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Short communication

An expeditious synthesis and anticancer activity of novel 4-(3′-indolyl)oxazoles

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ABSTRACT

A series of 4-(3′-indolyl)oxazole congeners have been synthesized and studied for their cytotoxicity against six cancer cell lines. Reaction of 3-acetyl-1′-benzenesulfonylindole with [hydroxy(tosyloxy)-iodo]benzene afforded pure 3-tosyloxyacetyl-1′-benzenesulfonylindole. Microwave-accelerated neat reaction of 3-tosyloxyacetyl-1-benzenesulfonylindole with amides resulted in the exclusive formation of 4-(1′-benzenesulfonylindol-3′-yl)-2-substituted oxazoles (**4**) in very good yield. Treatment of **4** with aqueous sodium hydroxide under refluxing conditions afforded pure 4-(3′-indolyl)-2-substituted oxazoles (**5**) in excellent yield. The 4-(3′-indolyl)oxazoles **5d** and **11** were found to be most cytotoxic and selective against various cancer cell lines. Compounds **5g**, **5j** and **5l** showed moderate anticancer activity.

1. Introduction

Five-membered heterocycles with nitrogen and oxygen atoms are among the privileged structures that play vital role in many biologically interesting natural products and useful therapeutic agents [1,2]. In particular, indolyl azoles have received significant attention during the last decade due to their diverse biological activities [3–6]. Many natural products (Fig. 1) containing 5-(3′-indolyl)oxazole ring system such as pimprinine (**1a**), pimprinethine (**1b**), pimprinaphine (**1c**) have been isolated and identified [3–6]. Pettit and co-workers have reported Laboradorin 1 (**1d**) and Laboradorin 2 (**1e**), isolated from Pseudomonas *syringae pv. Coronafaciens* as growth inhibitors of various cancer cell lines [7]. A number of indolyl thiazoles were synthesized and found to be cytotoxic against human breast cancer line [8]. Camalexin (3-thiazol-2-yl-indole) was found to exhibit cytotoxic activities [9]. A thiazole-substituted indolequinone, BE 10988 is a topoisomerase inhibitor [10]. The isomeric 4-(3′-indolyl)oxazole represent a common structural moiety of many biological potent natural products such as phenoxan [11], calyculins [12] and rhizoxin [13]. Most common methods for the preparation of 2,4-disubstituted oxazoles involve rhodium (II) promoted coupling of dialkyl diazomalonates with nitriles [14,15] and condensation of amides with α-halo ketones [16,17]. A recently reported multi-step synthesis of 2,4-disubstituted oxazoles utilizes vinyl sulfonamide as starting material [18]. We have recently reported synthesis and anticancer activity of indolyl-1,3,4-oxadiazoles **1f**, and discovered that some of the analogs are potent and selective against various cancer cell lines [19]. In view of the intriguing cytotoxicity of various indolyl azoles and in continuation of our efforts to discover novel and selective anticancer agents, we report herein synthesis and cytotoxic study of bioisosteric 4-(3′-indolyl)-2-substituted oxazoles.

2. Results and discussion

2.1. Chemistry

Compounds **5a–m** were prepared according to synthetic Scheme 1. Synthesis of **5** involves preparation of 3-tosyloxyacetyl-1′-benzenesulfonylindole (**3**) followed by reaction with appropriate amide. The α-tosyloxy ketones are very useful starting materials to synthesize various heterocyclic compounds and can be easily prepared from the reaction of enolizable ketones with [hydroxy(tosyloxy)iodo]benzene (HTIB) [20,21]. Further, α-tosyloxy ketones are good replacement for lachrymatory α-halo ketones in synthetic organic chemistry. Reaction of 3-acetyl-1-benzenesulfonylindole (**2**) with HTIB in acetonitrile at 45 °C afforded pure **3** in good yield. For the successful synthesis of **3**, protection of indole nitrogen was essential as the reaction of 3-acetylindole with HTIB led to a complex mixture. Use of 3-bromoacetyl-1′-benzenesulfonylindole is disadvantageous as the bromination of

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Pimprinine (**1a**, R= CH_3) Indolyl-1,3,4-oxadiazoles (**1f**)

Pimprinethine (**1b**, R = CH_2CH_3)

Pimprinaphine (**1c**, R = $CH_2C_6H_5$)

Laboradorin 1 (**1d**, R = $CH_2CH(CH_3)_2$

Laboradorin 2 (**1e**, R = $CH_2CH_2CH_2CH_2CH_3$)

Fig. 1. Structures of some 5-(3′-indolyl) azoles.

2 always produces minor dibromo derivative which requires further purification.

Our model reaction of **3** with amides under conventional condition produced moderate yield of product and required longer reaction time (8–10 h). In the past, microwave technique has been widely used in organic synthesis due to improved selectivity, shorter reaction time and high product yield. Further, the solvent-free reactions are easy to perform and have an improved selectivity and efficiency, ease of manipulation, pure product formation and avoid the use of organic solvents [22,23]. In view of demonstrated advantages of microwave-accelerated reactions under solvent-free conditions, we explored the reaction of **3** with amides under microwave irradiation to prepare a series of 4-(1′-benzenesulfonylindol-3′-yl)-2-substituted oxazoles (**4**) (Scheme 1). After several attempts under varying reaction conditions it was realized that the neat reaction of **3** with amides resulted in the exclusive formation of **4** within short time (6–15 min). Under similar reaction conditions analogs of 4-(1′-benzene-sulfonylindol-3′-yl)-2-substituted oxazoles (**4**) were prepared. Finally, treatment of 4 with aqueous sodium hydroxide under refluxing conditions afforded pure 4-(3′-indolyl)-2-substituted oxazoles (**5**) in excellent yield.

