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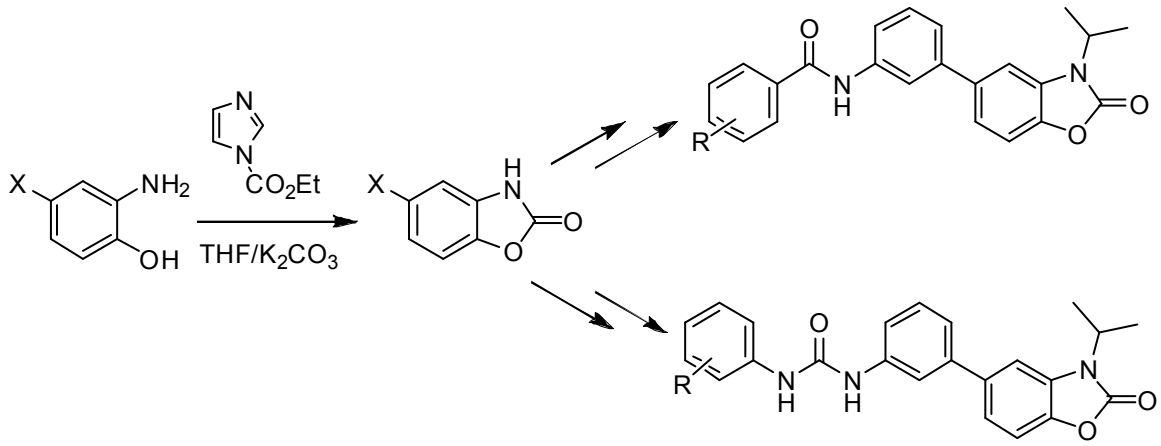
Graphical abstract



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ARTICLE TYPE

General and an efficient synthesis of benzoxazol-2(3*H*)-ones: Evolution of its anti-cancer and anti-mycobacterial activities

K. Indrasena Reddy[a, b], C. Aruna[b], K. Sudhakar Babu[a*], V. Vijayakumar,[c*] M. Manisha[d], J. Padma Sridevi[e], P. Yogeeswari[e], D. Sriram[e]

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A novel class of benzo[*d*]oxazol-2(3*H*)-one derivatives have been synthesized and evaluated their *in vitro* cytotoxicity against human pancreatic adenocarcinoma and human non small cell lung carcinoma cancer cell lines. Many of these compounds were found to display excellent to moderate activity. Among them, **6b, 6l, 6n** and **6x** are identified as lead molecules. In particular, **6l** and **6n** were found to be potent against pancreatic cell line whereas the **6x** was found to be effective against human non small cell lung carcinoma cell line. Conversely, the compounds **6l-x** were found to ineffective against *Mycobacterium tuberculosis*. Of various molecules, **6h** showed a promising anti-mycobacterial activity, which is equal to the IC_{50} value of ciprofloxacin.

1. Introduction

An increasing resistance of cancer and tuberculosis obviously demands for the development of novel chemical entities with improved activity profiles[1-5]. As per the latest information, it is predictable that the cancer may cause over 13.1 million deaths in 2030 worldwide[6]. The World Health Organization (WHO) estimates 11.4 million people worldwide are infected with both *Mycobacterium tuberculosis* (Mtb) and HIV. Currently, there are approximately 8 million new infections and 3 million deaths attributed to *M. tuberculosis* annually[7-9]. Irrespective of the untired efforts and viewing of the myriads of compounds for anti-cancer activity,[10-12] the ambiguity about the cause of cancer, boundaries in its finding at early stage, its direct relationship with process of cell division, metastatic scenery of cancer cells and deficient drug diffusion to cancer tissues are some of the features of this disease which confirm as hurdles in the winning treatment of cancer. A few of the highly effective drugs like pemetrexed,[13] methotrexate,[14] 5-fluorouracil[15] etc appeared in the market provides the hope for the cancer patients. In extension to former reports on the development of anti-cancer agents,[16-19] mainly from benzoxazol-2(3*H*)-one skeleton, we herein report an additional set of compounds with significant anti-cancer activity over certain human cell lines.

Tuberculosis (TB) is a traditional disease caused by infection with *Mycobacterium tuberculosis*. It is a serious public health issue due to its high risk of person-to-person transmission, and high level of morbidity and humanity. The primary cause of death in those infected with body microbes is from TB and not from AIDS. 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.[20] Therefore, the development of new drugs with enhanced activity against MDR-TB and XDR-TB is highly appreciated for the prevention of the disease.

In particular, benzo[d]oxazol-2(3*H*)-ones are considered as "privileged scaffolds" in the aim of pharmacological probes. They are very useful for the drug discovery to mimic a phenol or a catechol moiety in a metabolically stable template. This category of compounds has led to the discovery of a number of derivatives endowed with antibacterial, antifungal, analgesic, anti-inflammatory, anticonvulsant, dopaminergic, antioxidant, antitumor, HIV-1 reverse transcriptase activity,[21-33] and normolipenic agents.[34] Usually, the functionalization of nitrogen atom is of interest, since the electronic characteristic of this atom can be decisive for the biological activity. Recently it was reported that alkylation of benzoxazol-2(3*H*)-ones and benzothiazole-2(3*H*)-ones gave the intermediates, which are used in pharmacotherapy for their anticocaine activity, as these substituted heterocycles interact with signal receptors. Consequently, numerous methods such as Hofmann rearrangement of amides,[35] carbonylation of o-substituted aryl azides using Rhodium catalyst,[36] two steps cyclization of o-hydroxybenzoic acids,[37] cyclization of arenecarbohydroxamic acid,[38] photochemical rearrangements of 1,2-benisoxazolinones,[39] cyclization of azidoformates[40] have been developed for the synthesis of benzoxazol-2(3*H*)-one derivatives. Among them, the cyclization of o-aminophenols with various carbonylating reagents such as, 1,1-carbonyldimidazole,[41] chloroformates,[42]

