*Plant Archives* Vol. 20 Supplement 1, 2020 pp. 3321-3328 **e-ISSN:2581-6063 (online), ISSN:0972-5210**

# NEW DELHI METALLO-β-LACTAMASE-1 INHIBITORS: A REVIEW OF THE PATENT LITERATURE (2013-2019)

**Ajmer Singh Grewal[1], Sukhbir Singh[1*], Neelam Sharma[1] and Komal Thapa[2]**

[1*]Chitkara College of Pharmacy, Chitkara University, Punjab, India.
[2]Chitkara University School of Basic Sciences, Chitkara University, Himachal Pradesh, India.

## Abstract

The worldwide prevalence of New Delhi metallo-β-lactamase-1 (NDM-1) has created distress among clinicians. These NDM-1 producing pathogens are resistant to all β-lactam antibiotics including carbapenems and are greatest threat to public health as they can easily extend via horizontal gene transfer. In the past 10 years, various NDM-1 inhibitors have been reported showing diverse chemical structure, but haven't been approved for clinical use; this may be due to structural complexity of the enzyme that limits the development of clinically useful NDM-1 inhibitors. This review article covers the patent literature in the area of NDM-1 inhibitors from 2013 to 2019, along with background about role of NDM-1 in antibiotic resistance.

***Key words:*** Antibiotic Resistance, New Delhi metallo-β-lactamase-1, NDM-1 inhibitors, Patent, Super bug.

## Introduction

The swiftly growing case of antibiotic resistance in patients has grown serious in community and health care settings all over the world (Cosgrove, 2006). According to the reports, increased mortality arises due to infections caused by multidrug-resistant organisms than the susceptible bacteria, which has put a huge economic burden in US of over $20 billion per year. A global estimation of 300 million premature deaths by 2050 due to antibiotic resistance has been predicted that will force millions of people into severe poverty (Sydnor and Perl, 2011; O'Neill, 2016). There are several reasons of developing antibiotic resistance like mutation in bacterial enzyme due to environmental changes and the overuse of antibiotics (Adekunle, 2012; Adegoke *et al*., 2017). Overuse or abuse of antibiotics in a particular population leads to selective killing of susceptible bacteria but gives no effect on resistant bacteria (Llor and Bjerrum, 2014; Fair and Tor, 2014). The antibiotics which were clinically used to target prokaryotic cells (bacterial cell wall, ribosome and DNA gyrase) are now least effective (Fair and Tor, 2014). Increasing rate of bacterial resistance has threatened the effectiveness of the most reliable and potent antibiotics (Davies and Davies, 2016; Bush and Fisher, 2011; Ventola, 2015). Health experts had been warning over a decade about speedily approaching 'post-antibiotic era' which means effective antibiotic will no longer remain effective against infections causing pathogens (Zhang *et al*., 2017; Kashyap *et al*., 2017; Podolsky, 2018).

The hydrolysis of amide bond in β-lactam ring by beta-lactamases is the recurrent cause of resistance. Beta-lactamases are categorized in classes A, B, C and D according to Ambler's classification (Khan *et al*., 2017). Class B enzymes, also known as metallo-β-lactamases (MBLs) holds broad spectrum of catalyzing the hydrolysis of almost all β-lactam antibiotics (Zhang *et al*., 2011; Rogers *et al*., 2013). NDM-1 (EC 3.5.2.6) is a type of B1 MBL formed in pathogens especially Gram-negative bacteria carrying $bla_{NDM-1}$ gene (King *et al*., 2012). These pathogens are also called "super bugs" or "bad bugs" because they are resistant to all antibiotics including carbapenem and are responsible for severe infections in humans (Srivastava *et al*., 2011). NDM-1 was first detected in Swedish patient, who was infected with *Klebsiella pneumonia* and *Escherichia coli* in New Delhi; December 2009 (Struelens *et al*., 2010). A great challenge persists among health workers across the world for the treatment of infections caused by NDM-1 bearing pathogens such as *E. coli* and *K. pneumonia*. From the

***Author for correspondence :** E-mail: sukhbir.singh@chitkara.edu.in, singh.sukhbir12@gmail.com

past decade, the hydrolytic activity of the MBLs, especially NDM-1 has been largely studied (Groundwater *et al*., 2016).

