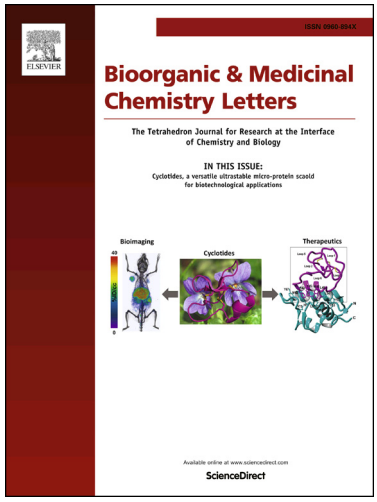


Design, Synthesis and Biological Evaluation of Spiropyrimidinetriones Oxazolidinone Derivatives as Antibacterial Agents.

Asher M. Siddiqui, Jitendra A. Sattigeri, Kalim Javed, Syed Shafi, M. Shamim, Smita Singhal, Zubbair M. Malik

PII: S0960-894X(18)30164-1
DOI: https://doi.org/10.1016/j.bmcl.2018.02.055
Reference: BMCL 25651

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 17 August 2017
Revised Date: 7 January 2018
Accepted Date: 27 February 2018

Please cite this article as: Siddiqui, A.M., Sattigeri, J.A., Javed, K., Shafi, S., Shamim, M., Singhal, S., Malik, Z.M., Design, Synthesis and Biological Evaluation of Spiropyrimidinetriones Oxazolidinone Derivatives as Antibacterial Agents., *Bioorganic & Medicinal Chemistry Letters* (2018), doi: https://doi.org/10.1016/j.bmcl.2018.02.055

Graphical Abstract

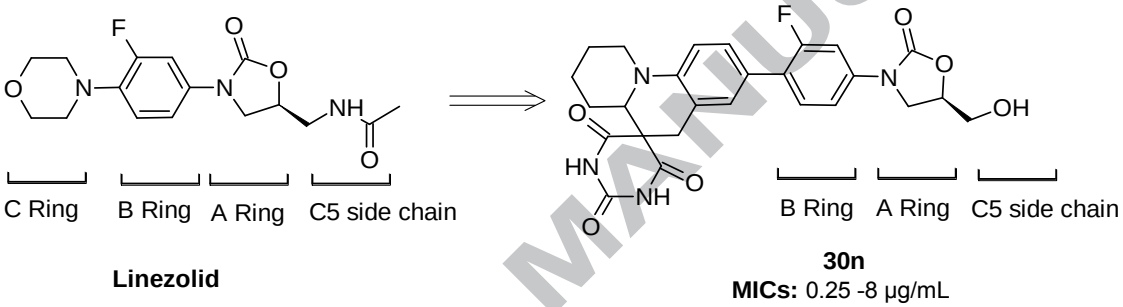
To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Design, Synthesis and Biological Evaluation of Spiropyrimidinetriones Oxazolidinone Derivatives as Antibacterial Agents.

Leave this area blank for abstract info.

Asher M Siddiqui[a,b*], JitendraA Sattigeri[a], Kalim Javed[b*], Syed Shafi[b], Shamim M[b],Smita Singhal[a] Zubbair M Malik[c]

[a]*Daiichi Sankyo India Pharma Pvt. Ltd., Gurgaon, Haryana 122015, India*
[b]*Department of Chemistry, Faculty of Science, Jamia Hamdard (Hamdard University), New Delhi 110062, India*
[c]*Centre for Interdisciplinary Research in Basic Sciences, Jamia Millia Islamia, New Delhi 110025, India*



* Corresponding author; e-mail: mohd.asher@gmail.com, kjaved@jamiahamdard.ac.in

ELSEVIER

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

Design, Synthesis and Biological Evaluation of Spiropyrimidinetriones Oxazolidinone Derivatives as Antibacterial Agents.

Asher M Siddiqui[a,b*], Jitendra A Sattigeri[a], Kalim Javed[b*], Syed Shafi[b], Shamim M[b], Smita Singhal[a], Zubbair M Malik[c]

[a] Daiichi Sankyo India Pharma Pvt. Ltd., Gurgaon, Haryana 122015, India

[b] Department of Chemistry, Faculty of Science, Jamia Hamdard (Hamdard University), New Delhi 110062, India

[c] Centre for Interdisciplinary Research in Basic Sciences, Jamia Millia Islamia, New Delhi 110025, India

Corresponding author: e-mail: mohd.asher@gmail.com, kjaved@jamiahamdard.ac.in

Abstract

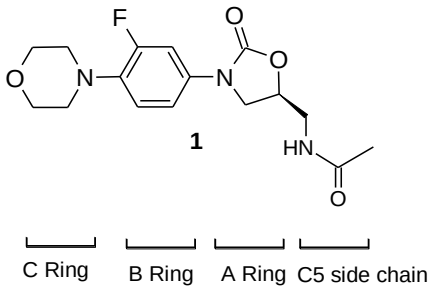
Gram-positive bacteria are among the most common human pathogens associated with clinical infections which range from mild skin infections to sepsis. Resistance towards existing class of drugs by Gram-positive bacteria including methicillin resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis* (MRSE) and vancomycin resistant *enterococci* (VRE) is a growing concern. There is an urgent need to discover new antibiotics which are active against resistant strains of Gram positive bacteria. We report herein a novel class of spiropyrimidinetrione oxazolidinone derivatives as novel antibacterial agents. Key step towards the synthesis of title compounds involved the use of *tert*-amino reaction with [1,5]-hydride shift leading to the new C-C bond formation. Compound **30n** has demonstrated potent antibacterial activity against a panel of Gram-positive microbial strains including MRSA, MRSE, and LNZ and vancomycin resistant strains of *E.faecalis*. Further, molecular docking studies suggest that **30n** has binding mode similar to that of LNZ in 50S RNA ribosome.

Keywords: spiropyrimidinetrione, oxazolidinone, [1,5]-hydride shift, drug resistance.

The emergence of antibacterial resistance to existing antibiotics is posing a serious concern in hospital settings and community[1-4]**.** Infections caused by multidrug-resistant Gram-positive bacteria represent a major public health burden, not just in terms of morbidity and mortality, but also in terms of increased financial burden on exchequer[5-7]. In recent decades, the discovery and development of new antibiotics have slowed dramatically as scientific barriers to drug discovery; regulatory challenges and diminishing returns on investment have led major drug companies to scale back or abandon their antibiotic research. Consequently, the antibiotic discovery—which peaked in the 1950s—has dropped precipitously resulting in a lack of new antibiotics coming to the market[8,9]. Treatment of infections caused by Gram-positive bacteria including Methicillin Resistant *Staphylococcus aureus*[10,11] (MRSA), Methicillin Resistant *Staphylococcus epidermidis*[12] (MRSE) and vancomycin resistant *enterococci*[13](VRE) [*E. faecalis and E. faecium*] is increasingly becoming a big challenge to health care professionals.