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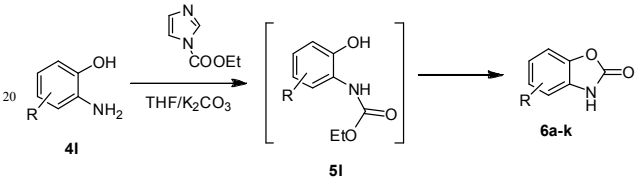
alkyl carbonates,[43] triphosgene,[44] pentafluorobenzoyl chloride[45] are the most commonly used reagents for the synthesis of benzoxazol-2(3*H*)-ones. Many of these reagents are either moisture sensitive or hazardous in nature. In order to overcome these difficulties, there is a need to develop a simple and convenient carbonylating reagent for the synthesis of benzo[d]oxazol-2(3*H*)-ones. So we used the 1-ethyl imdazole carbamates (EImC) as a carbonylating agent for the synthesis of benzoxazol-2(3*H*)-ones from amino phenols, since it is not moisture sensitive or hazardous in nature.

In continuation of our earlier work on EImC,[46-47] herein we report an efficient and simple method to synthesis benzoxazol-2(3*H*)-one using EImC as a carbonylating reagent.

2. Results and discussions

Following our interest on biologically active heterocycles, we herein report a simple and efficient method for the synthesis of benzoxazol-2(3*H*)-one using EImC as a carbonylating reagent.



Scheme 1: Synthesis of benzo[*d*]oxazol-2(3*H*)-one derivatives (6a-k)

Benzo[*d*]oxazol-2(3*H*)-one derivatives **6a-k** were synthesized from 2-aminophenol and ethyl 1*H*-imidazole-1-carboxylate. Initially, we performed the reaction of 2-aminophenol with ethyl 1*H*-imidazole-1-carboxylate in the presence of various bases and solvents and summarized in **Table 1**. Among them, K_2CO_3 in THF afforded the benzo[*d*]oxazol-2(3*H*)-one **6g** in 92% yield.

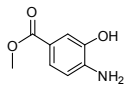
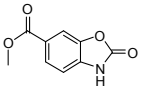
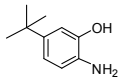
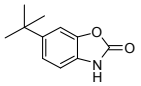
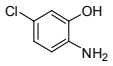
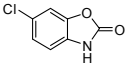
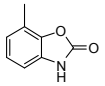
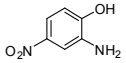
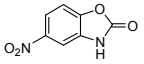
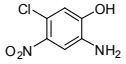
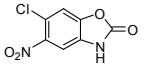
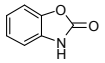
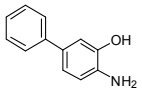
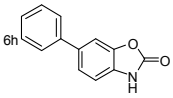
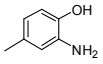
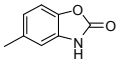
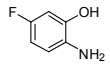
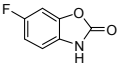
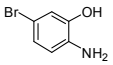
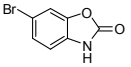
Table 1. Optimization of the reaction using different bases and solvents

Entry	Base	Temp.(°C)	Time (h)	5l[a]	6g[a]
1	K_2CO_3	25	15	92[b]	0
2	K_2CO_3	80	18	0	92[b]
3	Cs_2CO_3	80	12	0	91[b]
4	NaOMe	60	14	0	45[b]
5	NaH	RT	7	0	89[b]
6	tBuOK	RT	15	0	52[b]
7	NaH	RT	8	0	68[c]
8	NaH	RT	10	0	35[d]

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

Various substituted benzoxazol-2(3*H*)-ones were synthesized from the corresponding 2-aminophenols and the results are summarized in **Table 2**. In all cases, the products were obtained in good yields. Both electron-rich and electron-deficient substrates underwent smooth cyclization to give the desired products. Base sensitive substrates such as halogen substituted aminophenol derivatives are tolerated under the reaction conditions.

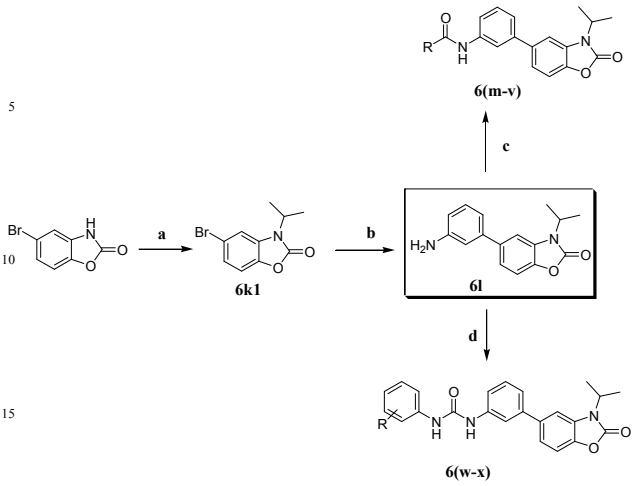
Table 2. Preparation of benzo[*d*]oxazol-2(3*H*)-ones (6a-k)

S.No.	Substrate	Product	Yield (%)[a]
1		6a 	88
2		6b 	82
3		6c 	91
4		6d 	84
5		6e 	87
6		6f 	70
7		6g 	90
8		6h 	78
9		6i 	88
10		6j 	72
11		6k 	85

[a]Isolated yield

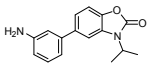
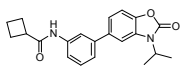
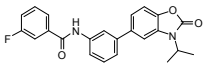
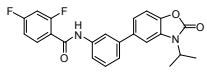
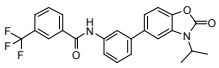
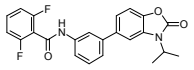
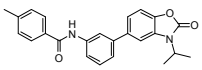
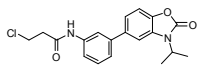
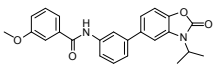
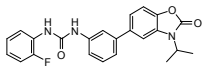
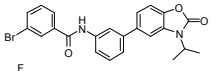
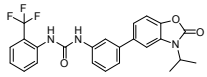
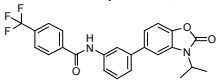
Compounds **6m-x** were synthesized in three steps starting from 5-bromobenzo[d]oxazol-2(3*H*)-one (**Scheme 2**). In the first step, **6k** was treated with isopropyl iodide in THF in the presence of K_2CO_3 to afford the isopropyl derivative **6k1**. In the second step, isopropyl derivative **6k1** was treated with (2-aminophenyl)boronic acid in the presence of $Pd(II)Cl_2(dppf)$ and potassium carbonate in ethanol:toluene (1:1) system under N_2 atmosphere to produce the amino derivative **6l**. In the final step, **6l** was reacted with various acid chlorides and isocyanates in dichloromethane to produce the corresponding amides (**6m-v**) and urea derivatives (**6w-x**).