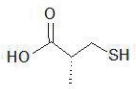
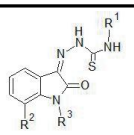
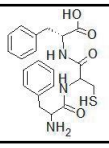
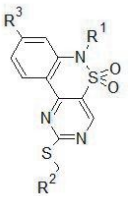
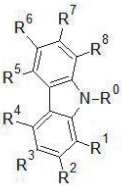
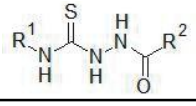
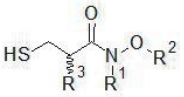
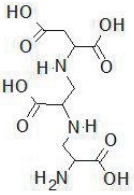
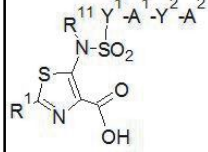
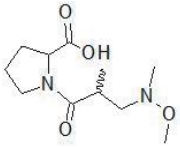
## NDM-1 INHIBITORS

The discovery of NDM-1 has prompted many researchers to identify and evaluate promising agents for NDM-1 inhibition which may protect antibiotics from hydrolysis. Currently maximum efforts are concentrated on the development of molecules which act synergistically with carbapenems to restore the effectiveness of antibiotic against NDM-1 as it presents the possibility to protect and prevent hydrolysis of β-lactam antibiotics (Livermore *et al*., 2013). In 2011, colistin (or polymyxin E, a mixture of cyclic polypeptides colistin A and B) was reported to have inhibitory effects against NDM-1 producing *E. coli* (minimum inhibitory concentration (MIC) was < 0.5 mg/L after 4 months in *E. coli* strain isolated from patient) and suggested that invasive infection with NDM-1 producers can be successfully treated with colistin, although with the risk of substantial toxicity (Stone *et al*., 2013). Thiophene-carboxylic acid derivatives were identified to have inhibitory action on NDM-1 as it gave synergistic effect in combination with meropenem against *E. coli* expressing NDM-1 (Shen *et al*., 2013). Recently ethanol extracts from the leaves of 240 medicinal plants were screened for antibacterial activity against NDM-1 expressing *E. coli* strain. Six plant extracts showed the MIC between 2.56 and 5.12 mg/ml and half maximal inhibitory concentration ($IC_{50}$) value ranged between 0.50 and 1.2 ng/µl for NDM-1 inhibition. All the plant extracts showed synergistic effects when combined with colistin, meropenem and tetracycline (Chandar *et al*., 2017). Cystatin 9 and cystatin C, significantly improved antimicrobial resistance against NDM-1 in mice infected intranasally with a 90% lethal dose challenge of NDM-1 producing *K. pneumoniae* (Holloway *et al*., 2018). Dipicolyl-vancomycin conjugate showed favorable inhibitory activity against NDM-1 producing bacteria and successfully restored meropenem activity against NDM-1 producing *K. pneumoniae* in a murine sepsis infection model (Yarlagadda *et al*., 2018). Thanatin inhibited the enzymatic activity of NDM-1 by displacing Zn ions from the active site and reversed carbapenem resistance in NDM-1 producing bacteria *in vitro* and *in vivo* (Ma *et al*., 2019). In the past 10 years various types of NDM-1 inhibitors were reported and a wide diversity was observed in the chemical nature of the NDM-1 inhibitors including natural plant based compounds (flavonoids, lignans, steroidal & saponins, terpenoids, alkaloids, benzophenones and stilbenoids), synthetic small molecule inhibitors (sulphonamides, pyrrolidines, thiophenes, alkanoic acids, indolines, thiols, thioacetamides, bisthiazolidines, organo-selenium compounds, salicylic acid analogues, thienyls, cyclic boronates, dipicolinic acid derivatives, triazoles, tetrazoles, benzoquinones, semicarbazones, bismuth compounds, benzamides, dicarboxylic acids, ebsulfurs, sulfonylureas and carbamates), β-lactams (N-sulfonyloxy β-lactams, cephalosporins and carbapenems), amino acid derivatives (homocysteine analogues, amino acid thioesters and poly-amino acids) and peptides (Groundwater *et al*., 2016; Linciano *et al*., 2019).