Linezolid (LNZ) **1** (Figure 1), an oxazolidinone class of synthetic antibiotic, was introduced into the clinic around 20 years[14,15] back for treating serious infections caused by Gram positive bacteria such as *S. aureus, S. epidermis* and *VRE*[16]**.** Unfortunately, the resistance to LNZ started to appear soon after its implementation for therapeutic use with the rate of resistance being high especially among *Enterococci* and *Staphylococcus epidermidis* strains[17,18]. The most common mechanism by which these pathogens develop resistance to LNZ is by manifesting G2576T/U mutation in the 23S rRNA sub-unit. The second mechanism of resistance involves the plasmid-encoded *cfr* gene, an enzyme with 23S rRNA methyltransferase activity, which confers a pan-resistant phenotype involving chloramphenicol, clindamycin and LZD[19].

Figure 1: Linezolid



The most common approach to overcome antibacterial resistance is the modification of existing classes of antibacterial agents to provide new analogues with improved attributes[20]. Since its discovery, a number of second generation oxazolidinones (eg. **2**&**3**, Figure 2) have been reported[21-22]. Additionally, a number of conformationally restricted oxazolidinone analogues[23-24] (e.g. **4**&**5**, Figure 2) having potent activity against Gram positive bacteria have also been reported. Recently,

AstraZeneca and Pfizer disclosed compounds **6** & **7** (Figure 3) [25-26] containing unique Spiropyrimidinetrione (tetracyclic) structural framework which exhibited potent antibacterial activity.

Figure 2: Oxazolidinone based potent antibacterials.

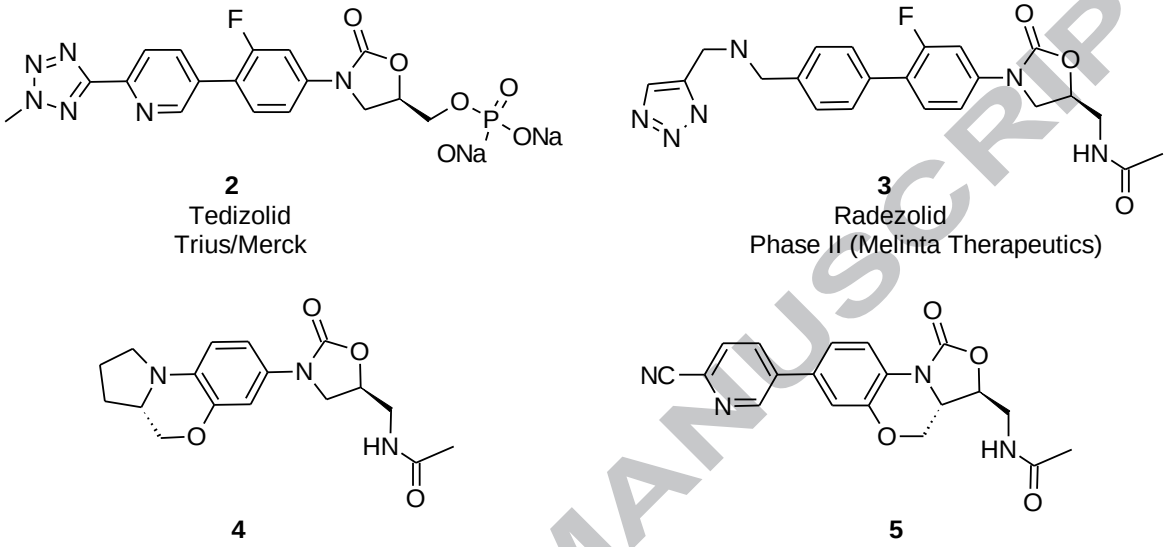
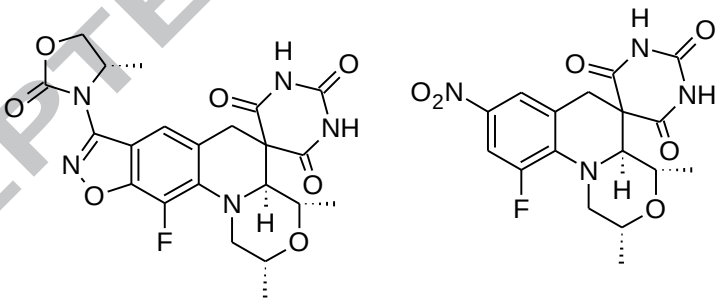


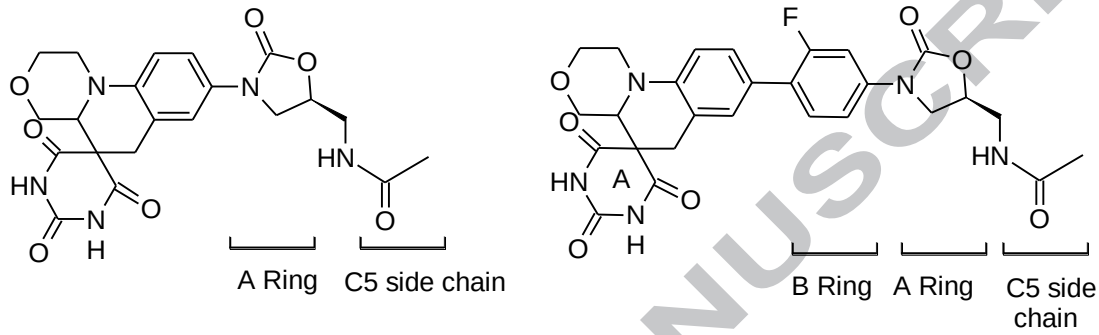
Figure 3: Recently reported spiropyrimidinetriones based antibacterials



Herein, we report the design and synthesis of novel spiropyrimidinetriones **23a-d** (Type I) and **30a-s** (Type II) as potential antibacterial agents (Figure 4). The key design aspect involved combining the structural features of oxazolidinone and spiropyrimidinetriones class of antibacterial compounds. Molecular framework of LNZ can be divided into A-ring (oxazolidinone), B-ring (phenyl), and C-ring (morpholine), and a C-5 acylaminomethyl side chain on the A-ring[27-28](Figure 1). In Type I class, ring B and C were replaced by a new spiropyrimidinetrione moiety while keeping the oxazolidinone ring A constant. While in Type II class of molecules, only ring C was replaced with the

Spiropyrimidinetrione moiety while keeping rings A and B constant. A key reaction in the synthesis of this class of compounds was *via tert*-amino effect reaction (T-amino reaction)[29] involving a[1, 5]-hydride shift (Scheme 1) thus providing a novel methodology[30-32] to construct pharmaceutically relevant tetrahydroquinoline skeleton[33].