The compounds **8**–**12** were prepared according to Scheme 2. The reaction of **3** with *N*-Boc isonicotinamide resulted in the formation of indolyl oxazole **6** which upon deprotection of benzenesulfonyl and *N*-Boc moieties produced **8**. Methylation of indolyl oxazole **7** followed by *N*-Boc deprotection yielded compound **9**. Compounds **10** and **11** were prepared by the *N*-alkylation of **5i** with methyl iodide and *p*-chlorobenzyl chloride, respectively. Deprotection of benzenesulfonyl group of **4n** followed by reaction with methyl iodide produced compound **12** in good yield. All the 4-(1′-benzenesulfonylindol-3′-yl)-2-substituted oxazoles (**5a**–**m**, **8**–**12**) were characterized by their spectral data (NMR and Mass).

3. Anticancer activity

A series of indolyl oxazoles **5a**–**m**, **8**–**12** were screened against prostate (PC3, DU145 and LnCaP), breast (MCF7 and MDA231) and pancreatic (PaCa2) cancer cell lines. The human cancer cell lines screened were cultured in RPMI 1640 medium containing 5% fetal bovine serum. Cells were seeded in 96-well microtiter plate, at an expected target cell density of 5000–10,000 cells per well, based on cell growth. Inoculates were allowed to pre-incubate for 12 h at 37 °C for stabilization. Test compounds were evaluated at different concentrations ranging from 100 nM to 1000 μM. Incubation lasted for 48 h in 5% CO_2 atmosphere. The anticancer activity was determined for each cell line using formazan dye (MTT) conversion assay. The results mentioned in Table 1 shows the cytotoxic effects of 4-(3′-indolyl)oxazoles **5a**–**m**, **8**–**12** against various cancer cell lines.

As shown in Table 1, compounds **5d**, **5g**, **5j**, **5l** and **11** are the active molecules against various cell lines. The compound **5d** is active against all the cancer cell lines, suggesting that *p*-fluorophenyl at C-2 position is beneficial for the activity. Alkylation of indole nitrogen improved the activity, however, *p*-chlorobenzyl as an alkylating group is preferred over methyl (**10** and **11**). The compound **11** with *N*-(*p*-chlorobenzyl) and C-2 *p*-chlorophenyl moiety is potent and showed selective cytotoxicity against MCF7 (14.1 μM) and $PaCa_2$ (26 μM) cell lines. Substitution at C-2 position of oxazole ring is important for the activity as compound **5k** without any substituent exhibited very poor activity. In general, an aromatic/heteroaromatic ring with an electronegative atom at C-2 position is beneficial for the activity. The compound **5l** with C-2 ethenyl moiety was found to be active against DU145 (59.8 μM) and $PaCa_2$ (37.6 μM) cell lines. Introduction of a *p*-methoxyphenyl group at C-2 position (compound **5j**) showed selective cytotoxicity against MCF7 (43.8 μM) and $PaCa_2$ (35 μM) cell lines. However, an additional electron-donating group at the *meta* position in C-2 aryl ring (compounds **5c**, **5m** and **12**) is detrimental for the activity. Compounds **8** and **9** with a piperidinyl ring at C-2 also exhibited poor activity.

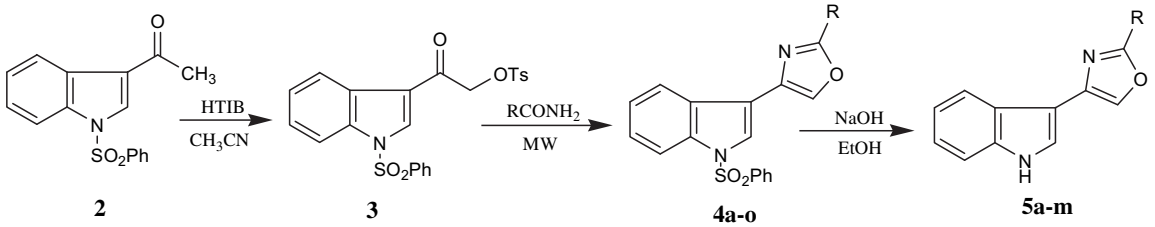
4. Conclusion

A series of 4-(3′-indolyl)oxazoles were prepared and studied for their cytotoxicity against various cancer cell lines. Of the synthesized 4-(3′-indolyl)oxazoles, compounds **5d** and **11** were found to be most cytotoxic against cancer cell lines. In addition, compound **11** was highly selective against MCF7 and Paca2 cell lines. Compounds **5g**, **5j** and **5l** showed moderate to good anticancer activity. The structure–activity relationship study showed that *N*-benzylation of indole nitrogen and *p*-fluorophenyl at C-2 position of oxazole ring are important for the activity and selectivity of 4-(3′-indolyl)oxazoles.