### Patent Literature

With the increasing frequency of multi-drug resistance due to NDM-1 producing strains, various NDM-1 inhibitors were developed. Numerous reports disclosing NDM-1 inhibitors had been appeared in the patent literature and were published in various reviews (Fast and Sutton, 2013; Buyank, 2013; Chaudhary and Payasi, 2013; Keating *et al*., 2014; Groundwater *et al*., 2016). Substituted maleic acid derivatives were patented as MBL inhibitors in 2007. Maleic acid derivatives showed better MBL inhibitory potency but regardless of their improved inhibitory potency, larger maleic acid analogs did not lower MICs of partner antibiotics against an MBL-producing *P. aeruginosa* strain (Chikauchi *et al*., 2007). Recently, a patent described the preparation of maleic acid derivatives with improved ability to inhibit NDM-1 and to synergize with imipenem (Morinaka *et al*., 2014). Another patent published traditional Chinese medicinal products for the treatment of infections due to bacteria producing NDM-1 (Jinjun, 2015). Tianjin International Biomedical Research Institute, China Pharmaceutical University, Jiangsu Normal University, Texas A&M University System, Tianjin International Biomedical Research Institute, Xiamen Jushengyuan Pharmaceutical Technology, Antabio Sas, Tianjin International Joint Academy of Biotechnology & Medicine, Nanjing Guangfang Biotechnology, Beijing University, Sun Yat-Sen University, Marquette University, Loyola University Chicago, University of Texas System, Jilin University, Chinese Academy of Medical Sciences, Northwest University, Zhengzhou University, Wuhan University People's Hospital, Loyola University Chicago, University of Texas System and Xuhe Pharmaceutical Technology, are the major academic and research institutions and companies, which published patents disclosing NDM-1 inhibitors recently. General chemical structures of NDM-1 inhibitors along with title of the patent application published in the recent patent literature by various research institutions and pharmaceutical companies are presented in table 1.

**Table 1:** Patents NDM-1 inhibitors reported in recent patent literature (from 2013 to 2019).

| Patent No. and Date | Title of Patent | Company / Assignee | General Structure | References |
|---|---|---|---|---|
| CN103156833A June 19, 2013 | "Application of (R)-2-Methyl-3-Mercaptopropionic Acid in Inhibiting NDM-1" | Tianjin International Biomedical Res. Institute |  | Zihe *et al.*, 2013 |
| CN102626408B October 16, 2013 | "Application of Isatin Thiosemicarbazone Compound in Inhibition of NDM-1 Activity" | Tianjin International Biomedical Res. Institute |  | Yu *et al.*, 2013 |
| CN103588861A February 19, 2014 | "New Delhi Metallo-Beta-Lactamase Inhibitory Peptide and Application Thereof" | China Pharmaceutical University |  | Yu *et al.*, 2014 |
| CN103951680A July 30, 2014 | "Application of Novel Metal Beta-Lactamase Inhibitor in Preparation of Medicines for Resisting Drug-Resistance Bacteria" | China Pharmaceutical University |  | Yang *et al.*, 2014 |
| WO2017084231A May 26, 2015 | "Series of Fluorine-Containing Carbazole Compounds, Preparation Method and Use Thereof" | Jiangsu Normal University |  | Changsheng *et al.*, 2015 |
| WO2015157618A October 15, 2015 | "Novel Inhibitors of the New Delhi Metallo Beta Lactamase (NDM-1)" | Texas A&M University System |  | Sacchettini *et al.*, 2015 |
| CN103130692B March 14, 2016 | "Application of 3-Mercapto Propionic Amides" | Tianjin International Biomedical Research Institute |  | Zihe *et al.*, 2016 |
| CN105646251A June 8, 2016 | "Aspergillomarasmin Compound and Synthesis Method Thereof" | Xiamen Jushengyuan Pharmaceutical Technology |  | Yuanjie *et al.*, 2016 |
| GB2533136A June 15, 2016 | "Compounds" | Antabio Sas |  | David *et al.*, 2016 |
| CN103159660B July 06, 2016 | "(2R)-1-(2-Methyl-3-(methoxy (methyl) amino)-propanoyl) pyrrolidine-2-carboxylic Acid and its Applications" | China Pharmaceutical University |  | Zihe *et al.*, 2016a |