Figure 4: Spiropyrimidinetrione oxazolidinone derivatives



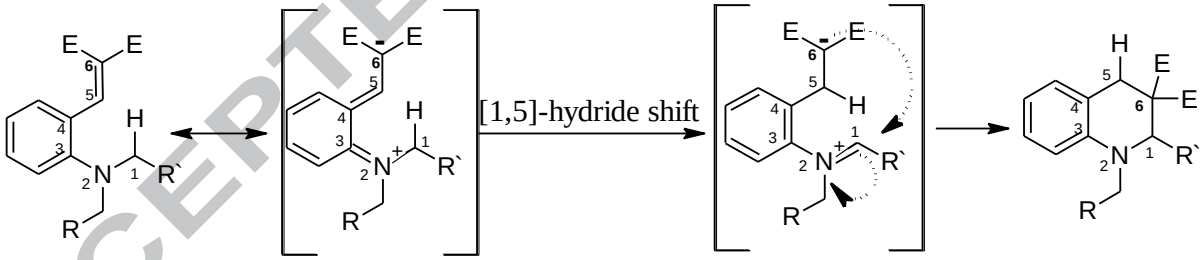
Type I

23a
(Representative eg)

Type II

30a
(Representative eg)

Scheme 1: Reaction mechanism of *tert*-amino effect

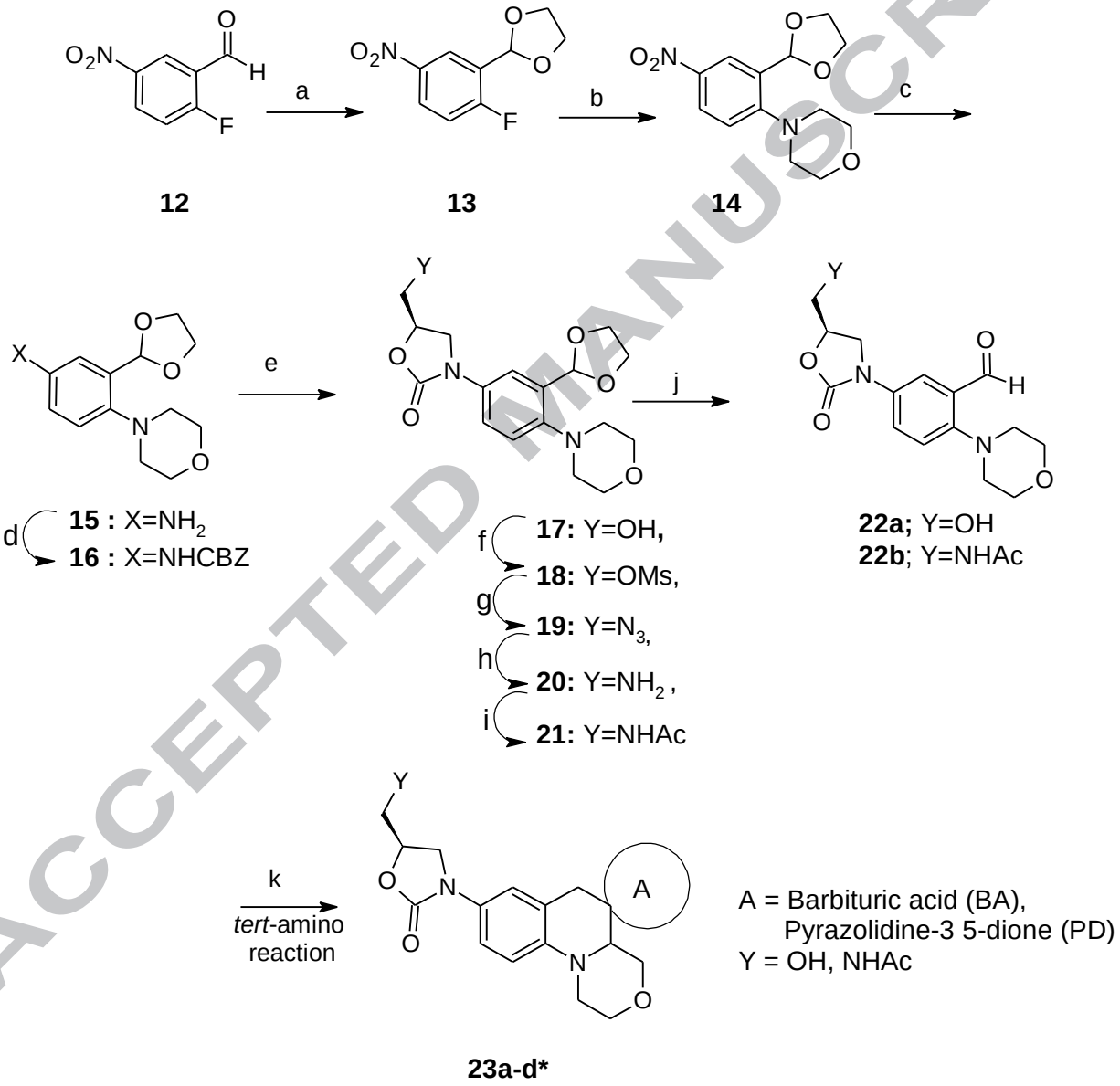


8 **9** **10** **11**

The synthesis of Type I compounds **23a-d** was initiated from the aldehyde **12** following standard synthetic protocol. Thus, **16** was obtained in an overall yield of 75% in 4 steps. The compound **16** was converted to oxazolidinone **17** by standard protocol[34]. Sequential functional group transformations led to the formation of key intermediate **21** in 4 steps in an overall yield of 74%. Usual acetal deprotection protocol afforded the aldehydes **22a-b**. Heating intermediates **22a-b** with barbituric acid under microwave condition at 120°C for 30 min led to the formation of **23a-d** in 80-90% yield *via* T-amino reaction (Scheme 2).

Scheme 2: Synthesis of Type I derivatives **23a-d**

Reagents and conditions: (a) PTSA, ethylene glycol, toluene, reflux 3h, 85%; (b) Morpholine, K_2CO_3, DMF, 70°C, 4h, 90% ; (c) H_2, Pd-C, MeOH, rt, 4h, 82%; (d)benzylchloroformate, aqueous $NaHCO_3$, acetone, 0°C-rt, 5h, 90% ; (e) n-BuLi, (R)-glycidyl butyrate, THF, -78°C - RT, 70%; (f) MsCl, Et_3N, DCM,0°C-rt, 4h, 90%; (g) NaN_3, DMF, 70°C, 10h, 75%; (h) Ph_3P, THF:H_2O (3:1), RT-50°C, 6h, 70%; (i) $(CH_3CO)_2O$, Et_3N, DCM, 0°C -RT, 2h , 60%; (j) 1N. HCl, THF, 50°C, 2h, 70%; (k) n-BuOH, barbituric acid/pyrazolidine-3,5-dione, microwave, 120°C, 30 min, 80-90%.

