* 2003, **44**, 1959-1961; (g) J. S. Yadav, B. V. Subba Reddy, G. Narasimhulu, N. S. Reddy and P. Janardhan Reddy, *Tetrahedron Lett.*, 2009, **50**, 3760-3762.

16 (a) N. G. Anthony, K. R. Fox, B. F. Johnston, A. I. Khalaf, S. P. Mackay, I. S. McGroarty, J. A. Parkinson, G. G. Skellern, C. J. Suckling and R. D. Waigh, *Bioorg. Med. Chem. Lett.,* 2004, **141**, 1353-1356; (b) B. R. Beno, K. S. Yeung, M. D. Bartberger, L. D. Pennington, and N. A. Meanwell, *J. Med. Chem.,* 2015, DOI: 10.1021/jm501853m; (c) C. S. Richards-Taylor, D. C. Blakemoreb and M. C. Willis, *Chem. Sci*., 2014, **5**, 222-228; (d) B. N. Rocke, K. B. Bahnck, M. Herr, S. Lavergne, V. Mascitti, C. Perreault, J. Polivkova and A. Shavnya, *Org. Lett*., 2014, **16**, 154-157.

17 (a) M. J. Daly, B. J. Price, In Progress in *Medicinal Chemistry,* G. P. Ellis, G.B.Eds.West, Elsevier: Amsterdam, 1983; Vol. **20**, pp 337-368 (b) Y. Ootsuka, H. Morita, H. Mori, Jpn. Kokai Tokyo Koho JP 07157465 A2, 1995; *Chem. Abstr*., 1995, **123**, 767921.

18 (a) K. P. Moder, Eur. Pat. Appl. EP 515121 A1, 1992,*Chem.Abstr.,* 1993, 118, 169100; (b) P.Gunasekaran, P.Prasanna, S.Perumal and A.I.Almansour, *TetrahedronLett.,* 2013, **54**, 3248-3252; (c) P.Gunasekaran, P.Prasanna and S.Perumal,*Tetrahedron Lett.,*2014, **55**, 329-332.

19 (a) C. Venkatesh, B. Singh, P. K. Mahata, H. Ila and H. Junjappa, *Org. Lett*., 2005, **7**, 2169-2172; (b) H. S. P. Rao and S. Sivakumar *J. Org. Chem*., 2005, **70**, 4524-4527; (c) H. S. P. Rao and K. Geetha , *Tetrahedron Lett.*, 2009, **50**, 3836-3839; (d) H. S. P. Rao, K. Geetha and M. Kamalraj, *RSC Adv.,* 2011, **1**, 1050-1059. (e) H. S. P. Rao and A. Parthiban, *Org. Biomol. Chem*., 2014, **12**, 6223-6238; (f) H. S. P. Rao, and A. V. B. Rao, *Eur. J. Org. Chem*., 2014, 3646-3655.

20 (a) G. Yan, A. J. Borah and L. Wang, *Org. Biomol. Chem*., 2014, **12**, 6049-6058; (b) T. Sugahara, K. Murakami, H. Yorimitsu and A. Osuka, *Angew. Chem. Int. Ed.,* 2014, **53**, 9329-9333; (c) L. Wang, W. Hea and Z. Yu, *Chem. Soc. Rev.,* 2013, **42**, 599-621; (d) Z. Fang, J. Liu, Q. Liu and X. Bi, *Angew. Chem. Int. Ed.,* 2014, **53**, 7209-7213; (e) F. Zhu and Z-X. Wang, *Org. Lett.,* 2015, **17**, 1601-1604; (f) W. Zhang, J. Xie, B. Rao and M. Luo, *J. Org. Chem*., 2015, **80**, 3504-3511.

21 (a) G. P. Desiraju and R. L. Harlow, *J. Am. Chem. Soc*., 1998, **111**, 6757; (b) A. C. Legon, *Angew. Chem.,* 1999, **38**, 2686-2714; (c) M. Rueping and A. Parra, *Org. Lett.,* 2010, **12**, 5281-5283; (d) G. R. Reddy, T. R. Reddy, S. C. Joseph, K. S. Reddy and M. Pal, *RSC Adv*., 2012, **2**, 3387–3395; (e) P. Xu, K. Huang, Z. Liu, M. Zhou and W. Zeng, *Tetrahedron Lett.,* 2013, **54**, 2929-2933; (f) A. Srivastava, G. Shukla, A. Nagaraju, G. K. Verma, K. Raghuvanshi, R. C. F. Jones and M. S. Singh, *Org. Biomol. Chem.,* 2014, **12**, 5484-5491.

22 P. R. Murray, E. J. Baron, M. A. Pfaller, F. C. Tenover and R. H. Yolke, *Manual of Clinical Microbiology*, ASM, Washington, 6th edn DC, 1995.

23 (a) A. Kothari, A. Pruthi and T. D. Chugh, *J Infect Developing Countries.,* 2008; **4**, 253-259; (b) J. A. Crump, S. P. Luby and E. D. Mintz, *Bulletin of the world health organization,* 2004, **82**, 346-353.

24 H. M. Verweyen, H. Karch, F. Allerberger and L. B. Zimmerhackl, Enterohemorrhagic *Escherichia coli* (EHEC) in pediatric hemolytic uremic syndrome: a prospective study in Germany and Austria, *Infection,* 1999, **27**, 341-347.

25 (a) S. Bentzmann and P. Plésiat, *Environmental Microbiology*, 2011, **13,** 1655-1665; (b) N. Cramer, J. Klockgether, K. Wrasman, M. Schmidt, C. F. Davenport and B. Tümmler, *Environmental Microbiology*, 2011, **13**, 1690-1704.

26 R. A. C. Siemieniuk, D. B. Gregson and M. J. Gill, (Nov 2011). "The persisting burden of invasive pneumococcal disease in HIV patients: an observational cohort study". *BMC Infectious Diseases,* 11: 314. Doi: 10.1186/1471-2334-11-314.

27 N. A. Logan, *Bacillus species* of medical and veterinary importance. *J. Med. Microbiol.,* 1988, **25**, 157-165.

28 A. Kotiranta, K. Lounatmaa and M. Haapasalo "Epidemiology and pathogenesis of Bacillus cereus infections". *Microbes Infect.,* 2000, **2** (2) 189-98. Doi: 10.1016/S1286-4579(00)00269-0.

29 (a) P. A. Wayne, *National committee for Clinical Laboratory Standards*, 1997, Approved Standard M7-A4; (b) P. A. Wayne, *National committee for Clinical Laboratory Standards*, 1997, Approved Standard M27.

30 (a) J. R. Zgoda, J. R. Porter, 2001. A convenient micro dilution method for screening natural products against bacteria and fungi. Pharmaceutical *Biology*, **39,** (3), 221-225.