Scheme 2. Synthesis of amide and urea derivatives (6m-x)



Reagents and conditions: (a) THF, K_2CO_3, isopropyl iodide, reflux; (b) $Pd(II)Cl_2(dppf)$, K_2CO_3, (2-aminophenyl)boronic acid, EtOH:toluene (1:1), reflux; (c) RCOCl (R = alkyl or aryl); (d) RNCO, CH_2Cl_2, 25 °C.

Table 3. Preparation of amide and urea derivatives **(6m-x)**

Cpd. No	Amide	Yield%	Cpd. No	Amide/Urea	Yield%
6l		80	**6s**		88
6m		91	**6t**		85
6n		89	**6u**		88
6o		90	**6v**		84
6p		92	**6w**		87
6q		88	**6x**		91
6r		92			

*Isolated yield

2.1. Cytotoxicity studies

All the synthesized compounds **6a-x** were subjected to WST-1 cytotoxicity assay against Panc-1 (human pancreatic adenocarcinoma), H-460 (human non small cell lung carcinoma) cell lines. Of various compounds **6a-x,** many of them except **6a**,**d**,**g**,**i**,**j**,**p**,**t**,**v** were found to exhibit cytotoxicity against the above cancer cell lines, hence the % of cytotoxicity at various concentrations of the compounds **6a-x** was determined and the respective IC_{50} values for the corresponding cell lines are shown in **Table 4**. The observed IC_{50} values reveal that the compounds **6b, 6h, 6l, 6m, 6n, 6u, 6w** and **6x** are active against both cell lines (Panc-1 as well as H-460). In particular, **6o, 6p, 6u** and **6v** are active against Panc-1 cell line, whereas the compounds **6r, 6s** and **6w** are active against as H-460 cell line. The compounds **6c, 6f, 6k, 6q** showed moderate activity against both the cell lines. The remaining compounds **6a, 6d, 6g, 6i, 6j** and **6t** are inactive against both the tested cell lines. Therefore, except **6r, 6s,** and **6w**, the remaining all compounds are highly active against human pancreatic adenocarcinoma cell lines. The IC_{50} values further indicate that the fluorine containing compounds are more active than the other compounds. Among the active compounds, **6b, 6l, 6n** and **6x** were identified as lead molecules. Out of these four molecules, **6l** and **6n** were found to be potent against pancreatic cell line whereas the **6x** was found to be potent against human pancreatic adenocarcinoma cell lines **(Panc-1)** and human non small cell lung carcinoma cell lines **(H-460)**.

Table 4. HTS data of compounds (6a-t) (in DMSO) against Panc-1 and H-460

Cpd. No	Panc-1 (IC_{50}) µg/mL	H- 460 (IC_{50}) µg/mL	Cpd. No	Panc-1 (IC_{50}) µg/mL	H-460 (IC_{50}) µg/mL
6a	>100	>100	**6m**	6±0.6	7±0.8
6b	6.5±0.7	8.5	**6n**	3±0.4	5±0.6
6c	33±1.2	58	**6o**	27±1.2	75±2.5
6d	>100	>100	**6p**	3±0.5	>100
6e	71±3.2	81	**6q**	76±2.3	100
6f	79±2.9	62	**6r**	15±1.1	5±0.6
6g	>100	>100	**6s**	15±1.3	6±0.9
6h	7±0.6	8	**6t**	>100	>100
6i	>100	>100	**6u**	5±0.9	27±2.1
6j	>100	>100	**6v**	3±0.4	>100
6k	22±2.4	43	**6w**	17±1.2	9±102
6l	3±0.5	4	**6x**	3±0.3	3±0.5
Positive control (Gemcitabine)	500nm	70			89

[a]Gemcitabine was used for the comparison of activity

Figure 1. %Viability of compounds **6n, 6l** and **6x** against Panc-1 cancer cell lines.

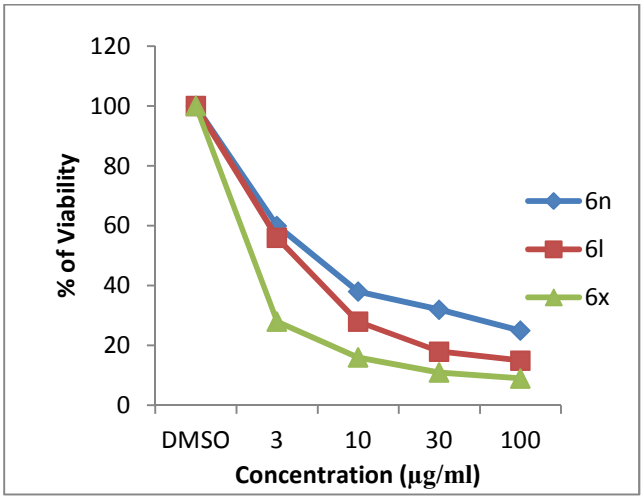
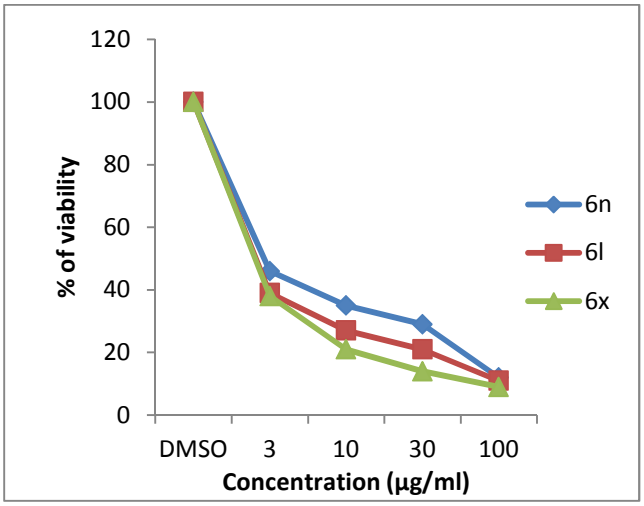