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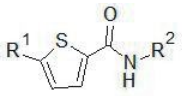
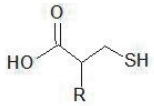
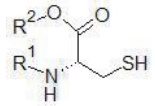
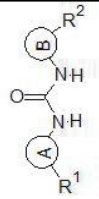
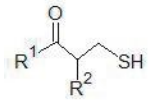
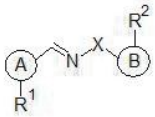
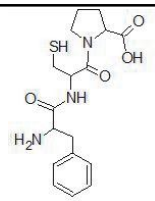
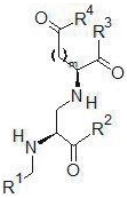
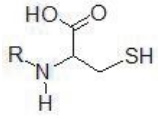
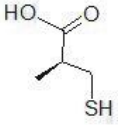
| CN103159733B July 13, 2016 | "Having NDM-1 Inhibitory Activity Thiophene Carboxamides" | Tianjin International Biomedical Res. Institute |  | Wei *et al*., 2016 |
| CN103156832B August 03, 2016 | "Application of 3-Mercaptopropionic Acid Compounds in Inhibiting NDM-1" | Tianjin International Biomedical Research Institute |  | Zihe *et al*., 2016b |
| CN103127048B August 03, 2016 | "Purpose of L-Cysteine Compound for Restraining New Delhi Metallo (NDM)-1 Activity" | Tianjin Int. Joint Academy of Biotechnology & Medicine |  | Zihe *et al*., 2016c |
| CN103130686B September 14, 2016 | "N,N'-Diaryl Substituted Asymmetric Urea Compounds and their Preparation and Use" | Tianjin International Biomedical Res. Institute |  | Cheng *et al*., 2016 |
| CN103156856B September 14, 2016 | "Application of 3-Mercaptopropionic Acid Amides of Compound" | Tianjin International Biomedical Res. Institute |  | Zihe *et al*., 2016d |
| CN103156844B November 16, 2016 | "Application of Schiff Base Compound in Inhibition of Activity of NDM-1" | Tianjin International Biomedical Res. Institute |  | Zihe *et al*., 2016e |
| CN106496303A March 15, 2017 | "Inhibition Peptide of Metal Beta-Lactamase and Application Thereof" | Nanjing Guangfang Biotechnology |  | Yi *et al*., 2017 |
| CN106518702A March 22, 2017 | "Aspergillomarasimine A and Derivative, Synthetic Method and Application Thereof" | Beijing University |  | Xiaoguang *et al*., 2017 |
| CN103127047B May 10, 2017 | "L-Cysteine Use the Active Compounds in Suppressing NDM-1" | Tianjin International Biomedical Research Institute |  | Zihe *et al*., 2017 |
| CN103156834B May 17, 2017 | S)-2-Methyl-3-mercaptopropionic acid in use in the inhibition ofNDM-1 | Tianjin International Biomedical Research Institute |  | Zihe *et al*. 2017a |

