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An efficient synthesis and biological study of novel indolyl-1,3,4-oxadiazoles as potent anticancer agents

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ABSTRACT

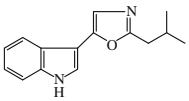
A facile, convenient and high yielding synthesis of a series of novel 5-(3′-indolyl)-2-(substituted)-1,3,4-oxadiazoles from readily available starting materials has been described. The key step of this protocol is oxidative cyclization of *N*-acylhydrazones 1 using [bis(trifluoroacetoxy)iodo]benzene under solvent-free condition. The 5-(3′-indolyl)-2-(substituted)-1,3,4-oxadiazoles were screened for their in vitro anticancer activity against various human cancer cell lines. Compounds **3c**, **3d** and **3j** exhibited potent cytotoxicity (IC_{50} ~1 μM) and selectivity against human cancer cell lines.

1,3,4-Oxadiazoles are an important class of heterocyclic compounds with a wide range of biological activities such as antiviral,[1] antimicrobial,[2] antineoplastic,[3] fungicidal,[4] inhibition of tyrosinase[5] and cathepsin K.[6] The five-membered 1,3,4-oxadiazole heterocycles are also useful intermediates in organic synthesis[7] and widely employed as electrontransporting and hole-blocking materials.[8] Further, 1,3,4-oxadiazole heterocycles are very good bioisosteres of amides and esters, which can contribute substantially in increasing pharmacological activity by participating in hydrogen bonding interactions with the receptors.[9] The strategy of using bioisosterism in developing new therapeutically active analogs has attained a noteworthy growth in the pharmaceutical industry.

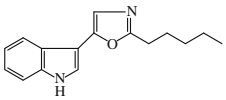
There are many reported synthetic approaches to 1,3,4-oxadiazole heterocycles. One such approach involves the cyclodehydration of 1,2-diacyl or 1,2-diaroylhydrazines with a variety of anhydrous reagents such as thionyl chloride,[10] phosphorous pentoxide,[11] phosphorous oxychloride,[12] triflic anhydride,[13] triphenylphosphine,[14] polyphosphoric acid,[15] and sulfuric acid.[16] An alternative route for synthesis of 1,3,4-oxadiazoles is by cyclization of isonicotinic acid hydrazide with either acid chlorides, aromatic acids or aromatic aldehydes followed by dehydration in the presence of dehydrating reagents like sulfuric acid, phosphorous oxychloride, etc.[17] However, most of these procedures involve the use of toxic and lachrymatory reagents, difficult handling procedures, and ultimately moderate yield of product.

Cancer treatment has been a major endeavor of research and development in academia and pharmaceutical industry for the last many years as it is one of the leading causes of death.[18] Many of the available anticancer agents exhibit undesirable side effects such as reduced bioavailability, toxicity and drug-resistance.[19–23] Therefore, the search for novel and selective anticancer agents is urgently required due to problems associated with currently available anticancer drugs.

The naturally occurring 5-(3′-indolyl) oxazoles are known to display diverse biological activities.[24] Labradorin 1 and Labradorin 2 were found to be cytotoxic against NCI–H 460 (lung-NSC) human cancer cell line with GI_{50} values of 9.8 μg/mL and 9.6 μg/mL, respectively.[24]



Labradorin 1



Labradorin 2

In view of interesting biological activities exhibited by naturally occurring 5-(3′-indolyl) oxazoles and our efforts to search for novel and selective antitumor agents, we report herein [bis(trifluoroacetoxy)iodo]benzene (BTI) mediated synthesis and antitumor activities of analogues 5-(3′-indolyl)-2-(substituted)-1,3,4-oxadiazoles (**3**)

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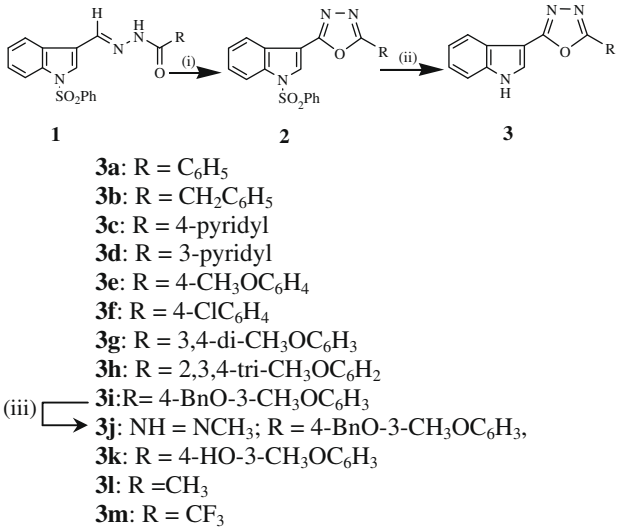
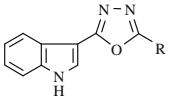