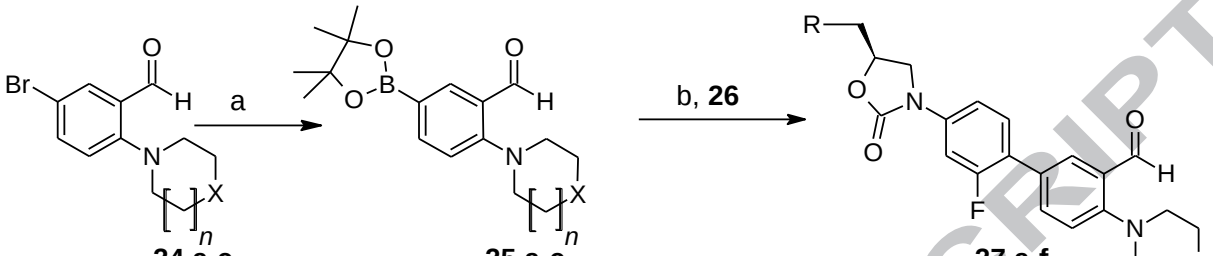


***for structure details please refer to Table 01**

Synthesis of Type II compounds **30a-s** was initiated from aldehyde **24a-c**[35]using standard organic transformations. Thus, intermediates**24a-c** were converted into their corresponding borate esters**25a-c** by Suzuki reaction. Palladium catalysed C-C coupling between **25a-c** and **26a-b**[34] afforded **27a-f** in up to 65% yields (Scheme 3). Deprotection of BOC from intermediate **27a-c** yielded free amines **28a-c** in up to 70% yield. Free amines were converted into corresponding amides **29a-f** (60-75% yield), carbamates **29g-j** (65-75% yield) and sulphonamides **29k-l** (70-80% yield) by standard derivatization protocols. These advanced intermediates **29a-l** were then converted to final compounds **30a-l** *via* T-amino reaction under microwave conditions by heating with barbituric acid for 30 min at 120°C (Scheme 4). Hydroxyl derivatives **30m-o** were synthesized from intermediate **27d-f**. Thus, TBS group was deprotected by TBAF to afford intermediate **28d-f**. Final compounds **30m-o** were synthesized *via* T-amino reaction using barbituric acid as the electron withdrawing group under microwave conditions (75-90% yield). Likewise, derivatives **30p-q** were synthesized from the corresponding intermediates **28f** & **29c** *via* T-amino reaction with pyrazolidine-3,5-dione as the participating electron withdrawing group. Intermediates **28a** & **28d** on reaction with dimethylmalonate gave the corresponding Knovenagel condensation products **29m-n**, which on T-amino reaction using $Gd(OTf)_3$ (lewis acid)[36] afforded **30r-s** (70-80%yield, Scheme 5).

Scheme 3: Synthesis of key intermediates **27a-f**.

Reagents and conditons: (a) bis(pinacolato)diboron, KOAc, $Pd(dppf)Cl_2$, dioxane, 80°C, 4h; 50-60% (b) $Pd(dppf)Cl_2$, $CsCO_3$, DMF/H_2O, 80°C, 6h, 50-65%

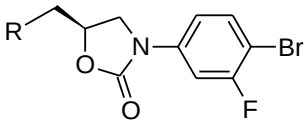


24 a-c **25 a-c** **27 a-f**

24a: X=O, n= 1
24b: X=CH, n= 1
24c: X=CH, n= 0

25a: X=O, n= 1
25b: X=CH, n= 1
25c: X=CH, n= 0

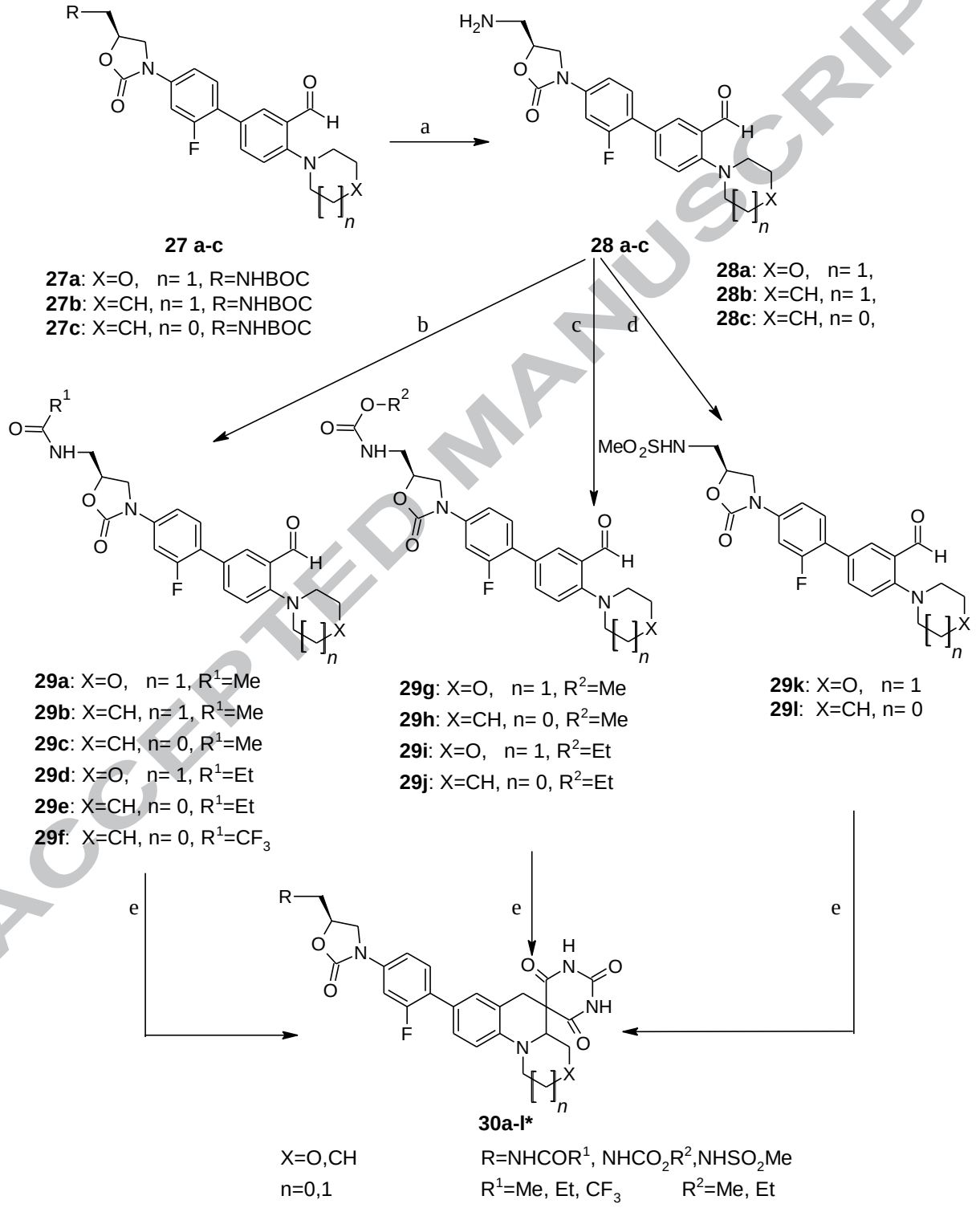
27a: X=O, n= 1, R=NHBOC
27b: X=CH, n= 1, R=NHBOC
27c: X=CH, n= 0, R=NHBOC
27d: X=O, n= 1, R=OTBS
27e: X=CH, n= 1, R=OTBS
27f: X=CH, n= 0, R=OTBS



26a: R=NHBOC
26b: R=OTBS

Scheme 4: Synthesis of Type II compounds **30a-l**

Reagents and Conditions: (a) dioxane 4.0 M HCl, MeOH, RT, 12h, 50-70%; (b)R^1-COCl, TEA, DCM, 0°C-RT, 2h (R^1=Me, Et, CF_3), 60-75%; (c) R^2-CO_2Cl, TEA, DCM, 0°C-RT, 2h (R^2=Me, Et), 65-75%; (d) $MeSO_2Cl$, TEA, DCM, 0°C-RT, 2h, 70-80%;(e) n-BuOH, barbituric acid,microwave, 120°C, 30 min, 75-90%;



27 a-c

27a: X=O, n= 1, R=NHBOC
27b: X=CH, n= 1, R=NHBOC
27c: X=CH, n= 0, R=NHBOC

28 a-c

28a: X=O, n= 1,
28b: X=CH, n= 1,
28c: X=CH, n= 0,

29a: X=O, n= 1, R^1=Me
29b: X=CH, n= 1, R^1=Me
29c: X=CH, n= 0, R^1=Me
29d: X=O, n= 1, R^1=Et
29e: X=CH, n= 0, R^1=Et
29f: X=CH, n= 0, R^1=CF_3

