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2011

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Recommended Citation

Rao, V. Kameshwara, et al. "3-Substitued indoles: one-pot synthesis and evaluation of anticancer and Src kinase inhibitory activities." *Bioorganic & medicinal chemistry letters* 21.12 (2011): 3511-3514. doi: 10.1016/j.bmcl.2011.05.010

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

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This is where the receipt/accepted dates will go; Received Month XX, 2000; Accepted Month XX, 2000 [BMCL RECEIPT]

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-SiO₂ 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 IC₅₀ values of 50.6 μM 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 anti-proliferative and anti-invasive agents in preclinical studies in different solid tumor types.^{23–26}

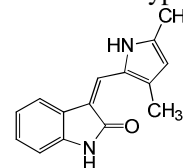
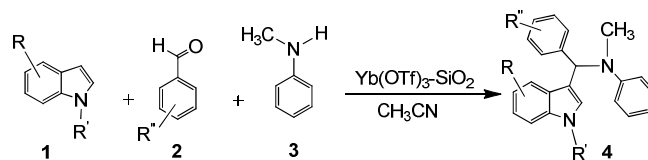


Figure 1. Chemical structure of SU5416.

In continuation of our efforts towards the development of organic transformations catalyzed by metal triflates²⁷ 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-SiO₂ (Scheme 1) and evaluation of their anticancer and *c*-Src kinase inhibitory activity.



Scheme 1. Synthesis of 3-substituted indoles.

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][BF₄], using Yb(OTf)₃-SiO₂ 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-SiO₂ (5–10 mol %), Ce(OTf)₃-SiO₂ (5 mol %), and Cu(OTf)₂-SiO₂ (5 mol %) were found to give good yield of **4a**. The Yb(OTf)₃-SiO₂ (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-SiO₂ (71%), FeCl₃-SiO₂ (59%) the yield of **4a** was moderate but accompanied with generation of bis(indolyl)methane (5–30%) as a side product.

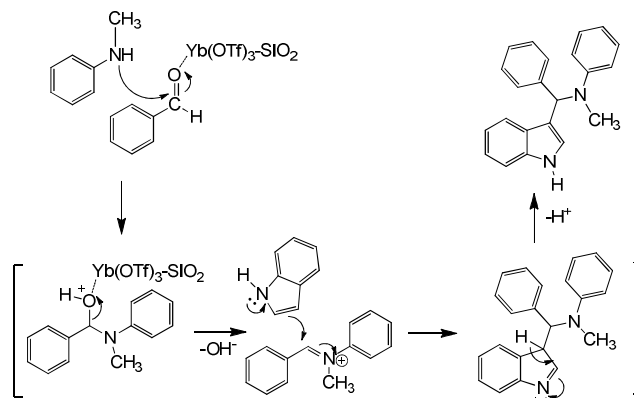
Table 1. Optimization of reaction condition for model reaction generating **4a**.

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
<i>p</i> TSA-SiO ₂	5	3	71

^aIsolated yield.

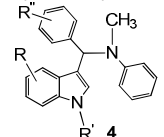
The standardized reaction conditions were used further for the synthesis of different 3-substituted indole derivatives.²⁹ Indole or *N*-methylandole, *N*-methylaniline, and a substituted or unsubstituted benzaldehyde were reacted to obtain 3-substituted indole derivatives (**4a–r**). The products and their yields are summarized in Table 2. All the compounds were characterized by ¹H NMR, ¹³C NMR, and mass spectroscopy. The reaction is assumed to proceed

through formation of imine through reaction of the benzaldehyde and *N*-methylaniline followed by nucleophilic attack of indole to give 3-substituted indoles 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



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

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

					
Product	R	R'	R''	Yield (%) ^a	IC ₅₀ (μM) ^b
4a	H	H	4-Cl	88	>150
4b	H	H	4-CH ₃	83	>150
4c	H	H	4-CH ₃ O	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 ₃ O	82	>150
4h	H	H	2,4-CH ₃ O	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

^aIsolated yield; ^bThe concentration at which 50% of enzyme activity is inhibited.

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

IC₅₀ values of 50.6–98.3 μ M. 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 IC₅₀ value of ≥ 100 μ M. The unsubstituted indole derivative **4d** showed an IC₅₀ value of 50.6 μ M while introduction of electron withdrawing group -NO₂ at 3-position of phenyl ring (**4l**) exhibited comparable inhibitory activity (IC₅₀ = 58.3 μ M).

DS visualizer docking studies³¹ were used to study the interactions of **4d** with the ATP binding site of the Src kinase. Compound **4d** was superimposed on a reference anilinoquanzoline AZD05030, a dual specific c-Src/Abl kinase inhibitor³² in complex with the Src kinase (PDB 2H8H).

