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Ethyl Imidazole-1-Carboxylate as a Novel Carbonylating Agent for the Synthesis of 1,2,4-Oxadiazol-5(4H)-Ones and Evaluation of their Anti-Mycobacterial Activity

Indrasena Reddy K[1*], Aruna C[2], Sudhakar Babu K[1], Yogeeswari P[2], and Sriram D[2]

[1]Department of Chemistry, Sri Krishnadevaraya University, Anantapur, India

[2]Department of Pharmacy, Birla Institute of Technology and Science-Pilani, Hyderabad Campus, India

[*]**Corresponding author:** Indrasena Reddy K, Department of Chemistry, Sri Krishnadevaraya University, Anantapur, India, Tel: +9104066303506; E-mail: indra111sena@gmail.com

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Abstract

Various highly substituted 1,2,4-oxadiazol-5(4H)-ones were synthesized from the corresponding amidoximes using ethyl imidazole-1-carboxylate (EImC) as a novel carbonylation agent. This method is simple and convenient to produce these biologically interesting heterocycles in high yields. Among them, 4a, 4b, 4c, 4e, 4f, 4h, and 4i are identified as lead molecules. In particular, 4e, and 4h are found to display promising activity as good as ciprofloxacin, whereas 4i showed an excellent activity, which is equal to the IC50 value of ethambutol against *Mycobacterium tuberculosis.*

Keywords: Novel carbonylation agent; Ciprofloxacin; Amidoximes

Introduction

1,2,4-Oxadiazol-5(4H)-ones are among the most important scaffolds in the field of medicinal chemistry. They are acidic heterocycles, which are used as carboxylic acid bio-isosteres [1]. They act as AT1 antagonists [2] COX-2 inhibitors, [3] PLA2 inhibitors, [4] and modulators of GluR [5] phospholipase A2 inhibitors [6] and antimicrobial [7]. The most commonly used method for the synthesis of these heterocycles is the carbonylative cyclization of amidoximes using different carbonylating reagents. A variety of reagents such as hazardous triphosgene [8] poisonous carbon monoxide [9] high temperature reactions using urea [10] moisture sensitive 1,1'-carbonyl di imidazole [11] carbonates [12] and two steps synthesis using chloroformates have been used for this cyclization [13]. By considering the above drawbacks, there is a need to develop a simple method for the carbonylative cyclization of amidoximes into the corresponding benzoxazol-2(3H)-ones.

1,2,4-Oxadiazol-5(4H)-ones are generally synthesized by carbonylative cyclization of amidoximes using different carbonylating reagents such as, 1,1'-carbonyl di imidazole [14] chloroformates [15] alkyl carbonates [16] diphosgene [17]

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pentafluoro benzoyl chloride [18-20]. These reagents are either moisture sensitive or hazardous in nature. In order to overcome these difficulties, there is a need to develop simple methodologies for the synthesis of 1,2,4-oxadiazol-5(4H)-ones.

Mycobacterium tuberculosis is a major health and challenging problem around the world for more than five millennia. Tuberculosis is an air borne disease and spreads from person to person through tiny droplets discharged into the air. The most commonly affected sites in humans are the lungs. TB can also occur in bones, especially in the spine and at the ends of the long bones. The most disturbing factor in the current TB problem is the occurrence of multidrug resistant (MDR) strains not only to the front-line drugs but also to second line drugs.

The World Health Organization (WHO) estimates that there are approximately 8 million new infections and 3 million deaths attributed to *M. tuberculosis* annually [21-23]. Enhanced sanitation of living condition is significantly compact the frequency of the disease. The expansion of multidrug-resistant TB (MDR-TB) and the emergence of extensively drug-resistant TB (XDR-TB) cause new confront for the prevention, cure and manage of this lethal disease [24]. Therefore, the development of new drugs with enhanced activity against MDR-TB and XDR-TB is highly appreciated for the prevention of the disease.

One of the major problems associated in control of TB is that the restart of the disease in patients who carry a latent syndrome, in which the bacteria is in slow budding or non-growing state and is refractory to treat with predictable anti-TB drugs. Directly observed treatment (DOT) is presently practicing for standard TB chemotherapy. It is well known that the resistance levels are poor in the areas with a strongly performing DOTS programmes [25].

As part of our research on biologically active heterocycles [26], we herein report an efficient method for the synthesis of 1,2,4-oxadiazol-5(4H)-ones derivatives.

Results and Discussion

Following our interest on the synthesis and biologically evaluation of novel heterocycles, we herein report an efficient method for the synthesis of 1,2,4-oxadiazol-5(4H)-ones from the carbonylation of amidoximes using ethyl imidazole-1-carboxylate as a novel reagent. It offers several advantages such as ease of handling and compatible with acid sensitive substrates. Imidazole is only the by-product whereas HCl is the by-product, if chloroformate is used as a carbonylating agent.