29g: X=O, n= 1, R^2=Me
29h: X=CH, n= 0, R^2=Me
29i: X=O, n= 1, R^2=Et
29j: X=CH, n= 0, R^2=Et

29k: X=O, n= 1
29l: X=CH, n= 0

30a-l*

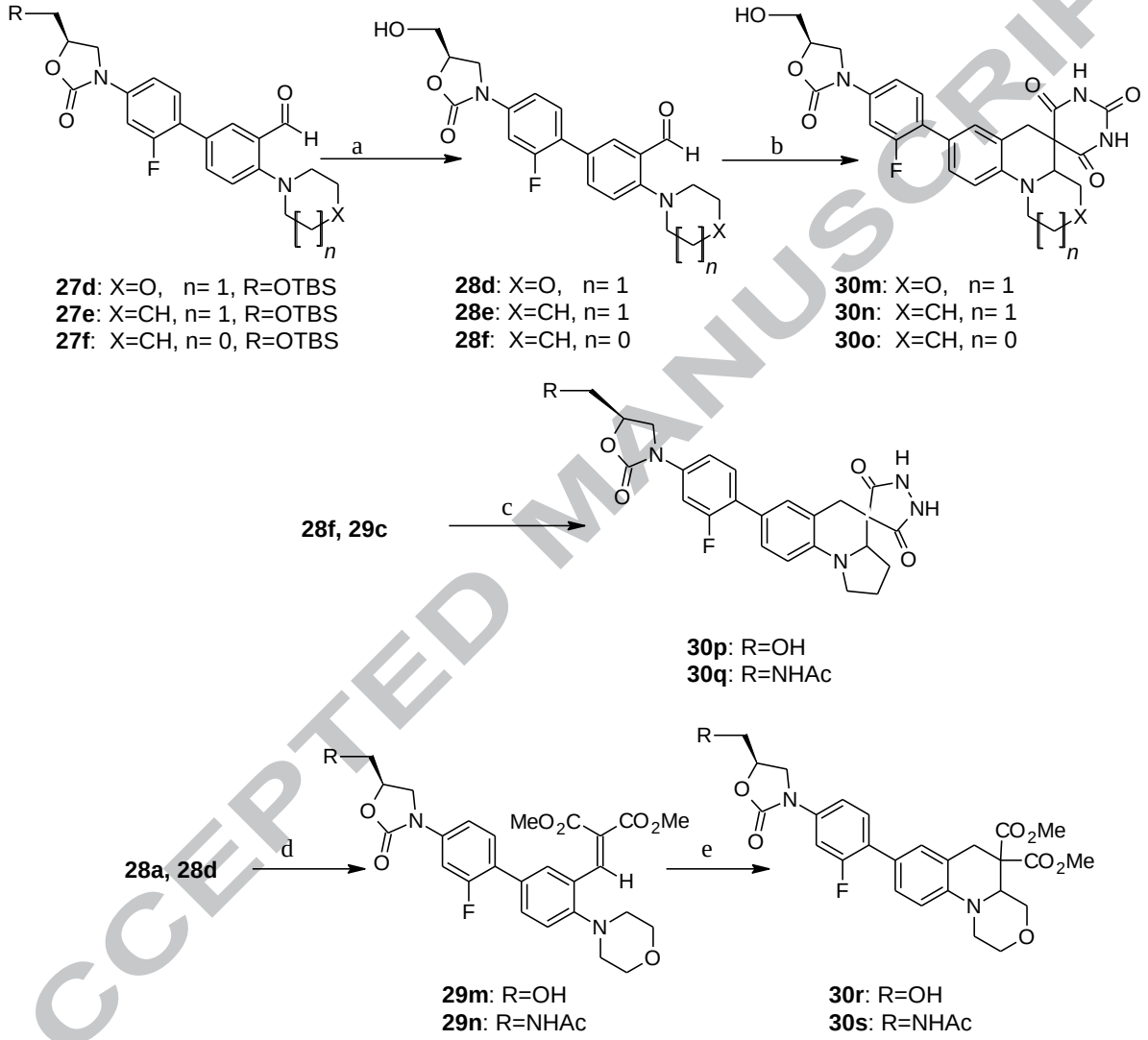
X=O,CH
n=0,1

R=$NHCOR^1$, $NHCO_2R^2$,$NHSO_2Me$
R^1=Me, Et, CF_3 R^2=Me, Et

***for structure details please refer to Table 02**

Scheme 5: Synthesis of Type II compounds **30m-s**

(a) TBAF, THF, 12h 70-85%; (b) n-BuOH, barbituric acid, microwave, 120°C, 30 min,75-90%; (c) n-BuOH, pyrazolidine-3,5-dione, microwave, 120°C, 30 min,75-85%; (d) Dimethylmalonate, piperidine, AcOH, toluene, reflux, 6h, 60-70%; (e) ACN, $Gd(OTf)_3$, RT, 3h, 70-80%.



27d: X=O, n= 1, R=OTBS
27e: X=CH, n= 1, R=OTBS
27f: X=CH, n= 0, R=OTBS

28d: X=O, n= 1
28e: X=CH, n= 1
28f: X=CH, n= 0

30m: X=O, n= 1
30n: X=CH, n= 1
30o: X=CH, n= 0

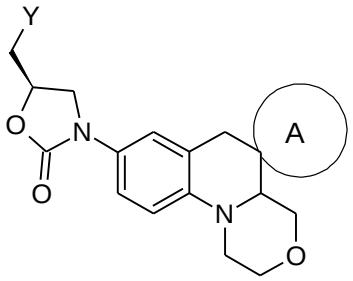
30p: R=OH
30q: R=NHAc

29m: R=OH
29n: R=NHAc

30r: R=OH
30s: R=NHAc

Antimicrobial activity of compounds **23a-d** was tested against a panel of Gram positive bacterial strains including *S. aureus* ATCC 29213, MRSA 562, MRSA DB-00026, LNZ^R(LNZ resistant) *S. aureus* ATCC 13709, *S. epidermidis* ATCC 12228, MRSE ATCC 35984 and LNZ^R*S. epidermidis*1117174. Compounds **23a-d** did not elicit any antimicrobial activity (MIC > 32 µg/mL) against this panel of Gram positive bacterial strains (Table 1).

Table 1: MICs (µg/mL) of Type I compounds **23a-d**.