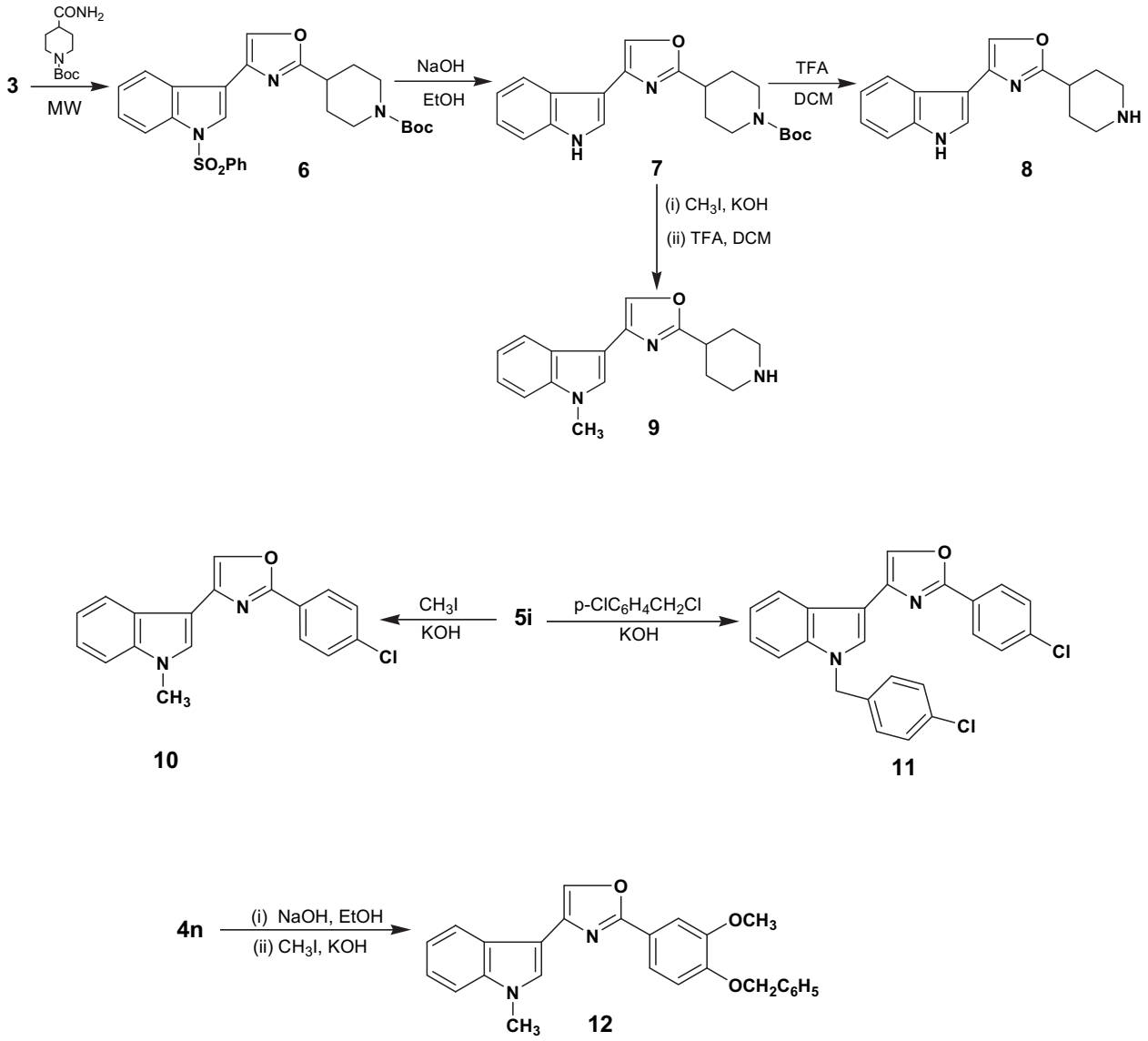
5. Experimental

5.1. Physical measurements

All the laboratory grade reagents were obtained commercially. The reaction was monitored by thin layer chromatography, which was performed on Merck precoated plates (silica gel. 60 F_{254}, 0.25 mm) and was visualized by fluorescence quenching under UV



Scheme 1. Synthetic route for indolyl oxazoles **5**.



Scheme 2. Synthetic route for indolyl oxazoles **8**–**12**.

light (254 nm). Column chromatography was performed using 100–200 mesh silica gel and appropriate mixture of hexane and ethyl acetate for elution. The solvents were evaporated using Buchi rotary evaporator. Melting points were determined with electrothermal capillary melting point apparatus (E-Z melting). ^{1}H NMR spectra were recorded on a Bruker Avance II (400 MHz) spectrometer. The coupling constant (J) values are in Hz. Mass spectra were obtained on a 'Hewlett–Packard' HP GS/MS 5890/5972. Reactions were performed in a domestic microwave with 900 W (Power 80%). HTIB was prepared according to literature procedure [24].

*5.1.1. Synthesis of 3-tosyloxyacetyl-1′-benzenesulfonylindole (**3**)*

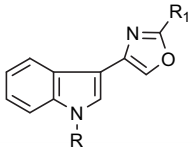
A mixture of 3-acetyl-1′-benzenesulfonylindole **2** (4.0 g, 13.36 mmol) and HTIB (6.44 g, 16.04 mmol) in acetonitrile (30 mL) was stirred at 45 °C for 8 h. Reaction mixture was concentrated under reduced pressure and washed with petroleum ether (20 mL). The residue so obtained was recrystallized from methanol to afford **3**. Yield 5.5 g (88%); mp 137–140 °C (lit.138–140 °C) [4].

*5.1.2. General procedure for the synthesis of 4-(1′-benzenesulfonylindol-3′-yl)-2-substituted oxazoles (**4**)*

A neat mixture of 3-tosyloxyacetyl-1′-benzene-sulfonylindole **3** (1 mmol) and amide (1 mmol) was irradiated in a microwave oven for appropriate time (6–15 min) with 1 min heating and 30 s cooling. After completion of reaction as indicated by TLC, the contents were taken into water (20 mL) and extracted with dichloromethane (2 × 10 mL). Organic phase was separated and dried over anhydrous sodium sulfate. Excess of dichloromethane was removed and the residue so obtained was percolated through a bed of silica gel using column chromatography (hexane:ethylacetate, 9:1) to afford **4** in good yield.