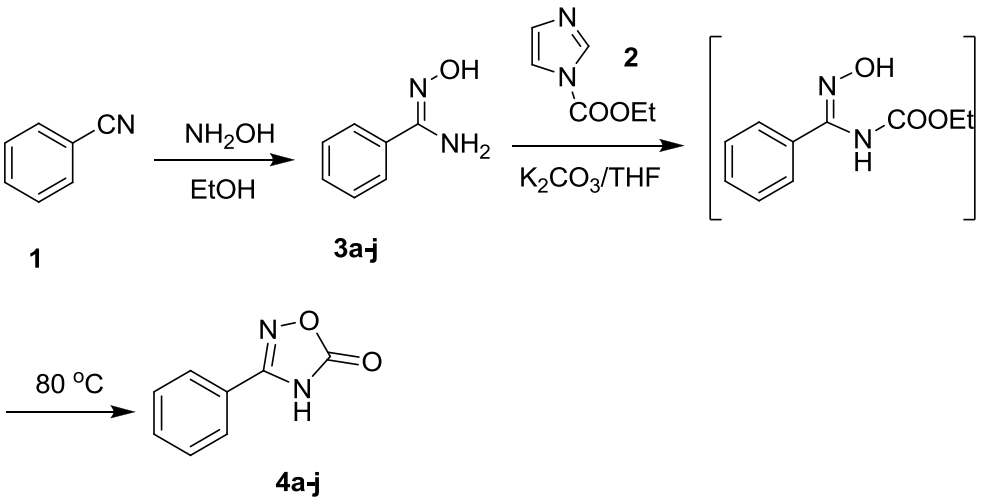
Chemistry

In the process of exploring the application of ethyl imidazole-1-carboxylate as a novel carbonylating reagent, we were interested to synthesize 1,2,4-oxadiazol-5(4H)-ones from the corresponding amidoximes. The required amidoximes were synthesized from the corresponding nitriles using known procedure (Supporting Information).

SCHEME 1

Initially, we performed the reaction of benzamidoxime (3a) with EImC (2) in THF/K_2CO_3 (Potassium Carbonate) (entry 1, TABLE 1) at room temperature. However, uncyclized carbamate was isolated as a sole product. Up on heating the reaction at 80°C, the desired product 4a was isolated in 88% yield (entry 2, TABLE 1). The reaction was further studied with different bases such as NaOMe, NaH, and t-BuOK. Among these, NaOMe in THF (TABLE 2, entry 3) at 60°C gave the desired oxadiazolone (4a) in 45% yield, without leaving any uncyclized product. Though the reaction proceeds at room temperature in the presence of either NaH, or t-BuOK, the desired product 4a was obtained in moderate yields (entries 4-7, TABLE 1). Of various solvents such as THF, DMF and toluene, THF gave the best results (TABLE 1). Therefore, 1,2,4-oxadiazol-5(4H)-

ones (4a-4j) were synthesized from amidoximes and ethyl imidazole-1-carboxylate in the presence of K_2CO_3 (Potassium Carbonate) in THF at 80°C (SCHEME 1).



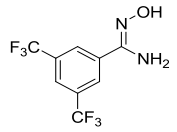
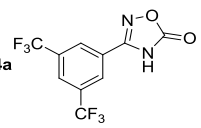
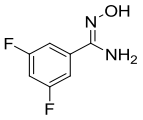
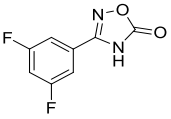
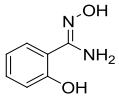
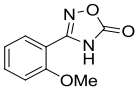
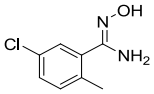
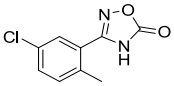
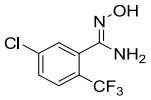
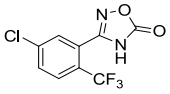
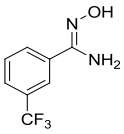
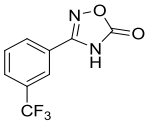
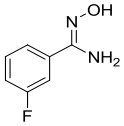
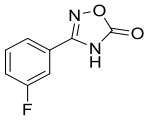
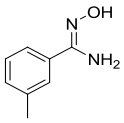
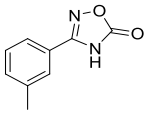
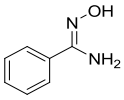
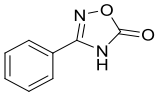
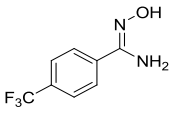
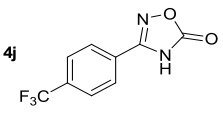
SCHEME 1. **Synthesis of 3-phenyl-1,2,4-oxadiazol-5(4*H*)-one.**