Figure 2. %Viability of compounds **6n, 6l** and **6x** against H-460 cancer cell lines.



2.2. In vitro anti-mycobacterial activity

Compounds **6a–x** were also 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 5**. Based on MIC values, we deduce the structure–activity relationship by the influence of substituent present on benzo[*d*]oxazol-2(3*H*)-one, N-(2-(2,3-dihydro-3-isopropyl-2-oxobenzo[d]oxazol-5-yl)phenyl) benzamide and 1-(2-(2,3-dihydro-3-isopropyl-2-oxobenzo[d]oxazol-5-yl)phenyl)-3-phenylurea skeleton. The observed MIC values are ranging from 3.125 to 50.0 µg/mL. Compounds **6h, 6i**, **6l** and **6p** displayed considerable activity, whereas compounds **6a, 6j**, **6n** and **6o** showed moderate activity. Among these derivatives, **6h** showed promising activity which is equal to the IC_{50} value of ciprofloxacin. In addition, *p*-CF_3-(**6n**), *p*-methyl-(**6o**), *m*-methoxy-(**6p**), difluoro-(**6t**) and *ortho*-CF_3-(**6x**) compounds displayed significant activity. However, *m*-methoxy-(**6p**) is more effective than *p*-methyl-(**6o**). Similarly, *ortho*-CF_3 (**6x**) is more active compared to *p*-CF_3 (**6n**) derivative.

Table 5. Anti-mycobacterial activity of compounds **6a-x**

Cpd No.	CLogP[b]	MIC (µg/mL)	MIC (µM)
6a	1.127	12.5	15.44
6b	2.984	6.25	30.56
6c	1.871	25	6.76
6d	1.657	25	5.96
6e	0.901	25	7.20
6f	1.464	12.5	17.12
6g	1.158	6.25	21.60
6h	3.046	3.12	67.52
6i	1.657	6.25	11.92
6j	1.301	12.5	6.12
6k	2.021	25	34.24
6l	2.583	6.25	42.92
6m	4.662	50	7.80
6n	5.553	12.5	35.23
6o	4.817	12.5	30.91
6p	4.519	6.25	64.39
6q	5.382	25	18.05
6r	5.553	50	8.80
6s	3.742	50	7.00
6t	4.466	12.5	32.64
6u	4.056	25	16.33
6v	3.421	12.5	28.70
6w	4.673	50	8.10
6x	5.210	12.5	36.43
Isoniazid		0.05	0.66
Ethambutol		1.56	7.63
Ciprofloxacin		3.13	9.44

3. Experimental section

General methods

Melting points reported in this work were recorded in capillary tubes on a Elchem lab melting point apparatus and uncorrected. ^{1}H and ^{13}C NMR were recorded on Bruker FT-NMR spectrometer either 300 MHz or 400 MHz using 5 mm PABBO BB-1H tubes. ^{1}HNMR spectra were recorded using approximately 0.03 M solutions in $CDCl_3$ with TMS as an internal reference. ^{13}C 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 $60F_{254}$ 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.

3.1. General procedure for the preparation of intermediates ***6a-x***

*3.1.1. Synthesis of benzoxazolidin-2-one (**6a-k**)*

2-Aminophenol was allowed to react with EImC (ethyl imidazole-1-carboxylate) in the presence of potassium carbonate in THF under reflux conditions for 12h to produce the substituted benzoxazolidin-2-one.

*3.1.2. Synthesis of 5-bromo-3-isopropylbenzo[d]oxazol-2(3H)-one **(6k1)***

To a solution of 5-bromobenzo[d]oxazol-2(3*H*)-one (1 mmol) in THF (10 vol), K_2CO_3 (1.5 mmol) was added and allowed it to stir for 30 min and then isopropyl iodide (1.5 mmol) was added. The resulting solution was stirred for overnight at 80 ^oC. The excess of THF was removed under reduced pressure and then the mixture was quenched with water and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine solution and dried over Na_2SO_4. Removal of the solvent followed by purification on silica gel column chromatography (eluted with Ethyl Acetate:Hexane, 1:5 mixture) afforded the pure isopropyl derivative. Off White solid, 91% yield, m.p. 171-173 ^oC; 1H NMR (400 MHz, CDCl3): δ 6.91 (d, J = 7.2 Hz, 2H), 7.20 (s, 1H), 8.99 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 154.5, 142.6, 132.7, 124.0, 115.1, 112.4, 111.0; IR: υmax 3204, 2951, 1682, 1425, 1106, 891 cm-1. HRMS: m/z 215.10752 [MH^+].