*5.1.2.1. 4-(1′-Benzenesulfonylindol-3-yl)-2-phenyloxazole (**4a**).* Yield 79%; mp 145 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.29–7.32 (m, 5H, Ar-H), 7.39–7.50 (m, 5H, Ar-H), 7.62 (s, 1H, Ar-H), 7.86 (s, 1H, Ar-H), 7.91 (d, 2H, J = 7.94 Hz, Ar-H), 7.97–8.01 (m, 2H, Ar-H). HRMS for $C_{23}H_{16}N_2O_3S$, calcd $(M+H)^+$: 401.096, found: 401.1105 $(M+H)^+$.

Table 1
Cytotoxicity profile of 4-(3′-indolyl)oxazoles **5a–m**, **8–12** against selected human cancer cell lines, IC_{50} (μM)



Compound	R	R^1	PC3	DU145	LnCaP	MCF7	MDA231	PaCa2
5a	H	C_6H_5	170.1	167.2	460.7	131.3	171.1	112.6
5b	H	CH_3	336.7	243.5	316.1	801.8	10^3	688.5
5c	H	3,4-$(CH_3O)_2C_6H_3$	358.6	299.9	277.9	758.7	10^3	10^3
5d	H	4-FC_6H_4	**42.8**	**31.8**	59.8	**28**	90.4	**40.6**
5e	H	4-HOC_6H_4	381.6	246.8	448.6	579.7	10^3	10^3
5f	H	$CH{=}CHC_6H_5$	221.2	134.9	182.8	354.7	10^3	872.5
5g	H	4-pyridyl	298.3	178.2	238	54.9	105	**38.4**
5h	H	$CH_2C_6H_5$	368.1	348.6	376.6	10^3	10^3	10^3
5i	H	4-ClC_6H_4	150.6	205.5	505.1	410.4	607.8	325.5
5j	H	4-$CH_3OC_6H_4$	133.1	164.5	507.3	**43.8**	108.4	**35**
5k	H	H	321.2	93.5	381.9	10^3	10^3	10^3
5l	H	$CH{=}CH_2$	426.2	59.8	529.5	10^3	10^3	**37.6**
5m	H	4-OH-3-$CH_3OC_6H_3$	302.9	174.6	445.1	10^3	10^3	10^3
8	H	Piperidin-4-yl	406.8	381.1	476.3	294.5	527.5	230.2
9	CH_3	Piperidin-4-yl	577.8	375.6	400.1	10^3	10^3	758.9
10	CH_3	4-ClC_6H_4	302	412.1	378	637.1	789.8	89.2
11	4-$ClC_6H_4CH_2$	4-ClC_6H_4	349.8	80.5	181.6	**14.1**	216.3	**26**
12	CH_3	4-$OCH_2C_6H_5$-3-$OCH_3C_6H_3$	450.1	382.5	367.6	197.6	10^3	317.5

These experiments were conducted in triplicates at three independent times. IC_{50} values were obtained using a dose response curve by nonlinear regression using a curve fitting program, GraphPad Prism 5.0. Bold values show IC_{50} of less than 50 μM.

*5.1.2.2. 4-(1′-Benzenesulfonylindol-3′-yl)-2-methyloxazoles (**4b**).* Yield 83%; mp 154 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.79 (s, 3H, CH_3), 7.32–7.44 (m, 5H, Ar-H), 7.50–7.52 (m, 1H, Ar-H), 7.62 (s, 1H, Ar-H), 7.91–7.94 (m, 2H, Ar-H), 7.98 (dd, 1H, $J = 7.12$, 1.12 Hz, Ar-H), 8.07 (s, 1H, Ar-H). HRMS for $C_{18}H_{14}N_2O_3S$, calcd $(M+H)^+$: 339.0803, found: 339.1200 $(M+H)^+$.

*5.1.2.3. 4-(1′-Benzenesulfonylindol-3′-yl)-2-(3,4-dimethoxyphenyl)-oxazoles (**4c**).* Yield 86%; mp 136 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.58 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 7.32–7.36 (m, 3H, Ar-H), 7.39–7.41 (m, 2H, Ar-H), 7.44–7.49 (m, 5H, Ar-H), 7.58 (s, 1H, Ar-H), 7.81 (s, 1H, Ar-H), 7.95–7.97 (m, 2H, Ar-H). HRMS for $C_{25}H_{20}N_2O_5S$, calcd $(M+H)^+$: 461.1171, found: 461.1202 $(M+H)^+$.

*5.1.2.4. 4-(1′-Benzenesulfonylindol-3′-yl)-2-(4′-fluorophenyl) oxazole (**4d**).* Yield 77%; mp 182 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.26–7.28 (m, 4H, Ar-H), 7.35–7.38 (m, 5H, Ar-H), 7.69 (s, 1H, Ar-H), 7.84–7.87 (m, 2H, Ar-H), 7.92 (s, 1H, Ar-H), 8.12–8.16 (m, 2H, Ar-H). HRMS for $C_{23}H_{15}FN_2O_3S$, calcd $(M)^+$ 418.0787, found: 418.1012 $(M)^+$.