TABLE 1. **Optimization of the reaction using different bases and solvents.**

Entry	**Base**	**Temp (°C)**	**Time (h)**	**5I[a]**	**6[a]-k[a]**
1	K_2CO_3	25	15	92[b]	0
2	K_2CO_3	80	18	0	88[b]
3	NaOMe	60	14	0	45[b]
4	NaH	RT	7	0	89[b]
5	tBuOK	RT	15	0	52[b]
6	NaH	RT	8	0	68[c]
7	NaH	RT	10	0	35[d]

[a] Isolated yield;
[b] THF was used as a solvent;
[c] DMF was used as a solvent;
[d] Toluene was used as a solvent

TABLE 2. **Preparation of synthesis of 1,2,4-oxadiazol-5(4H)-one (4a-4j).**

Entry	Substrate	Product	Yield[a]
1	**3a** 	**4a** 	74
2	**3b** 	**4b** 	81
3	**3c** 	**4c** 	86
4	**3d** 	**4d** 	78
5	**3e** 	**4e** 	72
6	**3f** 	**4f** 	82
7	**3g** 	**4g** 	87
8	**3h** 	**4h** 	91
9	**3i** 	**4i** 	89
10	**3j** 	**4j** 	76

a Isolated yield

Thus, synthesized compounds (4a-4j) were screened for their in vitro anti-mycobacterial activity against *M. tuberculosis* H37Rv (MTB) by agar dilution method recommended by National Committee for Clinical Laboratory Standards for the determination of MIC values of the synthesized compounds along with standard drugs Isoniazid, Ethambutol and Ciprofloxacin. The comparative results are presented in TABLE 3. In the present study, oxadiazol-5(4H)-ones (4a-4j) were

screened against *M. tuberculosis*. The observed MIC values are ranging from 1.56 µg/mL to 50.0 µg/mL. Compounds 4a, 4b, 4c, 4e, 4f, 4h and 4i displayed significant activity, whereas compounds 4a, 4b, 4c and 4f showed moderate activity. Among them, 4e and 4h showed promising activity which is equal to the IC50 value of ciprofloxacin whereas 4i is equally effective as ethambutol. Based on MIC values, we deduce the structure-activity relationship by the influence of substituent present on 1,2,4-oxadiazol-5(4H)-one skeleton (COMPOUNDS 4a-4j). The presence of symmetrical di substituents like 3,5-diCF3, and 3,5-diF, the compounds are moderately active. Among meta-substituents such as m-Fluoro, m-CH3, m-CF3, the m-CH3 is more active. Similarly, p-CF3 is ineffective. Among disubstituted compounds like 2-methyl-4-chloro-, 2-CF3-4-chloro-, the later compound is more active. Interestingly, the compound without a substituent is more potent than all other compounds tested.

TABLE 3. **Anti-mycobacterial activity studies of compounds (4a-4j).**

Compound No	**Yield[a] (%)**	**Clog P[b]**	**MIC (µg/mL)**	**MIC (µM)**
4a	74	3.145	6.25	47.68
4b	81	4.235	6.25	31.68
4c	86	0.738	6.25	30.74
4d	78	2.291	50	4.21
4e	72	2.975	3.125	84.66
4f	82	2.262	6.25	36.82
4g	87	1.522	25	7.20
4h	91	1.878	3.125	56.37
4i	89	1.379	1.56	103.94
4j	86	2.262	50	4.60
Isoniazid			0.05	0.66
Ethambutol			1.56	7.63
Ciprofloxacin			3.13	9.44

Experimental Section

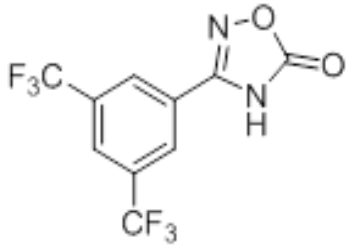
General methods

Melting points reported in this work were recorded in capillary tubes on a Elchem lab melting point apparatus and uncorrected. 1H and 13C NMR were recorded on Bruker FT-NMR spectrometer either 300 MHz or 400 MHz. using 5 mm PABBO BB-1H tubes. 1HNMR spectra were recorded using approximately 0.03 M solutions in $CDCl_3$ with TMS as an internal reference. 13C NMR spectra were recorded using approximately 0.05 M solutions in $CDCl_3$ at 100 MHz or 125 MHz. Chemical shift values were reported in parts per million (δ ppm) from internal standard TMS. UV-visible spectra were recorded on SYSTRONIC AU-2701 UV-Vis spectrophotometer. All reagents were purchased from Aldrich and used as received. Solvents were removed under reduced pressure on a rotavapour. Organic extracts were dried over anhydrous

Na_2SO_4. Silica gel $^{60}F_{254}$ coated aluminum sheets were used for TLC and silica gel (230-400 mesh) was used for column chromatography. Visualization of spots on TLC plates was effected by UV illumination, exposure to iodine vapor and heating the plates dipped in $KMnO_4$ stain.