23a-d

23	A	Y	MICs(µg/mL)
a	BA	NHAc	>32
b	BA	OH	>32
c	PD	NHAc	>32
d	PD	OH	>32

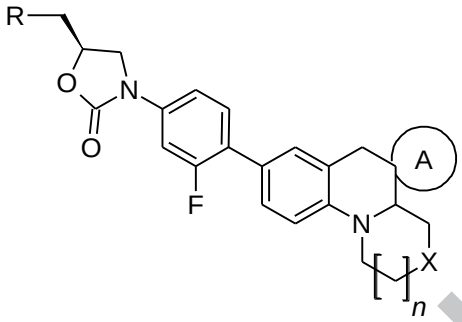
BA-Barbituric acid
PD-Pyrazolidine-3 5-dione

Interestingly, compound **30a** belonging to Type II class exhibited antibacterial activity comparable to LNZ against the tested panel of Gram-positive pathogens (Table 2). Extensive three-point modification around the structure **30a** was performed (Figure 5). Morpholine, pyrrolidine, and piperidine derivatives were synthesized in the tertiary amine portion. Barbituric acid, pyrazolidine-3 5-dione, and dimethyl malonate were utilised as electron withdrawing groups. Amides, carbamates, sulphonamides, and hydroxyl groups were used as substituents on C5 oxazolidinone side chain. We prepared a total of 19 new compounds by the multistep reactions (Scheme 3,4,5) for this SAR study (Table 2). From amongst all the compounds **30b, 30c, 30h & 30n** were found to be the most potent. These four potent compounds were further profiled against a panel of LNZ^R and vancomycin resistant *enterococci* strains (Table 3). These compounds exhibited moderate to good *in-vitro* antibacterial activity against the tested pathogens. In particular, **30n** showed appreciable activity against the LNZ and vancomycin resistant *enterococci* strains.

Based on these results it was possible to deduce some preliminary SAR. First, Methylcarbamates **(30g)** and acetamide **(30a)** were found to exhibit superior activity than other morpholine derivatives (**30d, 30i, 30k, 30m**). Second, barbituric acid derivatives **(30a, 30c)** showed better antibacterial activity profile than dimethyl malonate**(30s)** and pyrazolidine-3 5-dione**(30q).** Third**,** pyrrolidine **(30c,**

30o) and piperidine **(30b, 30n)** derivatives were found to exhibit better antibacterial profile than the morpholine derivative **(30a, 30m)**.

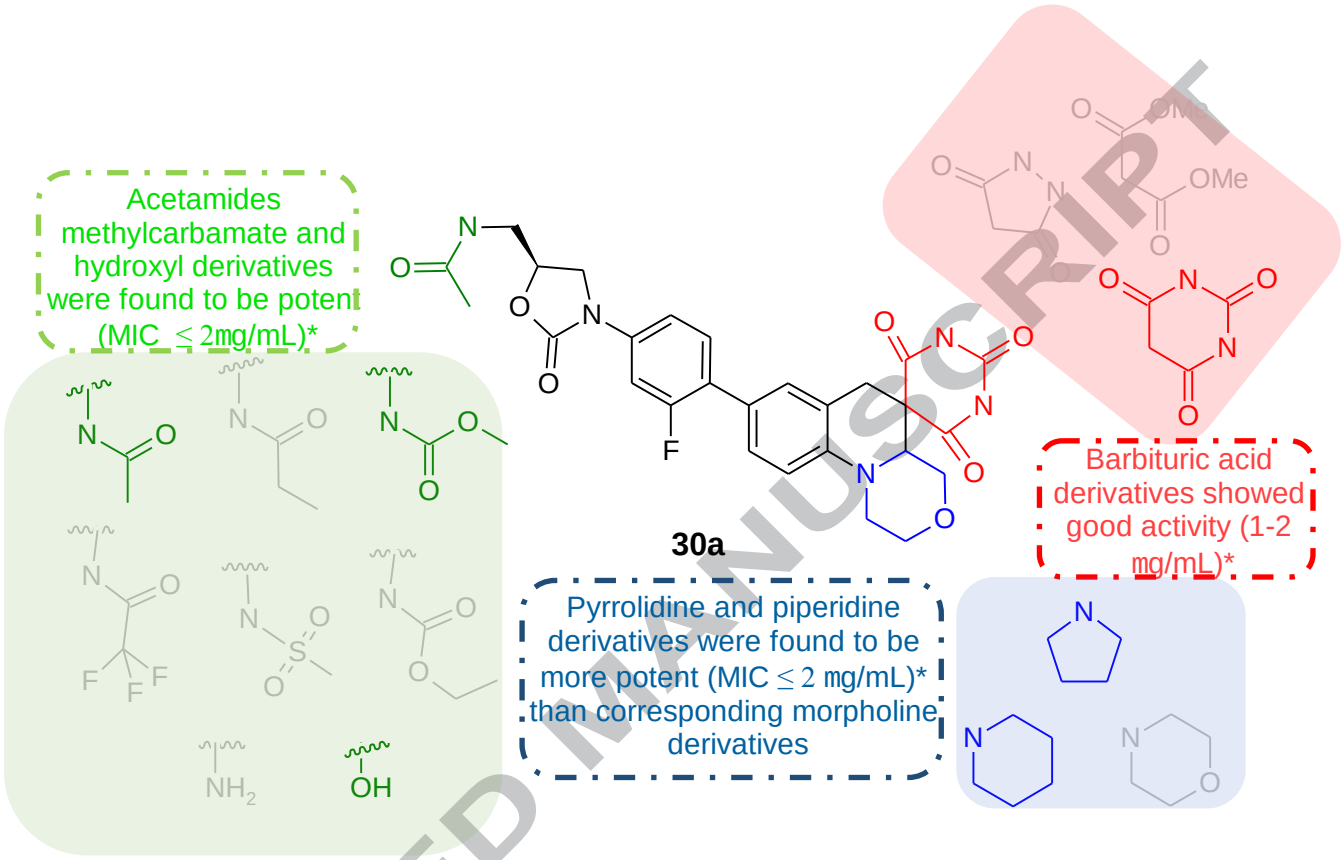
Table 2: MICs (µg/mL) of Type II compounds**30 a-s**.



					MICs (µg/mL)						
30	A	n	X	R	*S.aureus* ATCC 29213	MRSA 562	MRSA DB-00026	*S.aureus* ATCC 13709 Smith (LNZ^R)	*S.epidermidis* ATCC 12228	MRSE ATCC 35984	*S.epidermidis* 1117174 (LNZ^R)
a	BA	1	O	NHCOMe	4	4	8	32	4	2	32
b	BA	1	CH	NHCOMe	2	<1	2	16	2	<1	>32
c	BA	0	CH	NHCOMe	2	2	2	16	2	<1	32
d	BA	1	O	NHCOEt	8	4	16	>32	4	4	32
e	BA	0	CH	NHCOEt	16	4	8	32	8	4	32
f	BA	0	CH	$NHCOCF_3$	32	8	16	32	8	4	32
g	BA	1	O	$NHCO_2Me$	4	4	8	>32	4	2	32
h	BA	0	CH	$NHCO_2Me$	2	2	4	>32	2	2	32
i	BA	1	O	$NHCO_2Et$	16	8	16	>32	8	8	32
j	BA	0	CH	$NHCO_2Et$	8	4	8	>32	8	8	>32
k	BA	1	O	$NHSO_2Me$	32	32	32	>32	16	32	>32
l	BA	0	CH	$NHSO_2Me$	16	8	16	>32	8	4	32
m	BA	1	O	OH	8	4	8	32	4	2	32
n	BA	1	CH	OH	4	2	4	16	2	<1	32
o	BA	0	CH	OH	4	2	8	32	2	<1	32
p	PD	0	CH	OH	4	2	8	32	2	<1	32
q	PD	0	CH	NHCOMe	8	8	8	>32	8	4	>32
r	DM	1	O	OH	16	8	16	>32	8	8	>32
s	DM	1	O	NHCOMe	8	4	16	>32	4	4	32
	Linezolid				2	2	2	>32	2	2	>32

BA-Barbituric acid, DM-Dimethyl malonate,
PD-Pyrazolidine-3,5-dione

Figure 5: SAR of the synthesized spiropyrimidinetrione oxazolidinone derivatives.