*3.1.3. Synthesis of 5-(2-aminophenyl)benzo[d]oxazol-2(3H)-one **(6l)***

To a solution of 5-bromobenzo[d]oxazol-2(3*H*)-one (1 mmol) in ethanol:toluene (1:1) mixture (10 vol), (2-aminophenyl)boronic acid (1.2 mmol) in the presence of $Pd(II)Cl_2(dppf)$ (0.01mmol) and potassium carbonate (1.5 mmol) in ethanol:toluene (1:1) mixture (10 vol), was added under the N_2 atmosphere. The resulting solution was stirred for 3h at 80 ^oC. The excess of ethanol:toluene mixture was removed under reduced pressure and then the mixture was quenched with water and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine solution and dried over Na_2SO_4. Removal of the solvent followed by purification on silica gel column chromatography (Ethyl Acetate+Hexane, 1:3) afforded the pure isopropyl derivative. Brown solid, 80% yield; m.p. 226-228 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (m, 4H), 6.99 (d, *J* = 7.0 Hz, 1H), 6.92 (s, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 6.79 (d, *J* = 7.0 Hz, 1H), 4.60 (m, 1H), 1.59 (s, 6H); ^{13}C NMR (100 MHz, DMSO): δ 153.8, 146.6, 142.0, 141.9, 137.7, 130.3, 129.7, 120.9, 117.6, 114.2, 113.8, 109.8, 108.1, 46.5, 19.7. IR: υ_{max} 3252, 2862, 1746, 1654, 1335, 1118, 982 cm^{-1}. HRMS: m/z 269.10671 [MH+].

*3.1.4. General procedure for compound preparation of **(6m-v)***

To a solution of 5-(3-aminophenyl)benzo[*d*]oxazol-2(3*H*)-one (**6l**) in dichloromethane was added the corresponding acid chloride under N_2 atmosphere. The resulting mixture was stirred for 1 h at room temperature. Up on completion, the mixture was diluted with excess of DCM and the organic layer was washed with $NaHCO_3$ solution and then dried over Na_2SO_4. Removal of the solvent followed by purification on silica gel column chromatography (Ethyl Acetate:Hexane, 1:2) afforded the desired product.

*3.1.5. General procedure for compound preparation of **(6w-x)***

To a solution of 5-(3-aminophenyl)benzo[*d*]oxazol-2(3*H*)-one (6l) in dichloromethane was added the corresponding isocyanate under N_2 atmosphere. The resulting mixture was stirred for 12 h at room temperature. After completion, the mixture was diluted with dichloromethane and then washed with water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Compound was purified by column chromatography (Ethyl Acetate:Hexane, 1:2).

*3.1.6. Methyl 2-oxo-2,3-dihydrobenzo[d] oxazole-5-carboxylate **(6a)***

Off white solid, 92% yield; m.p. 142-144 ^oC; ^1H NMR (400 MHz, DMSO): δ 11.99 (s, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.58 (s, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 3.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 164.5, 154.6, 143.6, 129.5, 125.3, 122.4, 120.4, 107.5, 56.6; IR: υ_{max} 3155, 1768, 1598, 1432, 1142, 807 cm^{-1}. HRMS: *m/z* 194.20712 [MH^+].

*3.1.7. 5-tert-Butylbenzo[d]oxazol-2(3H)-one **(6b)***

White solid, 94% yield; m.p. 164-166 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.99 (s, 1H), 7.29 (s, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, DMSO): δ 156.4, 147.9, 141.7, 129.0, 119.6, 109.4, 107.3, 34.9, 31.5; IR: υ_{max} 3154, 1765, 1641, 1454, 1162, 851 cm^{-1}. HRMS: *m/z* 189.81236 [MH^-].

*3.1.8. 5-Chlorobenzo[d]oxazol-2(3H)-one **(6c)***

White solid, 89% yield; m.p. 186-188 ^oC; ^1H NMR (400 MHz, DMSO): δ 11.85 (s, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.16 (s, 1H), 7.12 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO): δ 154.9, 142.3, 129.9, 129.6, 122.8, 111.0, 110.3; IR: υ_{max} 3052, 1773, 1618, 1479, 1150, 707 cm^{-1}. HRMS: *m/z* 167.76892 [MH^-].

*3.1.9. 6-Methylbenzo[d]oxazol-2(3H)-one **(6d)***

Off White solid, 91% yield; m.p. 147-149 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.62 (s, 1H), 7.02 (s, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 156.0, 144.0, 132.8, 126.8, 124.5, 110.7, 109.6, 21.4. IR: υ_{max} 3269, 3082, 1632, 1498, 1269, 940 cm^{-1}. HRMS: *m/z* 147.80412 [MH^-].

*3.1.10. 5-Nitrobenzo[d]oxazol-2(3H)-one **(6e)***

Off White solid, 85% yield; m.p. 180-182 ^oC; ^1H NMR (400 MHz, DMSO): δ 7.92 (d, *J* = 8.4 Hz, 1H), 7.78 (s, 1H), 6.94 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO): δ 168.2,

156.5, 146.2, 136.3, 120.0, 109.5, 100.2. IR: υ_{max} 3382, 1709, 1657, 1279, 1163 cm^{-1}. HRMS: *m/z* 178.88412 [MH^-].

3.1.11. *5-Chloro-6-nitrobenzo[d]oxazol-2(3H)-one* ***(6f)***

Yellow solid, 93% yield; m.p. 190-192 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.62m (s, 1H), 7.21 (s, 1H), 7.20 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO): δ 154.9, 142.3, 130.0, 129.6, 122.8, 111.0, 110.3. IR: υ_{max} 3208, 1752, 1621, 1365, 851 cm^{-1}. HRMS: *m/z* 215.60584 [MH^-].

3.1.12. *Benzo[d]oxazol-2(3H)-one* ***(6g)***

Off White solid, 92% yield; m.p. 134-136 °C; ^1H NMR (400 MHz, CDCl3): δ 8.59 (s, 1H), 7.21 (m, 1H), 7.19 (m, 1H), 7.15 (m, 1H); ^{13}C NMR (100 MHz, DMSO): 156.2, 143.8, 129.4, 124.1, 122.6, 110.1, 110.1. IR: υ_{max} 3511, 1735, 1629, 1479, 1262, 953 cm^{-1}. HRMS: *m/z* 136.09812 [MH^-].