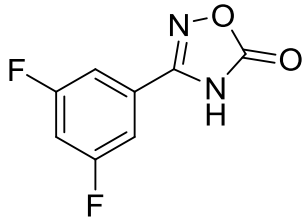
General procedure for the preparation of 4a-4j

To a solution of Benzonitrile (1 mmol) in EtOH (10 vol), $NH_2OH.HCl$ (Hydroxylamine Hydrochloride) (1.5 mmol) was added and allowed it to stir for 3h at 80°C, and then cool to room temperature. The excess of ethanol was removed by under vaccum. The resulting solution was dissolved in THF was added K_2CO_3 (Potassium Carbonate) (1.5 eq) and EImC (1 eq) and then stirred for 12 h at 80°C. The excess of THF was removed under reduced pressure and then the mixture was quenched with water and then neutralize with dil HCl. Solid was obtained and then filter and dried under vaccum.



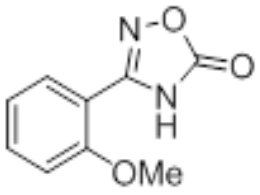
COMPOUND 4a. **3-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5(4H)-one.**

Off white solid, 92% yield; m.p. 168°C to 170°C; 1H NMR (400 MHz, $CDCL_3$): δ 8.41 (s, 2H), 8.03 (s, 1H), 13C NMR (70 MHz, $CDCl_3$+DMSO): δ 159.2, 154.6, 137.9, 131.3, 130.8, 127.9, 123.9, 123.5, 120.3. IR: υ max 3511, 1735, 1629, 1479, 1262, 953 cm^{-1}. LCMS: m/z 297.21 [MH-].



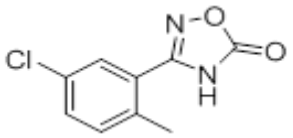
COMPOUND 4b. **3-(3,5-difluorophenyl)-1,2,4-oxadiazol-5(4H)-one.**

White solid, 94% yield; m.p. 176°C to 178°C; 1H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 2H), 7.08 (m, 1H); 13C NMR (70 MHz, DMSO+$CDCl_3$): δ 159.6, 156.5, 131.0, 128.1, 125.2, 122.6; IR: υmax 3154, 1765, 1641, 1454, 1162, 851 cm^{-1}. LCMS: m/z 197.2 [MH-].



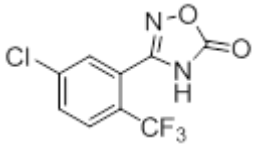
COMPOUND 4c. **3-(2-methoxyphenyl)-1,2,4-oxadiazol-5(4H)-one.**

Brown solid, 89% yield; m.p. 198°C to 200°C; 1H NMR (300 MHz, DMSO): δ 11.50 (s, 1H), 7.82 (d, J=7.9 Hz, 1H), 7.52 (m, 1H), 7.06 (m, 2H); 13C NMR (70 MHz, DMSOCDCl$_3$): δ 159.4, 156.3, 134.6, 131.0, 129.5, 126.7, 123.4, 120.6, 52.8; IR: υmax 3152, 1763, 1608, 1479, 1150, 851 cm^{-1}. LCMS: m/z 193.2 [MH+].



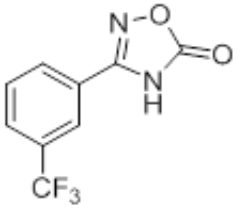
COMPOUND 4d. **3-(5-chloro-2-methylphenyl)-1,2,4-oxadiazol-5(4H)-one.**

Off White solid, 91% yield; m.p. 159°C to 161°C; 1H NMR (400 MHz, CDCl$_3$): δ 7.54 (d, J=2 Hz 1H), 7.44 (dd, J=2, 8.4 Hz, 1H), 7.30 (d, J=8.4 Hz, 1H), 2.54 (s, 3H); 13C NMR (70 MHz, DMSO+CDCl$_3$): δ 159.4, 156.4, 135.8, 132.3, 130.9, 130.4, 127.8, 123.7. IR: υmax 3269, 3082, 1632, 1498, 1269, 940 cm^{-1}. LCMS: m/z 209.4 [MH-].



