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3-Substitued indoles: One-pot synthesis and evaluation of anticancer and Src kinase inhibitory activities

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ABSTRACT

An efficient and economical method was developed for the synthesis of 3-substituted indoles by one-pot three-component coupling reaction of a substituted or unsubstituted benzaldehyde, *N*-methylaniline, and indole or *N*-methylindole using $Yb(OTf)_3$–SiO_2 as a catalyst. All the synthesized compounds were evaluated for inhibition of cell proliferation of human colon carcinoma (HT-29), human ovarian adenocarcinoma (SK-OV-3), and c-Src kinase activity. The 4-methylphenyl (**4o** and **4p**) and 4-methoxyphenyl (**4q**) indole derivatives inhibited the cell proliferation of SK-OV-3 and HT-29 cells by 70–77% at a concentration of 50 μM. The unsubstituted phenyl (**4d**) and 3-nitrophenyl (**4l**) derivatives showed the inhibition of c-Src kinase with IC_{50} values of 50.6 and 58.3 μM, respectively.

The 3-substituted indoles are structural units of many natural and biologically interesting compounds, which possess various pharmacological activities.[1–4] The indole derivatives serve as a scaffold in a number of antibacterial,[5] antiviral,[6] and protein kinase inhibitors.[7] Indole-based derivatives have been investigated for anticancer activities. Indole-3-carbinols have been previously reported to exhibit anticancer activities against a number of human cancers through acting on different cellular signaling pathways.[8] 1-Aroylindoles and 3-aroylindoles have shown potent cytotoxicity against different human cancer cell lines.[9].

Several indole derivatives have shown tyrosine kinase inhibition in low micromolar range.[7,10] 3-Substituted 2,2′-dithiobis(1*H*-indoles) have been reported to show inhibition against protein tyrosine kinases (PTKs), such as EGFR and non receptor v-Src tyrosine kinases.[11] SU5416 (Fig. 1) is an indole-based FIK-1/KDR inhibitor, and is currently in clinical trials against ovarian cancer.[12–14]

The Src family of tyrosine kinases (SFKs) is comprised of nine tyrosine kinases viz., Src, Lck, Fyn, Yes, Hck, Blk, Fgr, Lyn, and Yrk. SFKs have critical roles in multiple signaling pathways that control a diverse spectrum of biological activities, such as growth factor signaling, cell growth, division, differentiation, survival, adhesion, migration, and invasion.[16] c-Src tyrosine kinase is the prototype of SFKs. c-Src upregulation has been observed in a number of epithelial tumors, such as ovary, colon, lung, breast, prostate, and pancreas when compared with the normal tissues. c-Src serves as a key modulator of cancer cell invasion and metastasis through reducing cell adhesion and facilitating motility.[17–19] Thus, considerable interest has been evolved around the design of Src kinase inhibitors for the treatment of cancer and anti-invasion therapy.[20] A number of small molecule inhibitors[21,22] have shown potential biological activity as both

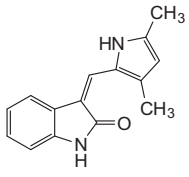
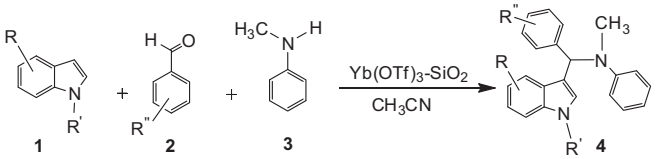


Figure 1. Chemical structure of SU5416.



Scheme 1. Synthesis of 3-substituted indoles.

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anti-proliferative and anti-invasive agents in preclinical studies in different solid tumor types.[23–26]

In continuation of our efforts towards the development of organic transformations catalyzed by metal triflates[27] and synthesis of small molecules as anticancer agents and/or c-Src kinase inhibitors,[15,28] herein we report an expeditious one-pot synthesis of 3-substituted indoles by three component condensation catalyzed by $Yb(OTf)_3$–SiO_2 (Scheme 1) and evaluation of their anticancer and c-Src kinase inhibitory activity.

The 3-indole derivatives were synthesized by one-pot condensation reaction of indole or *N*-methylindole, a substituted or unsubstituted benzaldehyde, and *N*-methylaniline. The reaction condition optimizations were performed by monitoring a model reaction between indole, 4-chlorobenzaldehyde and *N*-methylaniline. The model reaction was carried out in various solvents, such as DCM, DMSO, DMF, THF, acetonitrile, and ionic liquid [bmim][BF_4], using $Yb(OTf)_3$–SiO_2 as a catalyst. Among these solvents acetonitrile was found to be most efficient reaction media to give **4a** in good yield (88%) while the reaction yield in other solvents was very poor.

Furthermore, catalyst conditions were optimized by using different variations of catalyst, catalyst loading, and time period of reaction (Table 1). The yield of **4a** was poor and required longer time when reaction was performed with either $Yb(OTf)_3$ or silica gel alone. Among the screened catalysts $Yb(OTf)_3$–SiO_2 (5–10 mol %), $Ce(OTf)_3$-SiO_2 (5 mol %), and $Cu(OTf)_2$–SiO_2 (5 mol %) were found to give good yield of **4a**. The $Yb(OTf)_3$–SiO_2 (5 mol %) gave the highest yield (88%) of **4a** and, therefore, further studies were carried out using this as a catalyst of choice. In case of other acidic catalysts supported on silica gel such as *p*TSA–SiO_2 (71%), $FeCl_3$–SiO_2 (59%) the yield of **4a** was moderate but accompanied with generation of bis(indolyl)methane (5–30%) as a side product.