*5.1.2.5. 4-(1′-Benzenesulfonylindol-3′-yl)-2-(4′-hydroxyphenyl)oxazole (**4e**).* Yield 78%; mp 128 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 5.34 (s, 1H, OH), 7.32–7.36 (m, 5H, Ar-H), 7.39–7.42 (m, 4H, Ar-H), 7.69 (s, 1H, Ar-H), 7.72 (s, 1H, Ar-H), 7.86 (dd, 2H, $J = 6.56$, 1.76 Hz, Ar-H), 7.91–7.95 (m, 2H, Ar-H). HRMS for $C_{23}H_{16}N_2O_4S$, calcd $(M+H)^+$: 417.0909, found: 417.1024 $(M+H)^+$.

*5.1.2.6. 4-(1′-Benzenesulfonylindol-3′-yl)-2-(styryl)oxazole (**4f**).* Yield 79%; mp 156–159 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 6.79 (m, 2H, CH), 7.20–7.24 (m, 5H, Ar-H), 7.33–7.36 (m, 2H, Ar-H), 7.38–7.42 (m, 5H, Ar-H), 7.58 (s, 1H, Ar-H), 7.62–7.64 (m, 2H, Ar-H), 7.72 (s, 1H, Ar-H). HRMS for $C_{25}H_{18}N_2O_3S$, calcd $(M)^+$: 426.1038, found: 426.1101 $(M)^+$.

*5.1.2.7. 4-(1′-Benzenesulfonylindol-3′-yl)-2-(4′-pyridyl) oxazole(**4g**).* Yield 73%; mp 142 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.19–7.21 (m, 2H, Ar-H), 7.29–7.32 (m, 5H, Ar-H), 7.49–7.51 (m, 2H, Ar-H), 7.54 (d, 1H, $J = 2.56$ Hz, Ar-H), 7.61–7.62 (m, 2H, Ar-H), 7.75 (s, 1H, Ar-H), 7.90–7.93 (m, 2H, Ar-H). HRMS for $C_{22}H_{15}N_3O_3S$, calcd $(M+H)^+$: 402.0912, found: 402.1011 $(M+H)^+$.

*5.1.2.8. 4-(1′-Benzenesulfonylindol-3′-yl)-2-(benzyl) oxazole (**4h**).* Yield 81%; mp 172–175 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 4.37 (s, 2H, CH_2), 7.28–7.33 (m, 10H, Ar-H), 7.34–7.38 (m, 2H, Ar-H), 7.62 (s, 1H, Ar-H), 7.72 (m, 2H, Ar-H), 7.81 (s, 1H, Ar-H). HRMS for $C_{24}H_{18}N_2O_3S$, calcd $(M+H)^+$: 415.1116, found: 415.1201 $(M+H)^+$.

*5.1.2.9. 4-(1′-Benzenesulfonylindol-3′-yl)-2-(4′-chlorophenyl)oxazole (**4i**).* Yield 80%; mp 136 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.21–7.28 (m, 4H, Ar-H), 7.36–7.39 (m, 2H, Ar-H), 7.42–7.47 (m, 5H, Ar-H), 7.62 (s, 1H, Ar-H), 7.81 (s, 1H, Ar-H), 7.86–7.89 (m, 2H, Ar-H). HRMS for $C_{23}H_{15}ClN_2O_3S$, calcd $(M+H)^+$: 435.057, found 435.0721 $(M+H)^+$.

*5.1.2.10. 4-(1′-Benzenesulfonylindol-3′-yl)-2-(4′-methoxyphenyl)oxazole(**4j**).* Yield 75%; mp 176–179 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.41 (s, 3H, OCH_3), 7.35–7.42 (m, 4H, Ar-H), 7.45–7.47 (m, 5H, Ar-H), 7.49–7.52 (m, 4H, Ar-H), 7.58 (s, 1H, Ar-H), 7.76 (s, 1H, Ar-H). HRMS for $C_{24}H_{18}N_2O_4S$, calcd $(M+H)^+$: 431.1066, found: 431.1132 $(M+H)^+$.

*5.1.2.11. 4-(1′-Benzenesulfonylindol-3′-yl)oxazole(**4k**).* Yield 80%; mp 126 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): $\delta_H = 7.21$–7.24 (m, 4H, Ar-H), 7.31–7.34 (m, 5H, Ar-H), 7.53 (d, 1H, $J = 2.55$ Hz, Ar-H), 7.69 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H). HRMS for $C_{17}H_{12}N_2O_3S$, calcd $(M+H)^+$: 325.0647, found: 325.0901 $(M+H)^+$.

*5.1.2.12. 4-(1′-Benzenesulfonylindol-3′-yl)-2-(ethenyl)oxazole(**4l**).* Yield 78%; mp 138 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 5.19 (d, 2H, $J = 3.6$ Hz, CH_2), 6.12 (t, 1H, $J = 2.6$ Hz, CH), 7.35–7.38 (m, 5H, Ar-H), 7.40–7.43 (m, 2H, Ar-H), 7.52 (s, 1H, Ar-H), 7.55–7.58 (m, 2H, Ar-H), 7.79 (s, 1H, Ar-H). HRMS for $C_{19}H_{14}N_2O_3S$, calcd $(M+H)^+$: 351.0803, found: 351.1015 $(M+H)^+$.