3.1.13. *5-Phenylbenzo[d]oxazol-2(3H)-one* ***(6h)***

Off White solid, 91% yield; m.p. 196-198 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.0 Hz, 2H), 7.30 (t, *J* = 6.9 Hz, 1H), 7.15 (s, 1H), 7.10 (s, 2H); ^{13}C NMR (100 MHz, DMSO): δ 153.5, 145.3, 142.6, 140.9, 137.3, 131.3, 129.2, 121.2, 117.4, 114.1, 112.8, 109.8, 107.6. IR: υ_{max} 3222, 1766, 1634, 1493, 1310, 1090 cm^{-1}. HRMS: *m/z* 212.31874 [MH^-].

3.1.14. *5-Methylbenzo[d]oxazol-2(3H)-one* ***(6i)***

White solid, 90% yield; m.p. 157-159 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.45 (s, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.01 (s, 1H), 6.90 (d, *J* = 6.9 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 156.6, 143.6, 128.5, 125.3, 122.4, 120.4, 107.5, 16.1. IR: υ_{max} 3108, 1763, 1643, 1465, 955 cm^{-1}. HRMS: *m/z* 148.04874 [MH^-].

3.1.15. *6-Fluorobenzo[d]oxazol-2(3H)-one* ***(6j)***

White solid, 85% yield; m.p. 145-147 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.89 (s, 1H), 7.01 (m, 2H), 6.91 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO)**:** δ 156.8, 144.4, 134.2, 122.8, 114.1, 110.7, 109.6. IR: υ_{max} 3061, 1771, 1625, 1471, 1258, 942 cm^{-1}. HRMS: *m/z* 154.21096 (MH^-).

3.1.16. *5-Bromobenzo[d]oxazol-2(3H)-one* ***(6k)***

Off White solid, 91% yield, m.p. 172-174 °C^1H NMR (400 MHz, $CDCl_3$): δ 6.91 (d, *J* = 6.8 Hz, 2H), 7.20 (s, 1H), 8.99 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 154.5, 142.6, 132.7, 124.0, 115.1, 112.4, 111.0. IR: υ_{max} 3161, 1769, 1632, 1378, 1123, 824 cm^{-1}. HRMS: *m/z* 215.21798 [MH^-].

3.1.17. *5-(3-Aminophenyl)-3-isopropylbenzo[d] oxazol-2(3H)-one* ***(6l)***

Brown solid, 80% yield; m.p. 226-228 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (m, 4H), 6.99 (d, *J* = 7.0 Hz, 1H), 6.92 (s, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 6.79 (d, *J* = 7.0 Hz, 1H), 4.60 (m, 1H), 1.59 (s, 6H); ^{13}C NMR (100 MHz, DMSO): δ 153.8, 146.6, 142.0, 141.9, 137.7, 130.3, 129.7, 120.9, 117.6, 114.2, 113.8, 109.8, 108.1, 46.5, 19.7. IR: υ_{max} 3252, 2862, 1746, 1654, 1335, 1118, 982 cm^{-1}. HRMS: *m/z* 227.21892 [MH^-].

3.1.18. *3-Fluoro-N-(3-(3-isopropyl-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl)benzamide* ***(6m)***

White solid, 91% yield; m.p. 148-150 °C; ^1H NMR (400 MHz, DMSO): δ 10.42 (s, 1H), 8.05 (s, 1H), 7.85 (m, 3H), 7.60 (m, 3H), 7.45 (m, 4H), 7.39 (d, *J* = 7.0 Hz, 1H), 4.59 (m, 1H), 1.51 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO): δ 164.1, 164.1, 163.1, 160.7, 152.9, 141.6, 140.3, 139.3, 137.1, 137.0, 136.4, 130.8, 130.6, 130.5, 129.1, 123.8, 122.6, 120.5, 119.4, 119.0, 118.6, 118.4, 114.5, 114.3, 109.9, 107.9,46.1. IR: υ_{max} 3367, 1750, 1663, 1483, 1259, 1120, 986 cm^{-1}. HRMS: *m/z* 391.10712 [MH^+].

3.1.19. *N-(3-(3-Isopropyl-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl)-3-(trifluoromethyl) benzamide* ***(6n)***

White solid, 89% yield; m.p. 207-209 °C; ^1H NMR (400 MHz, DMSO): δ 10.65 (s, 1H), 7.92 (s, 1H), 7.84 (m, 2H), 7.72 (m, 3H), 7.54 (s, 1H), 7.42 (m, 3H), 7.33 (d, *J* = 7.2 Hz, 1H), 4.55 (m, 1H), 1.50 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO): δ 165.7, 152.9, 141.6, 140.5, 139.4, 136.4, 136.1, 132.6, 130.7, 130.0, 129.3, 128.5, 126.3, 126.0, 125.7, 125.1, 122.6, 122.4, 120.5, 118.5, 118.1, 110.0, 108.0, 107.9, 46.1, 19.2. IR: υ_{max} 3327, 1760, 1677, 1556, 1437, 1122, 984 cm^{-1}. HRMS: *m/z* 441.19872 [MH^+].

3.1.20. *N-(3-(3-Isopropyl-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl)-4-methyl-benzamide* ***(6o)***

Off White solid; 90% yield, m.p. 184-186 °C; ^1H NMR (400 MHz, DMSO): δ 10.29 (s, 1H), 8.08 (s, 1H), 7.93 (d, *J* = 7.0 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.61 (s, 1H), 7.44 (m, 6H), 4.60 (m, 1H), 2.40 (s, 3H), 1.51 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO): δ 165.3, 152.9, 141.6, 140.2, 139.7, 136.5, 131.9, 130.7, 129.2, 129.1, 128.9, 127.6, 122.2, 120.5, 119.3, 118.9, 109.9, 107.9, 64.8, 46.1, 40.1, 20.9, 19.3, 15.1. IR: υ_{max} 3358, 2986, 1748, 1661, 1542, 1259, 983 cm^{-1}. HRMS: *m/z* 387.10872 [MH^+].