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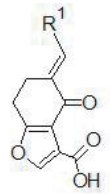
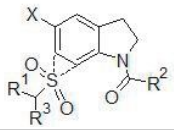
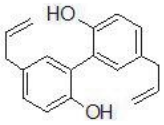
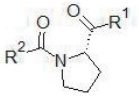
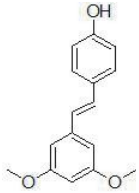
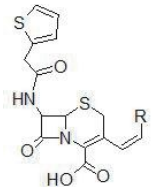
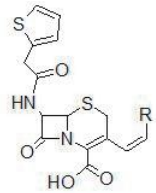
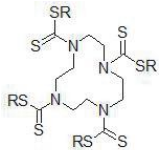
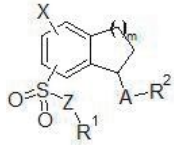
| CN106905273A1<br>June 30, 2017 | "4-Oxa-4,5,6,7-Tetrahydro Benzo[B] Furan-3-Carboxylic Compound and Application Thereof" | Sun Yat-Sen University |  | Yiqian *et al.*, 2017 |
| US20170226090A<br>August 10, 2017 | "Indoline Sulfonamide Inhibitors of DAPE and NDM-1 and Use of Same" | Marquette University |  | Becker *et al.*, 2017 |
| CN107320466A<br>November 7, 2017 | "Medical Applications of Magnolol in Preparing NDM-1 Enzyme Inhibitor" | Jilin University |  | Xuming *et al.*, 2017 |
| CN108084075A<br>May 29, 2018 | "Proline Derivatives Having Beta-Lactamase Inhibitory Effect" | Tianjin University |  | Qingzhi *et al.*, 2018 |
| CN108159029A<br>June 15, 2018 | "Application of Pterostilbene in Preparation of NDM-1 Enzyme Inhibitor" | Deng Xuming |  | Xuming *et al.*, 2018 |
| CN108272798A<br>July 13, 2018 | "Application of Thiazolidine-2, 4-Dicarboxylic Acid in Preparing Drug for Inhibiting Activity of Drug-Resistant Bacteria" | Northwest University |  | Junnan *et al.*, 2018 |
| CN108272800A<br>July 13, 2018 | "Application of Pyridine-2, 6-Dioctyl Phthalate to Preparation of Medicine for Inhibiting Drug-Resistant Bacteria Activity" | Northwestern University |  | Yuan *et al.*, 2018 |
| CN106220588B<br>August 7, 2018 | "Metal ²-Lactamase Inhibitor Cyclic Amino Acid Derivatives and Dithiocarbamates Prepared" | Zhengzhou University |  | En *et al.*, 2018 |
| CN109354606A<br>February 19, 2018 | "A Kind of Difunctional NDM-1 Carbapenem Enzyme Inhibition Peptide and its Application" | Wuhan University People's Hospital | Ile-Phe-Gly-Arg-Ile-Arg-Gly-Phe-Ile-Lys-Asn-Ile-Trp-Ser-Asp | Bingzheng *et al.*, 2019 |
| US201900849321<br>March 21, 2019 | "Indoline and Tetrahydroquinoline Sulfonyl Inhibitors of Dimetalloenzymes and Use of the Same" | Loyola University Chicago, University of Texas System |  | Becker *et al.*, 2019 |

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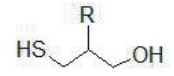
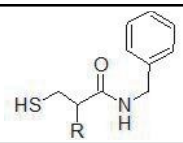
| CN104415017B May 7, 2019 | "Application of Mercapto-Propanol Compounds in Inhibition of NDM-1" | Xuhe (Tianjin) Pharmaceutical Technology |  | Yu *et al*., 2019 |
| CN104415019B May 7, 2019 | "3-Sulfydryl-N-Benzyl Propionamides Compound is Inhibiting the Purposes in NDM-1" | Xuhe (Tianjin) Pharmaceutical Technology |  | Honggang *et al*., 2019 |

## Conclusion

The fast-evolving resistance to carbapenems, since the origin of pathogens with NDM-1 gene has created seriousness among health care centers around the world. Infectious Disease Society of America has commenced a "bad bugs need drugs" campaign to encourage development of new antibiotics by 2020 that could fight with multi drug resistant infectious. Effective and novel drug design for NDM-1 producing pathogens is a great challenge for the medicinal chemists. Undoubtedly, only a robustly combined effort, merging drug design approaches with a deeper knowledge of NDM-1 structure and mechanism could orient a successful drug discovery campaign.

## Acknowledgement

The authors are thankful to Chitkara College of Pharmacy, Chitkara University, Punjab, India for providing facilities for compilation of this review.

## Conflict of Interest

The authors declare no conflict of interest.

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