*5.1.2.13. 4-(1′-Benzenesulfonylindol-3′-yl)-2-(4′-hydroxy-3′-methoxyphenyl)oxazole(**4m**).* Yield 82%; mp 192–194 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.61 (s, 3H, OCH_3), 5.37 (s, 1H, OH), 7.32–7.36 (m, 5H, Ar-H), 7.41–7.45 (m, 3H, Ar-H), 7.51–7.54 (m, 2H, Ar-H), 7.55 (s, 1H, Ar-H), 7.78 (s, 1H, Ar-H), 7.92–7.95 (m, 2H, Ar-H). HRMS for $C_{24}H_{18}N_2O_5S$, calcd $(M)^+$: 446.0936, found: 446.1101 $(M)^+$.

*5.1.2.14. 4-(1′-Benzenesulfonylindol-3′-yl)-2-(4′-benzyloxy-3′-methoxyphenyl)oxazole (**4n**).* Yield 70%; mp 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.44 (s, 3H, OCH_3), 5.02 (s, 2H, CH_2, Ar-H), 7.29–7.41 (m, 5H, Ar-H), 7.49–7.55 (m, 3H, Ar-H), 7.6–7.64 (m, 2H, Ar-H), 7.83 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.93–7.98 (m, 4H, Ar-H), 7.99 (s, 1H, Ar-H), 8.21 (d, $J = 8.1$ Hz, 1H, Ar-H), 8.36 (s, 1H, Ar-H). IR (KBr, ν cm^{-1}): 3360, 3169, 1633, 1454, 1126, 750. HRMS for $C_{31}H_{24}N_2O_5S$, calcd $(M)^+$: 536.14, found: 536.15 $(M)^+$.

*5.1.2.15. 4-(1′-Benzenesulfonylindol-3′-yl)-2-(4′-piperidinyl)oxazole (**4o**).* Yield 50%; mp 124–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.1–2.4 (m, 4H), 2.6–2.8 (m, 4H, CH_2), 2.9 (m, 1H, CH), 7.43–7.52 (m, 5H, Ar-H), 7.68(s, 1H, Ar-H), 7.93–7.98 (m, 4H, Ar-H), 7.9 (s, 1H, Ar-H). HRMS for $C_{22}H_{21}N_3O_3S$, calcd $(M+H)^+$: 408.1304, found: 408.1401 $(M+H)^+$.

*5.1.3. General procedure for the synthesis of 4-(3′-indolyl)-2-substituted oxazole (**5**)*

A stirred solution of 4 (1 mmol), sodium hydroxide (3 mmol) in ethanol (10 mL) and water (3 mL) was refluxed till the completion of reaction. The ethanol was evaporated under vacuum, and the remaining aqueous solution was extracted with dichloromethane (3 × 10 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under vacuum to afford 5 in excellent yield.

*5.1.3.1. 4-(3′-Indolyl)-2-phenyloxazole (**5a**).* Yield 82%; mp 172 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.28–7.32 (m, 2H, Ar-H), 7.39–7.50 (m, 5H, Ar-H), 7.94 (d, 1H, $J = 7.92$ Hz, Ar-H), 7.97–8.01 (m, 2H, Ar-H), 8.03 (s, 1H, Ar-H), 8.49 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 162.54, 153.07, 147.00, 137.52, 136.97, 131.87, 129.22, 128.63, 127.90, 126.01, 121.93, 119.90, 116.12, 112.12, 107.03 (Ar-C). HRMS for $C_{17}H_{12}N_2O$, calcd $(M+H)^+$: 261.1028, found: 261.1800 $(M+H)^+$.

*5.1.3.2. 4-(3′-Indolyl)-2-methyloxazole (**5b**).* Yield 80%; mp 163 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.75 (s, 3H, CH_3), 7.21–7.30 (m, 2H, Ar-H), 7.39–7.44 (m, 2H, Ar-H), 7.79 (s, 1H, Ar-H), 7.87 (d, 1H, $J = 7.84$ Hz, Ar-H), 8.36 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 165.0, 150.30, 136.56, 125.10, 123.72, 122.49, 120.57, 120.02, 112.80, 111.47, 109.62 (Ar-C), 19.25 (CH_3). HRMS for $C_{12}H_{10}N_2O$, calcd $(M+H)^+$: 199.0871, found: 199.0932 $(M+H)^+$.

*5.1.3.3. 2-(3′,4′-Dimethoxyphenyl)-4-(3′-indolyl)oxazole (**5c**).* Yield 83%; mp 182–185 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.62 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 7.35–7.39 (m, 2H, Ar-H), 7.42 (s, 1H, Ar-H), 7.49–7.52 (m, 2H, Ar-H), 7.95–7.97 (m, 4H, Ar-H), 8.33 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 163.13, 151.71, 148.66, 145.04, 137.34, 129.26, 126.59, 124, 90, 122.85, 122.30, 121.15, 120.71, 112.21, 112.02, 111.91, 111.25, 110.74 (Ar-C), 56.06 (OCH_3), 56.02 (OCH_3). HRMS for $C_{19}H_{16}N_2O_3$, calcd $(M+H)^+$: 321.1239, found: 321.1252 $(M+H)^+$.

*5.1.3.4. 2-(4′-Fluorophenyl)-4-(3′-indolyl)oxazole (**5d**).* Yield 81%; mp 145–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.22–7.29 (m, 1H, Ar-H), 7.42–7.51 (m, 4H, Ar-H), 7.78 (d, 1H, $J = 2.52$ Hz, Ar-H), 7.84–7.87 (m, 1H, Ar-H), 8.01 (s, 1H, Ar-H), 8.16–8.19 (m, 2H, Ar-H), 8.38 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 165.71, 162.82, 145.58, 137.39, 130.59, 130.39, 130.30, 129.69, 124.86, 122.90, 122.36, 120.76, 115.38, 112.05, 111.97 (Ar-C). HRMS for $C_{17}H_{11}FN_2O$, calcd $(M+H)^+$: 279.0934, found: 279.1013 $(M+H)^+$.