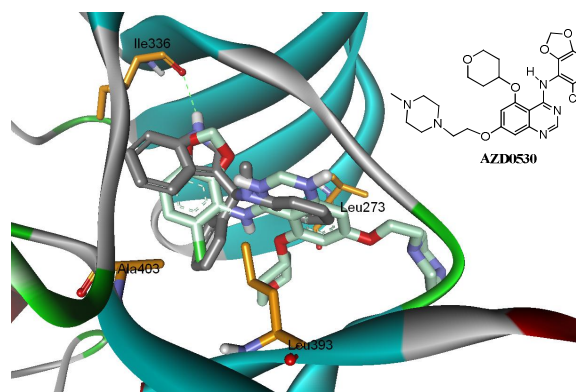


Figure 2: Comparison of interactions of **4d** (grey) and AZD05030 (oxygens (red), nitrogens (purple), carbons (light green), chlorine (green)) in ATP binding site of the Src kinase based on molecular modeling. The compounds and side chains of amino acids (yellow) are rendered in stick styles. Compounds are in the lowest energy conformers predicted. The Figure is drawn using the Accelrys DS visualizer 2.5 system.

As can be seen from Figure 2, **4d** interacts with the ATP binding pocket in slightly different orientation when compared with reference quinazoline ligand. The chloro group in reference ligand oriented towards and interacts with Ala403, whereas in **4d** phenyl rings lie in hydrophobic binding pocket. N₁-H of indole ring in compound **4d** shows specific hydrogen bonding interaction with Ile336. The hydrogen bonding interaction was not observed when N1 was methylated in **4i**. This interaction may have contributed to higher inhibitory activity of unmethylated compounds **4d** (IC₅₀ = 50.6 μ M) versus N1-methylated analog **4i** (IC₅₀ > 150 μ M). On the other hand, N₁-methylated compounds **4j** and **4k** exhibited improved inhibition activity versus **4a** and **4b**, respectively (Table 2), suggesting that hydrophobic interactions of methyl with Ile336 may also contribute to modest inhibitory activity. The binding energy for **4d** was observed as -7.42 kcal/mol

and estimated inhibition constant at 3.67 μ M while the reference ligand binding energy and estimated inhibition constant were -7.36 kcal/mol and 4.01 μ M, respectively. The RMSD from reference ligand is 1.230 Å.

The effect of the compounds on the cell proliferation of human ovarian adenocarcinoma (SK-OV-3) and colon adenocarcinoma (HT-29) cancer cells that also overexpress c-Src,^{33,34} was also evaluated at the concentration of 50 μ M (Fig. 3). In general, most of the compounds were more active against SK-OV-3 cells than HT-29 cells. Indole-based SU5416 is also currently in clinical trials against ovarian cancer. Consistently compounds **4o–r** inhibited the cell proliferation of both cancer cells significantly while **4a** only inhibited SK-OV-3. 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% whereas 4-cholorderivatives **4a** and **4r** inhibited the growth of ovarian cancer cells (SK-OV-3) by approximately 72% and 77%, respectively (Fig. 3). Structure–activity relationship studies suggest that the presence of bromo- or methoxy-substituent at position 5 of indole ring (R) in addition to methyl, methoxy, or chloro substituent at as R'' is critical for maximum anticancer activity as seen in compounds **4o–r**. In general, poor correlation was observed between Src kinase inhibitory potency of the compounds and the inhibition of cell proliferation in cancer cells, suggesting that differential cellular uptake and contribution of other mechanisms in anticancer activities of these compounds. Compounds **4d** and **4r** that showed modest Src kinase inhibition, also inhibited the growth of SK-OV-3 by 55% and 77%, respectively.

In conclusion, we have developed an ecofriendly and economical method for the synthesis of 3-substituted indoles by one pot three-component coupling reaction of a benzaldehyde, *N*-methylaniline, and indole or *N*-methylindole using Yb(OTf)₃–SiO₂ as catalyst. To the best of our knowledge, this is the first report of the synthesis and evaluation of 3-substituted indole derivatives as Src kinase inhibitors and anticancer agents. The compounds **4d**, **4j**, **4k**, **4l**, and **4r** showed modest inhibition of Src kinase while compounds **4o–r** inhibited the cell proliferation of ovarian and colon cancer cells significantly. Structure–activity relationship studies revealed the importance of the presence of a substituent at position 5 of indole ring (R) for anticancer activity. This study provides insights for further optimizing of substituted indoles for the discovery of the Src kinase inhibitors and/or anticancer agents.