3.1.21. *N-(3-(3-Isopropyl-2-oxo-2,3-dihydrobenzo[d] oxazol-5-yl)phenyl)-3-methoxybenzamide* ***(6p)***

Off White solid; 92% yield, m.p. 236-238 °C; ^1H NMR (400 MHz, DMSO): δ 10.35 (s, 1H), 8.08 (s, 1H), 7.85 (d, *J* = 7.2 Hz, 1H), 7.61 (m, 3H), 7.45 (m, 5H), 7.19 (d, *J* = 7.0 Hz, 1H), 4.61 (m, 1H), 3.89 (s, 3H), 1.55 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO): δ 165.3, 159.1, 152.9, 141.6, 140.3, 139.6, 136.4, 136.2, 130.7, 129.5, 129.1, 122.4, 120.5, 119.8, 119.4, 119.0, 117.3, 112.9, 109.9, 107.9, 55.3, 46.1, 40.1, 19.3. IR: υ_{max} 3363, 1748, 1663, 1546, 1480, 1259, 1051 cm^{-1}. HRMS: *m/z* 403.19875 [MH^+].

3.1.22. *3-Bromo-N-(3-(3-isopropyl-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl)benzamide* ***(6q)***

White solid; 88% yield, m.p. 214-216 °C; ^1H NMR (400 MHz, DMSO): δ 10.25 (s, 1H), 8.04 (s, 1H), 7.94 (d, *J* = 7.0 Hz, 2H), 7.82 (m, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.58 (s, 1H), 7.42 (m, 4H), 4.51 (m, 1H), 1.51 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, DMSO): δ 166.5, 164.5, 152.9, 141.6, 140.3, 139.4, 136.4, 133.8, 131.6, 131.3, 131.2, 130.7, 129.7, 129.1, 125.3, 122.5, 120.5, 119.4, 119.0, 109.9, 107.9, 46.1, 19.3. IR: υ_{max} 3350, 1744, 1665, 1484, 1258, 983 cm^{-1}. HRMS: m/z 451.206542 [MH^+].

3.1.23. *N-(3-(3-Isopropyl-2-oxo-2,3-dihydro-benzo[d] oxazol-5-yl)phenyl)-4-(trifluoromethyl)benzamide* ***(6r)***

Off White solid; 92% yield, m.p. 216-218 °C; ^{1}H NMR (400 MHz, DMSO): δ 10.35 (s, 1H), 8.41 (d, *J* = 7.2 Hz, 2H), 8.04 (s, 1H), 8.19 (d, *J* = 7.0 Hz, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.57 (m, 1H), 7.52 (s, 1H), 7.45 (m, 4H), 4.52 (m, 1H), 1.51 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO): δ 164.4, 152.9, 141.6, 140.3, 139.3, 138.6, 136.4, 131.5, 131.2, 130.8, 129.2, 128.6, 125.3, 125.2, 122.7, 122.5, 120.5, 119.4, 119.0, 109.9, 107.9, 46.1, 19.3. IR: υ_{max} 3334, 2740, 1765, 1642, 1437, 1274, 984, 725 cm^{-1}. HRMS: *m/z* 441.19742 [MH$^+$].

3.1.24. *N-(3-(3-Isopropyl-2-oxo-2,3-dihydro-benzo[d]oxazol-5-yl)phenyl)cyclobutane carboxamide* ***(6s)***

White solid; 88% yield, m.p. 224-226 °C; ^{1}H NMR (400 MHz, DMSO): δ 10.25 (s, 1H), 7.91 (s, 1H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.65 (d, *J* = 6.8 Hz, 1H), 7.55 (s, 1H), 7.39 (m, 4H), 4.60 (m, 1H), 3.22 (m, 1H), 2.23 (m, 2H), 2.15 (m, 2H), 1.98 (m, 1H), 1.81 (m, 1H), 1.45 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO): 172.9, 152.9, 141.5, 140.3, 139.8, 136.5, 130.5, 129.1, 121.7, 120.5, 118.1, 117.6, 109.3, 107.8, 46.0, 24.5, 19.2, 17.7. IR: υ_{max} 3353, 2945, 1750, 1676, 1435, 1218, 984 cm^{-1}. HRMS: *m/z* 351.11972 [MH$^+$].

3.1.25. *1-(2-Fluorophenyl)-3-(3-isopropoxy-1-isopropyl-4-(3,5-dimethyl-2H-pyrrol-2-yl)-1H-pyrazol-5-yl)urea* ***(6t)***

Off White solid; 85% yield, m.p. 258-260 °C; ^{1}H NMR (400 MHz, DMSO): δ 10.50 (s, 1H), 8.00 (s, 1H), 7.79 (m, 2H), 7.60 (s, 1H), 7.48 (m, 4H), 7.39 (d, *J* = 6.8 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 4.60 (m, 1H), 1.51 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO): δ 164.6, 162.2, 162.1, 161.9, 160.8, 160.7, 158.3, 158.2, 152.9, 141.6, 140.5, 139.2, 136.3, 131.7, 131.6, 130.7, 129.3, 122.6, 121.6, 121.5, 120.5, 118.7, 111.9, 111.7, 109.9, 107.9, 104.9, 104.6, 104.4, 46.1, 19.3. IR: υ_{max} 3353, 2945, 1750, 1676, 1435, 1218, 984 cm^{-1}. HRMS: *m/z* 407.00981 [MH$^-$].

3.1.26. *2,6-Difluoro-N-(3-(3-isopropyl-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl) benzamide* ***(6u)***

Off White solid; 88% yield, m.p. 228-230 °C; ^{1}H NMR (400 MHz, DMSO): δ 10.89 (s, 1H), 7.96 (s, 1H), 7.76 (m, 1H), 7.59 (m, 2H), 7.48 (m, 3H), 7.36 (d, *J* = 6.8 Hz, 1H), 7.26 (t, *J* = 7.2 Hz, 2H), 4.51 (m, 1H), 1.51 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO): δ 160.0, 159.9, 158.2, 157.5, 157.5, 152.9, 141.6, 140.7, 139.0, 136.3, 132.1, 130.8, 129.5, 123.0, 120.5, 118.3, 117.9, 115.3, 115.1, 112.2, 111.9, 110.0, 108.0, 46.1, 19.2. IR: υ_{max} 3325, 2932, 1743, 1676, 1466, 1256, 1008 cm^{-1}. HRMS: *m/z* 409.10942 [MH$^+$].