Scheme 1. Reagents and conditions: (i) $PhI(OCOCF_3)_2$,grinding, rt, 65–81%; (ii) NaOH, EtOH–H_2O, reflux, 3 h, 80–92%; (iii) CH_3I, KOH, DMSO, stirring, rt, 80%.

under solvent-free conditions. Reactions under solvent-free conditions have continuously attracted the attention of researchers both from academia and industry. This is due to the fact that organic reactions under solvent-free conditions have an improved selectivity and efficiency, ease of manipulation, pure product formation, avoids the use of toxic or volatile solvents.[25] This expeditious synthesis of **3** involves reacting 1-benzenesulfonyl-indole-3-aldehyde[26] with various substituted hydrazides in the presence of acetic acid under refluxing condition affording the corresponding indolyl-3-aldehyde *N*-acylhydrazones **1** in excellent yields. Our initial trials for the cyclization of indolyl-3-aldehyde *N*-acylhydrazones **1** using iodobenzenediacetate were unsatisfactory due to the poor yield of product and prolonged reaction time. However, a neat grinding of indolyl-3-aldehyde *N*-acylhydrazone **1** (1.0 mmol) with BTI (1.2 mmol) for 10 min at room temperature resulted in rapid formation of indolyl-1,3,4-oxadiazoles **2** in good yield without any by-product (Scheme 1).[26] Removal of the benzenesulfonamide group of **2** was achieved by refluxing with aqueous sodium hydroxide to furnish 5-(3′-indolyl)-2-phenyl-1,3,4-oxadiazole **3a** (Scheme 1). Encouraged by the successful synthesis of **3a**, the protocol was extended for the preparation of analogues 5-(3′-indolyl)-2-(substituted)-1,3,4-oxadiazole **3b–m**. All the synthesized compounds **(3a–m)** were characterized by ^1H NMR and MS data.

In order to study the structure–activity relationship (SAR), synthesized indolyl-1,3,4-oxadiazoles **3a–m** were screened in vitro for their anticancer potential against human cancer cell lines from prostate (PC3, DU145 and LnCaP), breast (MCF7 and MDMDA231), and pancreas (PaCa2). The cell viability results of **3a–m** are summarized in Table 1. With few exceptions, most of the compounds decreased cell viability significantly as established by colorimetric MTT mitochondrial assay with IC_{50} values ranging from 1 μM to 1 mM concentration. The SAR study reveals that substitution at the C-2 position of the 1,3,4-oxadiazole ring plays an important role. The compound **3a** with C-2 phenyl group exhibited moderate activity against MCF7 (388.4 μM) and poor activity against other cell lines. Interestingly, replacement of the phenyl ring with a benzyl group (**3b**) exhibited better inhibitory activity against MCF7 (39.2 μM) with 24-fold selectivity versus PaCa2 cancer cell line (934.3 μM). A significant increase in activity and selectivity was observed against PC3 (4.1 μM), MCF7 (1 μM) and PaCa2 (1.6 μM) for the analogue **3c** with a 4-pyridyl group indicating that it is a good replacement for the phenyl group. This result is intriguing since **3c** was cytotoxic in most of the cell lines at 1–10 μM concentration, but showed no effect in MDA-MB-231 cells even at 1 mM concentration. However, when the position of nitrogen atom was shifted to C-3′ in the C-2 pyridyl ring (**3d**), it was specific against PaCa2 cell line (0.9 μM). Subsequently, the SAR of the phenyl ring was investigated by introducing various groups. Substitution at the *para* position of C-2 phenyl ring with a methoxy group resulted in compound **3e** with a loss in cytotoxic activity against all the cell lines. Compound **3f** with a *p*-chloro substituent displayed relatively better activity against PC3 (41.6 μM) and MCF7 (48.2 μM) cell lines. Introduction of 3,4-dimethoxyphenyl or 3,4,5-trimethoxyphenyl group at the C-2 position of 1,3,4-oxadiazole ring gives compound **3g** or **3h** with weak activity against different cancer cell lines. The compound **3i** with bulkier 4-benzyloxy-3-methoxyphenyl moiety at the C-2 position showed very poor activity. However, N-methylation of the indole nitrogen was found to be beneficial for the activity as in the case of compound

Table 1
In vitro cytotoxicity data of 5-(3′-indolyl)-2-(substituted)-1,3,4-oxadiazoles **3**