*5.1.3.5. 2-(4′-Hydroxyphenyl)-4-(3′-indolyl)oxazole (**5e**).* Yield 84%; mp 138 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 5.36 (s, 1H, OH), 7.22–7.29 (m, 1H, Ar-H), 7.42–7.51 (m, 4H, Ar-H), 7.77 (d, 1H, $J = 2.52$ Hz, Ar-H), 7.86 (dd, 1H, $J = 6.56, 1.76$ Hz, Ar-H), 8.01 (s, 1H, Ar-H), 8.11–8.16 (m, 2H, Ar-H), 8.38 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 168.78, 162.58, 145.61, 140.79, 137.21, 136.18, 133.51, 132.64, 131.14, 129.56, 128.64, 126.47, 125.62, 124.45, 113.84 (Ar-C). HRMS for $C_{17}H_{12}N_2O_2$, calcd $(M+H)^+$: 277.0977, found: 277.0982 $(M+H)^+$.

*5.1.3.6. 4-(3′-Indolyl)-2-(styryl)oxazole (**5f**).* Yield 85%; mp 162 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 6.82 (m, 2H, C-H), 7.12–7.23 (m, 5H, Ar-H), 7.31–7.33 (m, 2H, Ar-H), 7.56 (d, 1H, $J = 2.53$ Hz, Ar-H), 7.58–7.60 (m, 2H, Ar-H), 7.72 (s, 1H, Ar-H), 8.38 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 160.72, 137.52, 136.95, 135.52 (C═C), 131.50, 129.23, 127.90, 127.21, 126.00 (C═C), 124.72, 123.64, 121.95, 119.92, 119.70, 114.02, 112.10, 107.09 (Ar-C). LCMS for $C_{19}H_{14}N_2O$, calcd $(M)^+$: 286.1, found: 286.1 $(M)^+$.

*5.1.3.7. 4-(3′-Indolyl)-2-(4′-pyridyl)oxazole (**5g**).* Yield 85%; mp 122 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.15–7.19 (m, 2H, Ar-H), 7.52–7.55 (m, 2H, Ar-H), 7.57 (d, 1H, $J = 2.53$ Hz, Ar-H), 7.62–7.64 (m, 2H, Ar-H), 7.78 (s, 1H, Ar-H), 7.93–7.96 (m, 2H, Ar-H), 8.42 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 159.50, 148.63, 133.17, 130.99, 129.66, 128.95, 128.14, 127.43, 126.46, 125.95, 124.41, 122.18, 120.06, 112.40 (Ar-C). HRMS for $C_{16}H_{11}N_3O$, calcd $(M+H)^+$: 262.0980, found: 262.1056 $(M+H)^+$.

*5.1.3.8. 2-(Benzyl)4-(3′-indolyl) oxazole (**5h**).* Yield 80%; mp 138 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 4.39 (s, 2H, CH_2). 7.15–7.40 (m, 9H, Ar-H), 7.69 (d, 1H, $J = 2.54$ Hz, Ar-H), 8.00 (s, 1H, Ar-H), 8.61 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 166.58, 143.66, 140.26, 137.84, 136.96, 132.96, 129.58, 128.46, 126.75, 125.30, 123.06, 122.15, 121.04, 111.36, 109.88 (Ar-C), 33.19 (CH_2). HRMS for $C_{18}H_{14}N_2O$, calcd $(M+H)^+$: 275.1184, found: 275.2200 $(M+H)^+$.

*5.1.3.9. 2-(4′-Chlorophenyl)4-(3′-indolyl) oxazole (**5i**).* Yield 84%; mp 158–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.25–7.32 (m, 4H, Ar-H), 7.39–7.41 (m, 2H, Ar-H), 7.59 (d, 1H, $J = 2.54$ Hz, Ar-H), 7.78 (s, 1H, Ar-H), 7.93–8.03 (m, 2H, Ar-H), 8.41 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 159.70, 148.31, 137.68, 135.64, 133.45, 131.39, 129.82, 128.20, 127.65, 126.27, 124.78, 122.21, 120.30, 112.44, 106.75 (Ar-C). HRMS for $C_{17}H_{11}ClN_2O$, calcd $(M+H)^+$: 295.0638, found: 295.0739 $(M+H)^+$.

*5.1.3.10. 4-(3′-Indolyl)-2-(4′-methoxyphenyl)oxazole (**5j**).* Yield 86%; mp 164 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.39 (s, 3H, OCH_3), 7.39–7.43 (m, 4H, Ar-H), 7.54 (d, 1H, $J = 2.54$ Hz, Ar-H), 7.65 (d, 2H, $J = 8$ Hz, Ar-H), 7.79 (s, 1H, Ar-H), 7.96 (d, 2H, $J = 5.96$ Hz, Ar-H), 8.20 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 162.44, 162.16, 144.87, 137.49, 136.23, 130.56, 129.78, 126.55, 124.83, 123.06, 122.52, 120.80, 114.10, 112.57, 112.29 (Ar-C), 55.86 (OCH_3). LCMS for $C_{18}H_{14}N_2O_2$, calcd $(M+H)^+$: 291.1, found: 291.1 $(M+H)^+$.