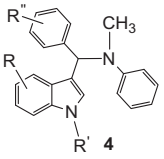
The standardized reaction conditions were used further for the synthesis of different 3-substituted indole derivatives.[29] Indole or *N*-methylindole, *N*-methylaniline, and a substituted or unsubstituted benzaldehyde were reacted to obtain 3-substituted indole derivatives (**4a**–**r**). The products and their yields are summarized in Table 2. All the compounds were characterized by ^1H NMR, ^{13}C NMR, and mass spectroscopy. The reaction is assumed to proceed through formation of imine after reaction of the benzaldehyde and *N*-methylaniline followed by nucleophilic attack of indole to give a 3-substituted indole as shown in Scheme 2. The structure of product is consistent with the synthesis of 3-substituted indoles via multicomponent condensation reaction of indoles, aldehyde, and amines.[30]

Table 1
Optimization of reaction condition for model reaction generating **4a**

Catalyst	Catalyst (mol %)	Time (h)	Yield[a] (%)
SiO_2	—	6	15
$Yb(OTf)_3$	5	4	72
$Zn(OTf)_2$	5	4	52
$Ce(OTf)_3$	5	4	71
$Cu(OTf)_2$	5	4	68
$Ba(OTf)_2$	5	4	50
$Yb(OTf)_3$–SiO_2	1	2	47
$Yb(OTf)_3$–SiO_2	2	2	58
$Yb(OTf)_3$–SiO_2	3	2	67
$Yb(OTf)_3$–SiO_2	4	2	74
$Yb(OTf)_3$–SiO_2	5	2	88
$Yb(OTf)_3$–SiO_2	10	2	84
$Zn(OTf)_2$–SiO_2	5	2	62
$Ce(OTf)_3$–SiO_2	5	2	81
$Cu(OTf)_2$–SiO_2	5	2	81
$Ba(OTf)_2$–SiO_2	5	2	67
$FeCl_3$–SiO_2	5	2	59
*p*TSA–SiO_2	5	3	71

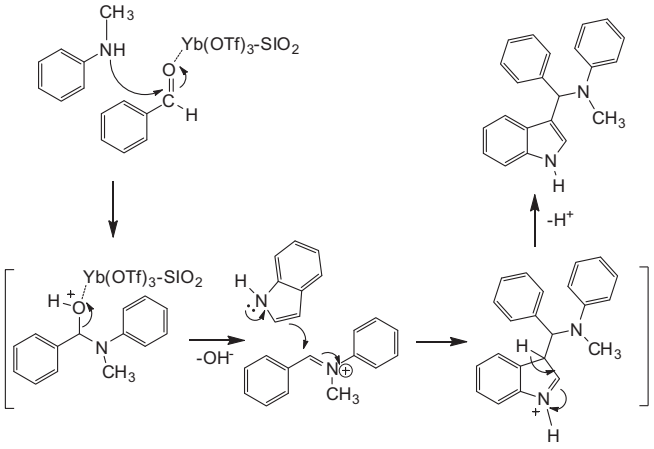
[a] Isolated yield.

Table 2
Chemical structures of 3-substituted indoles (**4a**–**r**) and their Src kinase inhibitory activity



Product	R	R′	R″	Yield[a] (%)	IC_{50}[b] (μM)
4a	H	H	4-Cl	88	>150
4b	H	H	4-CH_3	83	>150
4c	H	H	4-CH_3O	86	>150
4d	H	H	H	78	50.6
4e	H	H	4-OH	75	>150
4f	H	H	3-Br, 4-OH	84	>150[a]
4g	H	H	3-CH_3O	82	>150
4h	H	H	2,4-CH_3O	81	>150
4i	H	CH_3	H	79	>150
4j	H	CH_3	4-Cl	81	98.3
4k	H	CH_3	4-CH_3	82	60.5
4l	H	H	3-NO_2	51	58.3
4m	5-Br	H	H	72	71.6
4n	5-OCH_3	H	4-OCH_3	88	100.0
4o	5-OCH_3	H	4-CH_3	85	>150
4p	5-Br	H	4-CH_3	78	>150
4q	5-Br	H	4-OCH_3	80	106
4r	5-OCH_3	H	4-Cl	83	87

[a] Isolated yield.
[b] The concentration at which 50% of enzyme activity is inhibited.



Scheme 2. Plausible mechanism for synthesis of **4**.

An array of 18 diversely substituted indoles was evaluated against Src kinase. The results of Src kinase inhibitory activity of compounds (**4a**–**r**) are shown in Table 2. Among all the screened compounds, **4d**, **4j**, **4k**, **4l**, and **4r** showed modest inhibition of Src kinase with IC_{50} values of 50.6–98.3 μM. The data suggest that the presence of either electron donating or electron withdrawing groups on the phenyl ring (R″ position) was mostly less tolerated as shown in compounds **4a**–**c**, **4e**–**i**, and **4n**–**p** with IC_{50} value of $\geqslant$100 μM. The unsubstituted indole derivative **4d** showed an IC_{50} value of 50.6 μM while introduction of electron withdrawing group –NO_2 at 3-position of phenyl ring (**4l**) exhibited comparable inhibitory activity (IC_{50} = 58.3 μM).

DS visualizer docking studies[31] were used to study the interactions of **4d** with the ATP binding site of the Src kinase. Compound **4d** was superimposed on AZD05030, an anilinoquanzoline dual specific c-Src/Abl kinase inhibitor[32] in complex with the Src kinase (PDB 2H8H).