* MICs in µg/mL against MRSA 562 strains

Table 3: MICs (µg/mL) of selected Type II compounds against *enterococci*.

30	MICs (µg/mL)						
	E.faecalis ATCC 51299	E.faecalis 29212 ATCC LNZ^R	E.faecalis ATCC 19434	E.faecalis ATCC 29212	E.faecium R1 VRE	E.faecium 303 LNZ^R	E.faecium 31/132 VRE
b	1	4	2	2	1	16	2
c	2	4	2	2	2	16	2
h	8	16	16	8	8	>32	16
n	1	**2**	2	2	**0.25**	8	**2**
Linezolid	4	>32	2	2	4	>32	2
Vancomycin	>32	2	0.5	2	0.5	2	>32

Computational studies have become a very prominent tool in drug discovery[37]. In order to understand the potency of the synthesized compounds and guide the further structure activity relationship, molecular docking studies were performed in relation with LNZ. For the purpose of this study, crystal structure of 50S ribosome unit of *E.coli* (PDB ID: 3CPW) was used.

The key interaction of LNZ is that of oxazolidinone ring A. The oxazolidinone ring along with C5 acylacetamide has good shape complimentary with ribosome. Fluorophenyl ring B is involved in the typical aromatic shifted π stacking interaction. The morpholine ring apparently does not make significant interaction with the ribosome. This has been substantiated with the fact that many different functional groups have been substituted without appreciable loss in activity[38].Docking studies with **30n** was then performed using 50S ribosome unit of *E.coli* (PDB ID: 3CPW). The OH attached to the oxazolidinone ring makes a hydrogen bond with base portion of G2646 (estimated bond length 3.18 A). Oxygen of the barbituric acid also shows hydrogen bond with G2540 (estimated bond length 2.94 A). Spiropyrimidinetriones moiety is stabilised through hydrophobic interaction with C2487, U2541, A2486 and G2102. The aromatic fluorophenyl ring proximal to oxazolidinone is stabilised by A2099, A2100 and A2538 (Figure 6). We also performed an overlay of LNZ and **30n** and observed that both bind in the same region (Figure 7). Interestingly, spiropyrimidinetriones moiety (barbituric acid) played a key role in addition to the oxazolidinone ring.

Figure 6: Molecular docking studies of compound **30n**

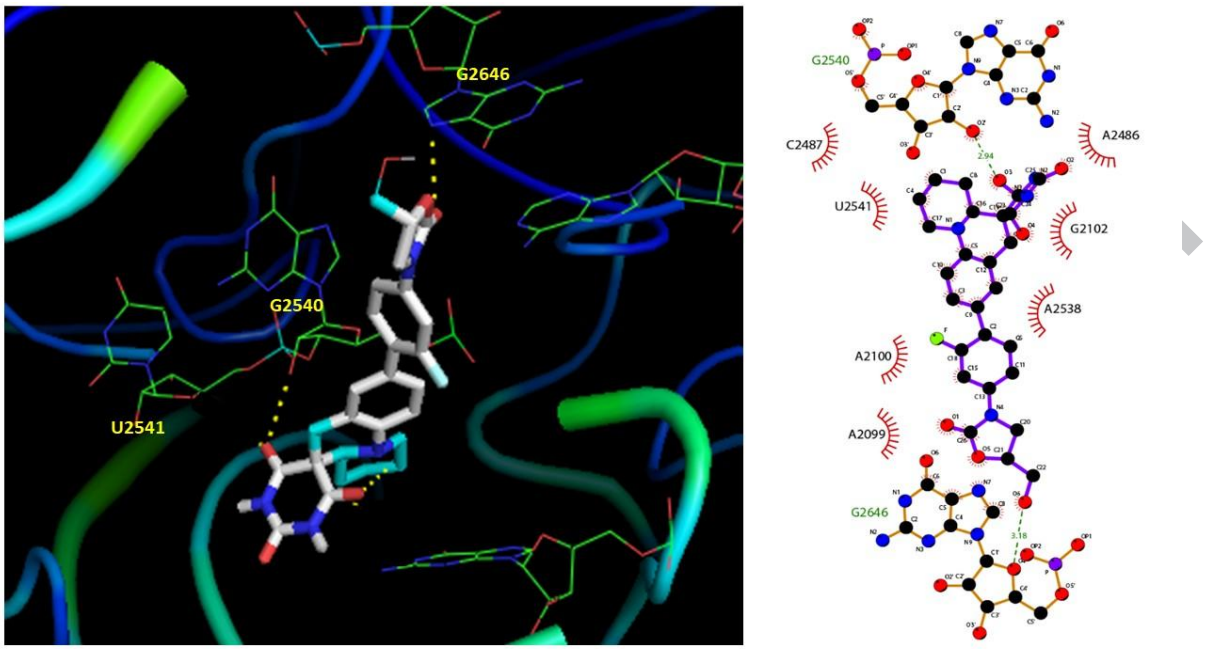
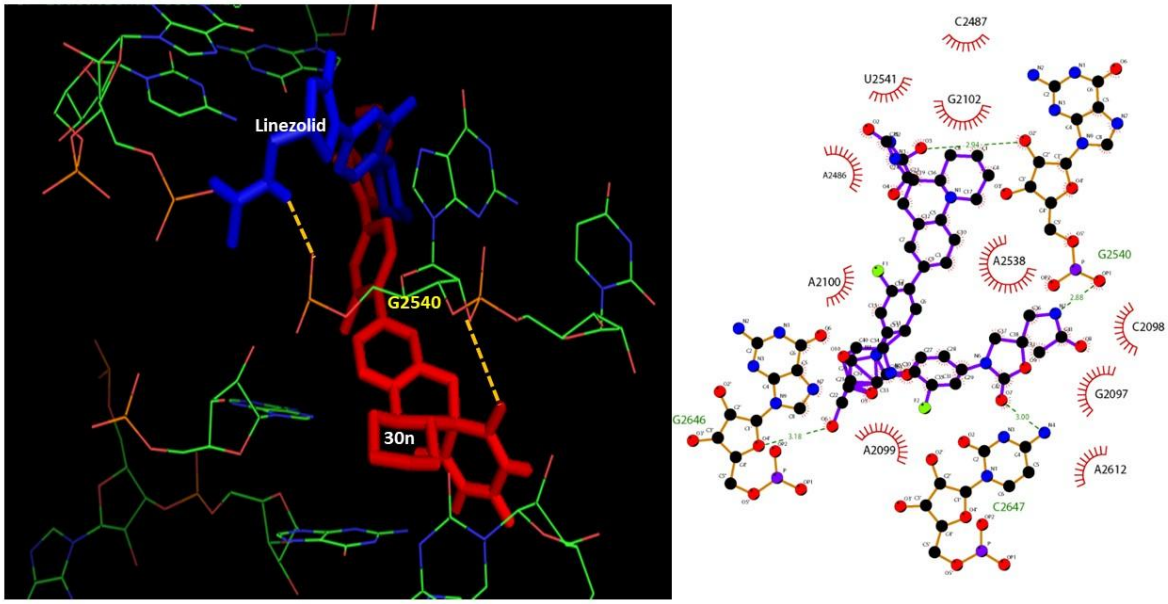


Figure 7: Overlay of **30n** and Linezolid.