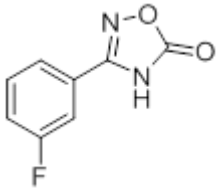
COMPOUND 4e. **3-(5-chloro-2-(trifluoromethyl) phenyl)-1,2,4-oxadiazol-5(4H)-one.**

Off White solid, 93% yield; m.p. 179°C to 181°C; 1H NMR (400 MHz, CDCl$_3$): δ 10.05 (b, 1H), 7.82 (d, J=8.4 Hz 1H), 7.74 (m, 2H); 13C NMR (70 MHz, DMSO+CDCl$_3$): δ 160.9, 156.9, 132.8, 129.2, 126.4, 125.4, 122.8, 121.5. IR: υmax 3169, 3022, 1732, 1428, 1369, 840 cm^{-1}. LCMS: m/z 263.3 [MH-].



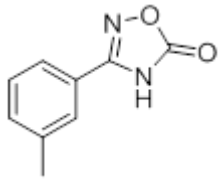
COMPOUND 4f. **6-methyl-3H-[1,2,4] oxadiazolo[4,3-f]phenanthridin-3-one.**

Brown solid, 93% yield; m.p. 182°C to 184°C; 1H NMR (400 MHz, CDCl$_3$): δ 1150 (b, 1H), 8.14 (s, 1H), 7.97 (d, J=8 Hz, 1H), 7.87 (d, J=7.6 Hz, 1H), 7.72 (t, J=8 Hz, 1H); 13C NMR (70 MHz, DMSO+CDCl$_3$): δ 159.8, 155.1, 134.8, 131.8, 129.9, 128.7, 125.9, 123.3. IR: υmax 3218, 1742, 1631, 1267, 851 cm^{-1}. LCMS: m/z 231.4 [MH+].



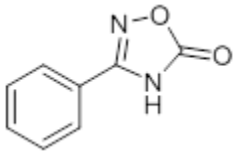
COMPOUND 4g. **3-(3-fluorophenyl)-1,2,4-oxadiazol-5(4H)-one.**

Off White solid, 69% yield; m.p. 154°C to 156°C; 1H NMR (300 MHz, $CDCl_3$): δ 10.35 (s, 1H), 7.21 (m, 1H), 7.19 (m, 1H), 7.15 (m, 1H); 13C NMR (70 MHz, DMSO+$CDCl_3$): 159.8, 156.5, 134.3, 132.8, 128.9, 126.3, 125.0, 120.7. IR: υmax 3311, 1742, 1632, 1432, 1162, 953 cm^{-1}. LCMS: m/z 181.2 [MH+].



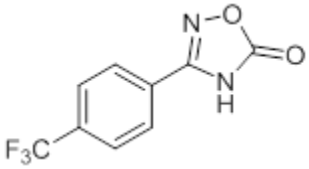
COMPOUND 4h. **methyl 3-oxo-3H-[1,2,4] oxadiazolo [4,3-f]phenanthridine-10-carboxylate.**

Off White solid, 69% yield; m.p. 178°C to 180°C; 1H NMR (300 MHz, $CDCl_3$): δ 10.92 (s, 1H), 7.61 (m, 2H), 7.05 (m, 1H); 13C NMR (70 MHz, DMSO+$CDCl_3$): 158.0, 155.9, 133.6, 131.0, 128.7, 126.2, 125.4, 119.3, 13.1. IR: υmax 3212, 1742, 1638, 1471, 1162, 953 cm^{-1}. LCMS: m/z 177.2 [MH+].



COMPOUND 4i. **3-phenyl-1,2,4-oxadiazol-5(4H)-one.**

Brown White solid, 92% yield; m.p. 172°C to 174°C; 1H NMR (400 MHz, $CDCl_3$): δ 11.20 (b, 1H), 7.81 (d, J=7.2 Hz, 2H), 7.57 (m, 3H); C NMR (70 MHz, DMSO+$CDCl_3$): 159.7, 156.6, 131.1, 128.2, 125.2, 122.7. IR: υmax 3511, 1735, 1629, 1479, 1262, 953 cm^{-1}. LCMS: m/z 161.2 [MH-].



COMPOUND 4j. **3-(4-(trifluoromethyl) phenyl)-1,2,4-oxadiazol-5(4H)-one.**

Off White solid, 94% yield; m.p. 184°C to 186°C; 1H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J=8 Hz, 1H), 8.32 (d, J=8.4 Hz, 1H); 13C NMR (70 MHz, DMSO+$CDCl_3$): 159.6, 156.9, 133.1, 130.4, 126.7, 124.7. IR: υmax 3511, 1735, 1629, 1479, 1262, 953 cm^{-1}. LCMS: m/z 231.2 [MH+].

Conclusion

In summary, we have developed a novel procedure for the synthesis of highly substituted 1,2,4-oxadiazol-5(4H)-ones from the corresponding amidoximes using ethyl imidazole-1-carboxylate (EImC). These molecules were screened against Mycobacterium tuberculosis. Of various compounds tested, 4a, 4b, 4c, 4e, 4f, 4h, and 4i are identified as lead molecules. In

particular, 4e, and 4h are found to display promising activity as good as ciprofloxacin, whereas 4i showed an excellent activity, which is equal to the IC50 value of ethambutol.