3.1.27. *3-Chloro-N-(3-(3-isopropyl-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl)propanamide* ***(6v)***

White solid; 84% yield, m.p. 208-210 °C; ^{1}H NMR (400 MHz, DMSO): δ 10.2 (s, 1H), 7.88 (s, 1H), 7.66 (d, *J* = 6.8 Hz, 1H), 7.56 (s, 1H), 7.42 (m, 4H), 4.59 (m, 1H), 3.85 (t, *J* = 7.2 Hz, 2H), 2.89 (t, *J* = 7.2 Hz, 2H), 1.57 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO): δ 168.0, 152.9, 141.6, 140.4, 139.4, 136.4, 130.7, 129.3, 122.0, 120.5, 118.0, 117.6, 109.9, 107.9, 64.8, 46.0, 40.7, 19.2, 15.1. IR: υ_{max} 3318, 2970, 1733, 1696, 1437, 1236, 984, 791 cm^{-1}. HRMS: *m/z* 359.10872 [MH$^+$].

3.1.28. *1-(2-Fluorophenyl)-3-(3-(3-isopropyl-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl) urea* ***(6w)***

White solid; 87% yield, m.p. 180-182 °C; ^{1}H NMR (400 MHz, DMSO): δ 9.50 (s, 1H), 8.15 (s, 1H), 7.95 (d, *J* = 6.8 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.65 (m, 4H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.35 (m, 5H), 4.52 (m, 1H), 1.51 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO): 152.9, 152.4, 141.5, 140.6, 139.9, 136.6, 136.2, 132.8, 130.7, 129.4, 125.8, 125.6, 125.3, 123.7, 122.6, 121.0, 120.5, 117.2, 116.8, 109.9, 107.9, 46.0, 19.2. IR: υ_{max} 3368, 2981, 1741, 1705, 1541, 1316, 1184, 752 cm^{-1}. HRMS: *m/z* 406.10742 [MH$^+$].

3.1.29. *1-(3-(3-Isopropyl-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl)-3-(2-(trifluoromethyl)phenyl)urea* ***(6x)***

White solid; 91% yield, m.p. 191-193 °C; ^{1}H NMR (400 MHz, DMSO): δ 9.19 (s, 1H), 8.59 (s, 1H), 8.15 (t, 1H), 7.72 (s, 1H), 7.59 (s, 1H), 7.49 (m, 1H), 7.35 (m, 4H), 7.25 (t, J = 8.2 Hz, 1H), 7.15 (t, J = 7.2 Hz, 1H), 7.02 (m, 1H), 4.61 (m, 1H), 1.50 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO): δ 153.2, 152.9, 152.2, 150.8, 141.5, 140.6, 139.9, 136.6, 130.7, 129.4, 127.5, 127.4, 124.4, 122.5, 122.4, 120.9, 120.6, 120.5, 117.2, 116.7, 115.0, 114.8, 109.9, 108.0, 46.0, 19.2. IR: υ_{max} 3370, 2930, 1741, 1705, 1542, 1357, 1184, 781cm^{-1}. HRMS: m/z 454.09872 [MH$^-$].

4. Procedure adopted for cytotoxicity studies

All the synthesised compounds **6a-x** were subjected to WST-1 cytotoxicity assay. The cancer cells used in this study such as Panc-1 (human pancreatic adenocarcinoma), H460 (human non small cell lung carcinoma) were obtained from ATCC (American Type Culture Collection). Cells were maintained in DMEM (Dulbecco's modified Eagle's medium) medium containing 10% heat inactivated Fetal Bovine Serum and kept in humidified 5% CO_2 incubator at 37 °C. Logarithmically growing cells were plated at a density of 5×10^3 cells/well in a 96-well tissue culture grade micro-plate and allowed to recover overnight. The cells were challenged with varying concentration of compounds for 48 h. Control cells received standard media containing dimethylsulfoxide vehicle at a concentration of 0.2%. After 48 h of incubation, cell toxicity was determined by CCK-8 (Cell Counting Kit-8) reagent (Dojindo Molecular Technologies, Inc, Maryland, Japan); (WST-1 [2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)]-2H-tetrazolium mono sodium salt assay). In accordance with the manufacturer's instructions[41], 5µL/well CCK-8 reagent was added and plates were incubated for 2 h. Cytotoxicity of all the compounds have been determined by measuring the absorbance on Tecan Sapphire multi-fluorescence micro-plate reader (Tecan, Germany, GmbH; in English: company with limited liability) at a wavelength of 450 nm corrected to 650 nm and normalized to controls. Each independent experiment was performed thrice and tabulated in **Table 4**.

5. Conclusion :

In summary, we developed the general procedure for the synthesis of benzo[*d*]oxazol-2(3*H*)-ones (**6a-k)** from 2-aminophenols applying ethylimidazole-1-carboxylate under mild reaction conditions in good to excellent yields. A novel class of *N*-(2-(3-isopropyl-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl) benzamides (**6m-v)** and 1-(2-(3-isopropyl-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl)-3-phenylurea derivatives (**6w-x)** were synthesized from 5-bromo-benzo[*d*]oxazol-2(3*H*)-

one. The cytotoxicity of these molecules was tested against Panc-1 (human pancreatic adenocarcinoma), H460 (human non small cell lung carcinoma) cell lines by a WST-1 cytotoxicity assay. Many of these compounds were found to display excellent to moderate activity. Among them, **6b, 6l, 6n** and **6x** are identified as lead molecules. In particular, **6l** and **6n** were found to be potent against pancreatic cell line whereas the **6x** was found to be effective against human non small cell lung carcinoma cell line. Of various molecules, **6h** showed a promising anti-mycobacterial activity, which is equal to the IC_{50} value of ciprofloxacin.

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