In summary, several novel oxazolidinone type antibacterial bearing a unique spiropyrimidinetriones moiety were synthesized and evaluated for their antibacterial properties. Most of the Type II synthesized compounds exhibited *in-vitro* antibacterial activity (MIC range 1-8µg/mL) and several

compounds **30b, 30c, 30h & 30n** showed potent activity against multidrug resistant pathogens (MIC range 0.25-2µg/mL). Compound **30n** in particular exhibited potency similar to Linezolid with activity on Linezolid and Vancomycin resistant strains. The detailed evaluation of this compound is ongoing and would be the subject matter of future communications.

Acknowledgments

AMS, JAS acknowledge DAIICHI SANKYO INDIA PHARMA LTD for providing the appropriate facilities to accomplish the work.

References and notes

1. Ventola, C. L. *P&T.* **2015**, *40*, 277–83.
2. Antimicrobial resistance: global report on surveillance **2014**, WHO.
3. Editors, T. P. M. *PLoS Medicine.***2016**, *13* (9), e1002130.
4. Antibiotic Resistance Threats in the United States, **2013**; Antibiotic/Antimicrobial Resistance ; CDC https://www.cdc.gov/drugresistance/threat-report-2013/
5. O'Neill, J. Review on AMR. Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations; *Wellcome Trust*. **2014**.
6. Health matters: Antimicrobial Resistance, *Public Health England*, December **2015.**
7. Fischbach, M. A.; Walsh, C. T. *Science.***2009**, *325*, 1089–1093.
8. Lewis, K. *Nat. Rev. Drug Discov.***2013**, *12*, 371–387.
9. Norrby, S. R.; Nord, C. E.; Finch, R. *Lancet Infect Dis.***2005**, *5*, 115–119.
10. David, *JAMA.* **2008**, *299*, 519.
11. Bhattacharya, P. K *Revista da Sociedade Brasileira de Medicina Tropical*.**2014**, *47*, 815–816.
12. J. R. Lentino, M. Narita, and V. L. Yu, *Eur. J. Clin. Microbiol. Infect. Dis*, **2008**, *27*(1), 3–15.
13. Warnke, P. H.; Lott, A. J. S.; Sherry, E.; Wiltfang, J.; Podschun, R. *J Craniomaxillofac Surg.***2017**, *41* (4), 321–326.
14. Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673.
15. Dresser, L. D.; Rybak, M. J. *Pharmacotherapy* **1998**, *18*, 456.
16. Brickner, S.; Barbachyn, M.; Hutchinson, D.; Manninen, P *J. Med. Chem.* **2008**, *51*, 1981-1990.
17. Tsiodras, S.; Gold, H. S.; Sakoulas, G.; Eliopoulos, G. M.; Wennersten, C.; Venkataraman, L.; Moellering, R. C.; Ferraro, M. J. *Lancet.***2001**, *358*, 207–208.
18. Gales, A. C.; Sader, H. S.; Andrade, S. S.; Lutz, L.; Machado, A.; Barth, A. L *Int J Antimicrob Agents.***2006**, *27*, 300–302.
19. Long, K. S.; Vester, B. *Antimicrob. Agents Chemother.***2012**, *56*, 603–612.
20. O'Connell, K. M. G.; Hodgkinson, J. T.; Sore, H. F.; Welch, M.; Salmond, G. P. C.; Spring, D. R. Antibacterials. *Angew. Chem. Int. Ed.***2013**, *52* (41), 10706–10733.

21. Michalska, K.; Karpiuk, I.; Król, M.; Tyski, S. *Bioorganic Med. Chem.***2013**, *21*, 577–591.
22. Im, W. Bin; Choi, S. H.; Park, J.-Y.; Choi, S. H.; Finn, J.; Yoon, S.-H. *Eur. J. Med. Chem.***2011**, *46*, 1027–1039.
23. Selvakumar, N.; Srinivas, D.; Khera, M.; Kumar, M.; Mamidi, R.; Sarnaik, H.; Charavaryamath, C.; Rao, B.; Raheem, M.; Das, J. et al. *J. Med. Chem.* **2002**, *45*, 3953-3962.
24. Xin, Q.; Fan, H.; Guo, B.; He, H.; Gao, S.; Wang, H.; Huang, Y.; Yang, Y. *J. Med. Chem.* **2011**, *54*, 7493-7502.
25. Ruble, J.; Hurd, A.; Johnson, T.; Sherry, D.; Barbachyn, M.; Toogood, P.; Bundy, G.; Graber, D.; Kamilar, G. *J. Am. Chem. Soc.***2009**, *131*, 3991-3997.
26. Basarab, G.; Doig, P.; Galullo, V.; Kern, G.; Kimzey, A.; Kutschke, A.; Newman, J.; Morningstar, M.; Mueller, J.; Otterson, L. et al. *J. Med. Chem.***2015**, *58*, 6264-6282.
27. Ippolito, J.; Kanyo, Z.; Wang, D.; Franceschi, F.; Moore, P.; Steitz, T.; Duffy, E; *J. Med. Chem.* **2008**, *51*, 3353-3356.
28. Barbachyn, M. R.; Ford, C. W. *Angew. Chem. Int. Ed.***2003**, *42* (18), 2010–2023.
29. Meth-Cohen, O.; Suschitzky, H. *Adv. Heterocycl. Chem.***1972**, *14*, 211
30. Platonova, A. Y.; Glukhareva, T. V.; Zimovets, O. A.; Morzherin, Y. Y. *Chem. Heterocycl. Compd.***2013**, *49*, 357–385.
31. Quintela, J. M. *Recent Res Dev Org Chem.* **2003**, *7*, 259.
32. Haibach, M. C.; Seidel, D. *Angew. Chem. Int. Ed.***2014**, *53*, 5010–5036.
33. Michael, J. Quinoline, Quinazoline and Acridonealkaloids. *Nat. Prod. Rep.* **2008**, *25*, 166-187.
34. Ding, Charles Z. et al.; *PCT* 2009120789, **2009.**
    Piperidine aldehyde preparation
35. Glukhareva, T. V; Kropotina, P. E.; Kosterina, M. F.; Nein, Y. I.; Deeva, E. V; Morzherin, Y. Y. *Chem. Heterocycl. Compd.***2007**, *43*, 76–81.

    Chen, D.-F.; Han, Z.-Y.; He, Y.-P.; Yu, J.; Gong, L.-Z. *Angew. Chemie Int. Ed.***2012**, *51*, 12307–12310.
36. S. Murarka, C. Zhang, M. D. Konieczynska, and D. Seidel, *Org. Lett*., **2009**,*11*, 129.
37. Kitchen, D. B.; Decornez, H.; Furr, J. R.; Bajorath, J. *Nat. Rev. Drug Discov.***2004**, *3* (11), 935–949.
38. Ippolito, J. A.; Kanyo, Z. F.; Wang, D.; Franceschi, F. J.; Moore, P. B.; Steitz, T. A.; Duffy, E. M. *J. Med. Chem.***2008**, *51*, 3353–3356.