*5.1.3.11. 4-(3′-Indolyl)oxazole (**5k**).* Yield 83%; mp 110 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.22–7.30 (m, 4H, Ar-H), 7.56 (d, 1H, $J = 2.55$ Hz, Ar-H), 7.71 (s, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 8.35 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 152.26, 148.60, 128.96, 128.14, 125.95, 124.64, 124.40, 123.50, 121.45, 120.50, 119.50 (Ar-C). HRMS for $C_{11}H_8N_2O$, calcd $(M+H)^+$: 185.0715, found: 185.0813 $(M+H)^+$.

*5.1.3.12. 2-(Ethenyl)-4-(3′-indolyl) oxazole (**5l**).* Yield 79%; mp 140–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 5.21 (d, 2H, $J = 3.7$ Hz, CH_2), 6.14 (t, 1H, $J = 2.6$ Hz, CH), 7.39–7.42 (m, 2H, Ar-H), 7.54 (d, 1H, $J = 2.54$ Hz, Ar-H), 7.56–7.59 (m, 2H, Ar-H), 7.81 (s, 1H, Ar-H), 8.34 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 162.21, 145.08, 137.85, 136.98, 133.40 (C═C), 132.84, 129.53, 128.56, 125.33, 123.10 (C═C), 121.04, 111.38, 109.91 (Ar-C). HRMS for $C_{13}H_{10}N_2O$, calcd $(M + H)^+$: 211.0871, found: 211.1023 $(M + H)^+$.

*5.1.3.13. 2-(4′-Hydroxy-3′-methoxyphenyl)-4-(3′-indolyl) oxazole (**5m**).* Yield 88%; mp 152 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.59 (s, 3H, CH_3), 5.39 (s, 1H, OH), 7.39–7.43 (m, 3H, Ar-H), 7.48–7.53 (m, 2H, Ar-H), 7.55 (d, 1H, $J = 2.57$ Hz, Ar-H), 7.81 (s, 1H, Ar-H), 7.95–7.97 (m, 2H, Ar-H), 8.32 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 165.29, 162.81, 160.49, 137.17, 136.36, 135.35, 130.63, 129.28, 127.30, 126.03, 124.13, 123.68, 121.90, 116.97, 116.75, 114.38, 113.86 (Ar-C), 57.80 (OCH_3). HRMS for $C_{18}H_{14}N_2O_3$, calcd $(M + H)^+$: 307.1083, found: 307.1092 $(M + H)^+$.

*5.1.3.14. 2-(4′-Chlorophenyl)-4-(N-methyl-3′-indolyl)oxazole (**10**).* Yield 70%; mp 133–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.83 (s, 3H, NCH_3), 7.24–7.49 (m, 5H, Ar-H), 7.65 (s, 1H, Ar-H), 7.83 (d, $J = 8.8$ Hz, 1H, Ar-H) 7.99 (s, 1H, Ar-H), 8.08 (d, $J = 8.8$ Hz, 2H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 159.72, 137.49, 137.34, 135.66, 133.44, 129.80, 128.67, 128.20, 126.27, 125.08, 122.31, 120.51, 120.28, 110.69, 106.00 (Ar-C), 33.09 (NCH_3). IR (KBr, ν cm^{-1}): 3360, 3169, 1633, 1454, 1126, 750. HRMS for $C_{18}H_{13}ClN_2O$, calcd $(M)^+$: 308.0716, found: 308.9692 $(M)^+$.

*5.1.3.15. 4-(N-(4-Chlorobenzyl)-2-(4′-chlorophenyl)-3′-indolyl) oxazole (**11**).* Yield 75%; mp 181–183 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 5.36 (s, 2H, CH_2), 7.12 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.25–7.32 (m, 6H, Ar-H), 7.47 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.71 (s, 1H, Ar-H), 7.99 (s, 1H, Ar-H), 8.06–8.09 (m, 2H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 159.79, 137.44, 137.12, 136.79, 135.72, 133.77, 132.55, 129.82, 129.52, 129.07, 128.24, 126.00, 125.35, 122.62, 120.73, 120.59, 111.14, 106.92 (Ar-C), 48.89 (CH_2). IR (KBr, ν cm^{-1}): 3385, 2960, 1670, 1390, 1126, 750, 770. HRMS for $C_{24}H_{16}C_{l2}N_2O$, calcd $(M + H)^+$: 419.0718, found: 242.20 $(M/2 + CH_3OH + H)^+$.

*5.1.3.16. 2-(4′-Benzyloxy-3-hydroxyphenyl)-4-(N-methyl-3′-indolyl) oxazole (**12**).* Yield 60%; mp 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.87 (s, 3H, OCH_3), 4.02 (s, 3H, NCH_3), 5.24 (s, 2H, CH_2), 6.98 (d, $J = 8.4$ Hz, 1H, Ar-H), 7.22–7.48 (m, 9H, Ar-H), 7.66 (s, 1H, Ar-H), 7.02 (d, $J = 2$ Hz, 1H, Ar-H), 7.82 (d, $J = 8.0$ Hz, 1H, Ar-H), 7.95 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 166.03, 155.14, 150.50, 148.97, 138.19, 137.23, 135.82, 128.92, 128.42, 128.35, 127.23, 126.29, 125.60, 123.19, 122.71, 121.29, 120.44, 112.91, 111.55, 110.96, 110.80 (Ar-C), 70.23 (CH_2), 56.02 (OCH_3), 33.32 (NCH_3). IR (KBr, ν cm^{-1}): 3460, 3265, 1633, 1180, 780. HRMS for $C_{26}H_{22}N_2O_3$, calcd $(M + H)^+$: 411.17, found: 411.02 $(M + H)^+$.

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