Compound	R	Cytotoxicity IC_{50}[a] (μM)					
		PC3	DU145	LnCaP	MDA-MB-231	MCF7	PaCa2
3a	C_6H_5	>10[3]	>10[3]	>10[3]	>10[3]	388.4	>10[3]
3b	$CH_2C_6H_5$	>10[3]	>10[3]	>10[3]	>10[3]	39.2	934.3
3c	4-Pyridyl	4.1	20.4	10.0	>10[3]	1.0	1.6
3d	3-Pyridyl	710.8	170	69.4	>10[3]	5.4	0.9
3e	4-$CH_3OC_6H_4$	>10[3]	>10[3]	>10[3]	>10[3]	>10[3]	>10[3]
3f	4-ClC_6H_4	41.6	192	582.6	>10[3]	48.2	6459
3g	3,4-$(CH_3O)_2C_6H_3$	>10[3]	>10[3]	>10[3]	>10[3]	556.7	>10[3]
3h	3,4,5-$(CH_3O)_3C_6H_2$	>10[3]	>10[3]	>10[3]	>10[3]	121.2	>10[3]
3i	4-BnO-3-$CH_3OC_6H_3$	>10[3]	>10[3]	>10[3]	>10[3]	>10[3]	>10[3]
3j[b]	4-BnO-3-$CH_3OC_6H_3$	>10[3]	>10[3]	>10[3]	>10[3]	35.2	1.4
3k	4-HO-3-$CH_3OC_6H_3$	>10[3]	>10[3]	>10[3]	>10[3]	>10[3]	>10[3]
3l	CH_3	>10[3]	>10[3]	>10[3]	>10[3]	198.3	145
3m	CF_3	>10[3]	>10[3]	>10[3]	>10[3]	>10[3]	>10[3]

[a] Data obtained for each compound was done in triplicates and IC_{50} values given in micromolar concentrations were obtained using a dose response curve by nonlinear regression using a curve fitting program, GraphPad Prism 5.0.
[b] NH=NCH_3.

3j, a significant increase in activity and specificity was observed against PaCa2 (1.4 μM) cell line. A free hydroxyl group at the *para*-position of C-2 phenyl ring is detrimental for the activity as evident from the activity of compound **3k**. Finally, we explored the replacement of the aromatic group with an aliphatic substituent. The compound **3l** with C-2 methyl group was moderately cytotoxic towards PaCa2 (145 μM) while it exhibited very poor activity against other cell lines. When a trifluoromethyl substituent was introduced at C-2 position, activity reduced significantly as shown by compound **3m**. Among the compounds synthesized and screened for cytotoxic activity, compounds **3c**, **3d** and **3j** exhibited higher specificity and cytotoxic activity against different cancer cell lines (IC_{50} values against MCF7 (1.0 μM) PaCa2 (1.6 μM); PaCa2 (0.9 μM); and PaCa2 (1.4 μM)).

In conclusion, a series of diverse 5-(3-indolyl)-2-(substituted)-1,3,4-oxadiazoles have been synthesized which represent a novel class of potent and selective anticancer agents. Through SAR studies, we have found that compounds either with 4-pyridyl or 3-pyridyl substitution were potent and selective. It is interesting to note that the 3-pyridyl substitution exhibited selective cytotoxic activity against PaCa2 cancer cell line. Also, N-methylation of indole ring nitrogen dramatically improved the cytotoxic activity. Studies are being conducted to determine mode of action of 5-(3′-indolyl)-2-(substituted)-1,3,4-oxadiazoles, and further modification of these compounds may successfully lead to development of a potent anticancer agent.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.03.172.

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26. *Synthesis of indolyl-1,3,4-oxadiazoles* **3a–k**: The indole-3-carboxaldehyde *N*-acylhydrazone **1** (1 mmol) and BTI (1.2 mmol) were ground in a mortar and pestle at room temperature for 10 min. During the admixing, reaction was initiated and turned dark brown rapidly. The completion of reaction was confirmed by TLC (7:3 hexane/ethylacetate). The reaction mixture was taken into water and extracted with ethylacetate (2 × 5 mL). Organic phase was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was percolated through a bed of silica gel using ethyl acetate/hexane (1/9, v/v) as eluent to afford the pure product **3a–k** in good yield. Compound **3a**: ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.22 (s, 1H, NH), 8.29 (dd, 1H, J = 6.08, 3.12 Hz), 8.17–8.13 (m, 2H), 8.02 (d, 1H, J = 2.92 Hz), 7.57–7.50 (m, 4H), 7.30 (dd, 2H, J = 6.10, 3.18 Hz). Calcd m/z for $C_{16}H_{11}N_3O$: 261.0902, found: 262.1002 $(M+H)^+$.