REFERENCES

1. Wustrow DJ, Belliotti TR, Capiris T, et al. Oxadiazolone bioisosteres of pregabalin and gabapentin. Med Chem. 2009;19:247.
2. Kohara Y, Kubo K, Imamiya E, et al. Synthesis and angiotensin II receptor antagonistic activities of Benzimidazole derivatives bearing acidic heterocycles as novel tetrazole bioisosteres. Med Chem. 1996;39:5228.
3. Boschelli DH, Connor DT. Oxadiazolones and derivatives thereof as peroxisome proliferator-activated receptor (PPAR) delta agonists. U. S. Patent 5. 1992;114:958.
4. Indrasena Reddy K, Aruna C, Manisha M, et al. Synthesis, DNA binding and *in-vitro* cytotoxicity studies on novel bis-pyrazoles. J Photochem Photobiol B: Biol. 2017;168:89-97.
5. Valgeirsson J, Nielsen EO, Peters D, et al. Bioisosteric modifications of 2-arylureidobenzoic acids: Selective noncompetitive antagonists for the homomeric kainate receptor subtype GluR5. Med Chem. 2004;47:6948.
6. (a) Meddad Belhabich N, Aoun D, Djimde A, et al. Design of new potent and selective secretory phospholipase A2 inhibitors. 6-Synthesis, structure–activity relationships and molecular modelling of 1-substituted-4-[4,5-dihydro-1,2,4-(4H)-oxadiazol-5-one-3-yl(methyl)]-functionalized aryl piperazin/one/dione derivatives. Med Chem. 2010;18:3588.
   (b) Boukli L, Touaibia M, Meddabiad Belhch N, et al. Design of new potent and selective secretory phospholipase A2 inhibitors. Part 5: Synthesis and biological activity of 1-alkyl-4-[4,5-dihydro-1,2,4-[4H]-oxadiazol-5-one-3-ylmethylbenz-4′-yl(oyl)] piperazines. Bioorg Med Chem. 2005;13:3797.
7. Mamolo MG, Zampieri D, Vio, L, et al. Antimycobacterial activity of new 3-substituted 5-(pyridin-4-yl)-3H-1,3,4-oxadiazol-2-one and 2-thione derivatives. Preliminary molecular modeling investigations. Med Chem. 2005;13:3797.
8. Mohammed I, Indrasena K, Gatikrushna, et al. 1,2,3-Triazoles as peptide bioisosteres: Discovery of a new class of potent HIV-1 Vif antagonists. Med Chem. 2016;59:7677-682.
9. (a) Gabriele B, Mancuso R, Salerno G, et al. An improved procedure for the palladium-catalyzed oxidative carbonylation of β-amino alcohols to oxazolidin-2-ones. J Org Chem. 2003;68:60.
   (b) Fu-Wei L, XinGao P, Chun Gu X, et al. An efficient synthesis of 2-oxazolidinones by palladium-catalyzed oxidative carbonylation of β-amino alcohols and 2-aminophenol under mild conditions. J Chem. 2005;23:643.
   (c) Li F, Xia CJ. Synthesis of 2-oxazolidinone catalyzed by palladium on charcoal: A novel and highly effective heterogeneous catalytic system for oxidative cyclocarbonylation of β-aminoalcohols and 2-aminophenol. Catalysis. 2004;227:542.
   (d) Troisi L, Grantio C, Perrone S, et al. Synthesis of benzo-fused five- and six-membered heterocycles by palladium-catalyzed cyclo carbonylation. 2011;52:4330.
   (e) Mizuno T, Toba H, Miyata T, et al. Convenient synthesis of heterocycles by sulfur-assisted carbonylation at ordinary pressure and temperature. Heteroatom Chem. 1994;5:437.
   (f) Sonoda N, Yamamoto G, Natsukawa K. A new synthesis of heterocycles by the reaction of amino alcohols or amino thiolswith carbon monoxide in the presence of selenium. Tetrahedron Lett. 1975;24:1969.
   (g) Li F, Xia C. Pd(Phen)Cl_2 stabilized by ionic liquid: An efficient and reusable catalyst for biphasic oxidative cyclocarbonylation of β-aminoalcohols and 2-aminophenol. Tetrahedron Lett. 2007;48:4848.

(h) Braunstein P, Rose J, Tiripicchio A, et al. Novel high-nuclearity HgCoRu and HgCoFe sandwich complexes. Synthesis and Structure of [Hg{$RuCo_3(\mu\text{-}CO)_3(CO)9$}2]. Chem Int Engl. 1985;97:762.

(i) Kihlberg T, Karimi F, Langstrom BJ. [(11)C] Carbon monoxide in selenium-mediated synthesis of (11)C-carbamoyl compounds. Org Chem. 2002;67:3687.

10. (a) Bhanage BM, Fujita S, Ikushima Y, et al. Non-catalytic clean synthesis route using urea to cyclic urea and cyclic urethane compounds. Green Chem. 2004;6:78.

(b) Eren G, Unlu S, Nunez MT, et al. Synthesis, biological evaluation, and docking studies of novel heterocyclic diaryl compounds as selective COX-2 inhibitors. Bioorg Med Chem. 2010;18:6367.

(c) Veeraswamy S, Indrasena Reddy K, Venkat Ragavan R, et al. An efficient one-pot chemoselective reduction of alkyl ketones over aryl ketones in diketones using LiHMDS and lithium aluminium hydride. Tetrahedron Lett. 2012;53:4651-653.

(d) Nagano T, Itoh M, Matsumura KJ. Preparation of certain derivatives of benzoxazole. Am Chem Soc. 1953;75:2770.

11. (a) Quaranta L. Chiral relay effect: 4-substituted 1,3-benzoxazol-2-(3H)-ones as achiral templates for enantioselective diels: Alder reactions. Org Lett 2002;4:39;

(b) Fukaya T, Kodo T, Ishiyama T, et al. Design, synthesis and structure-activity relationships of novel benzoxazolone derivatives as 18 kDa translocator protein (TSPO) ligands. Med Chem. 2012;20:5568;

(c) Joon Kwan M, Agri J. Photodegradation pathways and mechanisms of the herbicide metamifop in a water/acetonitrile solution. Food Chem. 2010;58:12357.

12. (a) Indrasena Reddy K, Aruna C, Sudhakar Babu K, et al. General and efficient synthesis of benzoxazol-2(3H)-one derivatives: Evaluation of anticancer and anti-mycobacterial biological activities. 2014;4:59594-602.

(b) Kim S, Ko Y. Preparation of cyclic carbonates and 2-oxazolidones using Di-2-pyridyl carbonate heterocycles. 1986;24:1625.

(c) Pulla S, Unnikrishnan V, Ramidi P, et al. J Mol Catalysis A: Chemical. 2011;338:38.

13. (a) Maleski RJ. Improved procedures for the preparation of 2-nitro-5-methoxyphenol and 6-methoxy-2(3H)-benzoxazolone from 3-Methoxyphenol. Syn Comm. 1993;23:343.

(b) Atkinson RS, Judkins BD. The mechanism for interconversion of stereoisomers in N-(2,3-dihydro-2-oxobenzoxazol-3-yl)-and-N-(1,2-dihydro-2-oxoquinolin-1-yl)-N-1-methylallylarenesulphenamides. J Chem Soc Perkin Trans. 1981;3:509.

(c) Singh MS, Singh P, Singh S. Synthesis of benzoxazole-2-ones, benzothiazole-2-ones and their 2-thione derivatives: Efficient conversion of 2-thione to 2-oxo derivatives. Ind J Chem Section B. 2007;46:1666.

(d) Hare AA, Leng L, Gandavadi S, et al. Optimization of N-benzyl-benzoxazol-2-ones as receptor antagonists of macrophage migration inhibitory factor (MIF). Bio org Med Chem. 2010;20:5811;

(e) El Faham A, Chebbo M, Abdul-Ghani M, et al. Chloroformamidinium salts: Efficient reagents for preparation of 2-aminobenzoimidazole, 2-aminobenzoxazole, and 2-aminobenzothiazole derivatives. J Het Chem. 2006;43:599.

(f) Patonay T, Hegedus L, Mogyorodi F, et al. α-Haloalkyl haloformates and related compounds. 2. Synthesis of dichloromethyl carbonates and their transformation to carbamates. Syn Comm. 1994;24:2507.

(g) Maleski RJ, Osborane CE, Cline SM, et al. A simple synthesis of 2(3H)-benzoxazolones using phenyl chloroformate. J Het Chem. 1991;28:1937.

14. (a) Kitamura S, Fukushi H, Miyawaki T, et al. Orally active GPIIb/IIIa antagonists: Synthesis and biological activities of masked amidines as prodrugs of 2-[(3S)-4-[(2S)-2-(4-Amidinobenzoylamino)-3-(4-methoxy phenyl) propanoyl]-3-(2-methoxy-2-oxoethyl)-2-oxopiperazinyl] acetic Acid. Chem Pharm Bull. 2001;49:268.
(b) Charton J, Cousaert N, Bochu C, et al. A versatile solid-phase synthesis of 3-aryl-1, 2, 4-oxadiazolones and analogues. Tetrahedron Lett. 2007;48:1479.
(c) Charton J, Deprez poulaine R, Hennuyer N, et al. Novel non-carboxylic acid retinoids: 1,2,4-oxadiazol-5-one derivatives. Bioorg Med Chem Lett. 2009;19:489.
15. (a) Tabei K, Kawashima E, Takad T, et al. Cyclization of O-acetoacetyl benzamide oxime derivatives. Cyclization of O-acetoacetyl benzamide oxime derivatives. Chem Pharm Bull. 1982;30:336.
(b) Tagad HD, Hamada Y, Nguyen JT, et al. Design of pentapeptidic BACE1 inhibitors with carboxylic acid bioisosteres at P1' and P4 positions. T Bioorg Med Chem Lett. 2010;18:3175.
(c) Kimura T, Hamad Y, Stochaj M, et al. Design and synthesis of potent β-secretase (BACE1) inhibitors with image carboxylic acid bioisosteres Bioorg. Med Chem Lett. 2006;16:2380.
(d) Unangst PC, Shrum GP, Connor DT, et al. Novel 1,2,4-oxadiazoles and 1,2,4-thiadiazoles as dual 5-lipoxygenase and cyclooxygenase inhibitors. J Med Chem. 1992;35:3691.
(e) Assogba L, Ahamada Himidi A, Habich NM, et al. Inhibition of secretory phospholipase A2. 1-design, synthesis and structure-activity relationship studies starting from 4-tetradecyloxybenzamidine to obtain specific inhibitors of group II sPLA2s. J Med Chem. 2005;40:850.
(f) Fujii S, Ohta K, Goto T, et al. Acidic heterocycles as novel hydrophilic pharmacophore of androgen receptor ligands with a carborane core structure Bioorg. Med Chem. 2009;17:344.
(g) Touaibia M, Djimde A, Cao F, et al. Inhibition of secreted phospholipase A2. 4-glycerol derivatives of 4,5-dihydro-3-(4-tetradecyloxybenzyl)-1,2,4-4H-oxadiazol-5-one with broad activities. J Med Chem. 2007;50:1618.
16. (a) Valgeirsson J, Nielsen E, Peters D, et al. Bioisosteric modifications of 2-arylureidobenzoic acids: Selective noncompetitive antagonists for the homomeric kainate receptor subtype GluR5. J Med Chem. 2004;47:6948.
(b) Ruble JC, Wakefield BD, Kamilar GM, et al. Structure-activity relationships of bioisosteres of a carboxylic acid in a novel class of bacterial translation inhibitors. J Bioorg Med. Chem Lett. 2007;17:4040.
17. Indrasena Reddy K, Srihari K, Renuka J, et al. An efficient synthesis and biological screening of benzofuran and benzo[d]isothiazole derivative for *Mycobacterium tuberculosis* DNA GyrB inhibition. Bioorg Med Chem. 2014;23:6552-63.
18. Gerfaud T, Wei HL, Neuville L, et al. Unexpected C-C bond cleavage: Synthesis of 1,2,4-oxadiazol-5-ones from amidoximes with pentafluorophenyl or trifluoromethyl anion acting as leaving group. Org Lett. 2011;13:6172.
19. Behera M, Ragavan RV, Sambaiah M, et al. An efficient method for the preparation of mono α-aryl derivatives of diethyl malonate and ethyl cyanoacetate using ethyl-1-imidazole carbamate (EImC). Tetrahedron Lett. 2012;53:1060.
20. Veeraswamy S, Reddy KI, Ragavan RV, et al. Ethyl imidazole-1-carboxylate (EimC) as a carbonylating agent: Efficient synthesis of oxazolidine-2-ones from amino alcohols. Chem. Lett. 2013;42:109.
21. World Health Organization. Global tuberculosis control: Surveillance, planning, financing; WHO Report 2004: Geneva, Switzerland. 2004.
22. Cegielski JP, Chin DP, Espinal MA, et al. The global tuberculosis situation. Progress and problems in the 20th Century, prospects for the 21st century. Infect Dis Clin North Am. 2002;161:1.

23. Espinal MA. The global situation of MDR-TB. Tuberculosis. 2003;83:44.
24. Renuka J, Indrasena Reddy K, Srihari K, et al. Design, synthesis and biological evaluation of substituted benzofurans as *Mycobacterium tuberculosis* and DNA gyrase B inhibitors. Bioorg Med Chem. 2014;22:4924-934.
25. Biaya M, Porretta GC, Poce G, et al. 25.1,5-diphenylpyrrole derivatives as antimycobacterial agents. Probing the influence on antimycobacterial activity of lipophilic substituents at the phenyl rings. J Med Chem. 2008;51:3644.
26. Reddy PL, Kumar KP, Satyanarayana S, et al. An efficient synthesis of 2-aryl-1,4-diketones via hydroacylation of enones. Tetrahedron Lett. 2012;53:1546.