Acknowledgements

We acknowledge University Grant Commission (UGC), New Delhi and the American Cancer Society Grant #RSG-07-290-01-CDD for the financial support. We

thank Mr. Vadiraj for his help in molecular modeling studies.

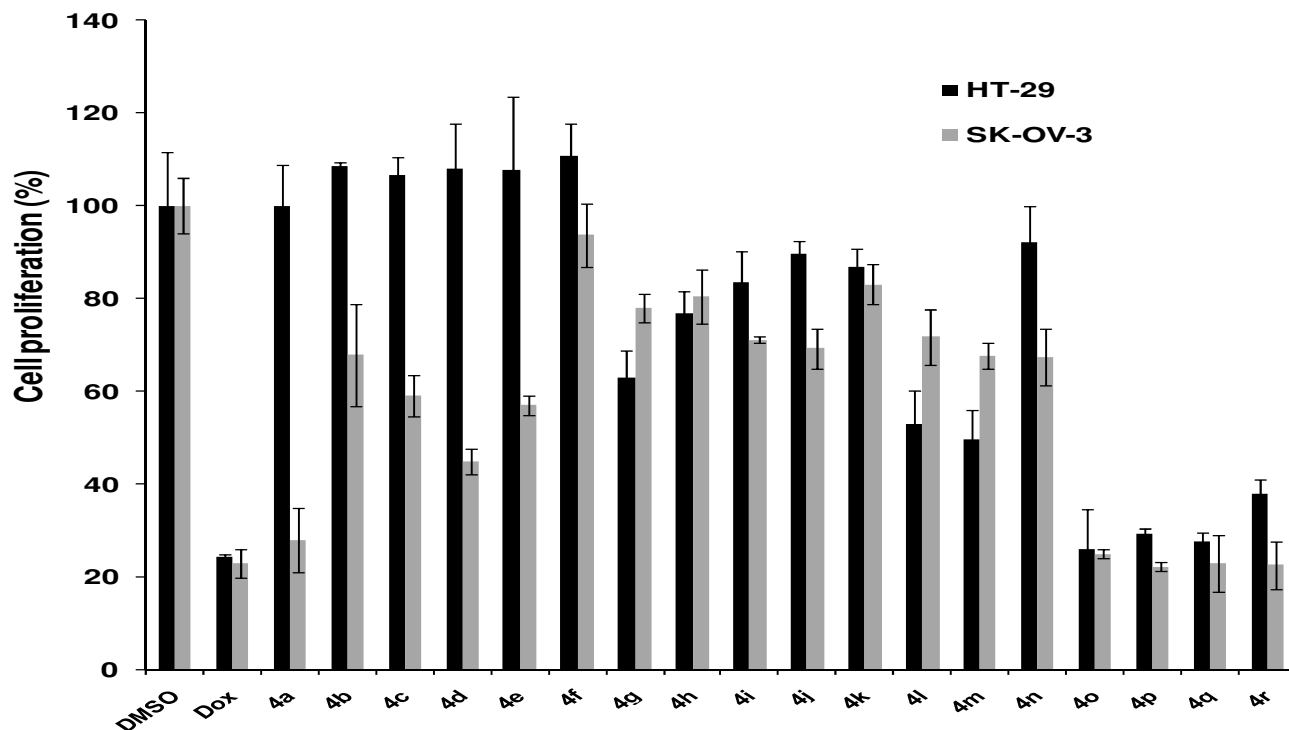


Figure 3. Inhibition of HT-29 and SK-OV-3 cell proliferation by compounds **4a–r** (50 μ M) after 72 h incubation. The results are shown as the percentage of the control DMSO that has no compound (set at 100%). All the experiments were performed in triplicate.

Supplementary data

Supplementary data (experimental procedures and characterization of compounds) can be found in the online version of this article.

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29. General procedure for preparation of 3-substituted indoles: To a solution of *N*-methylaniline (114 mg, 1.2 mmol) and a benzaldehyde (1.0 mmol) in acetonitrile (10 mL) was added Yb(OTf)₃-SiO₂ (30 mg on 300 mg SiO₂). The reaction mixture was stirred at room temperature. After 30 min, indole or *N*-methylandole (0.71 mmol) was added to the reaction and the mixture was allowed to stir for additional 90 min. The progress of reaction was monitored by TLC. After completion of the reaction Yb(OTf)₃-SiO₂ was removed by filtration and washed with ethyl acetate (3 × 5 mL). The filtrate was dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by column chromatography on silica gel (100-200 mesh) using ethyl acetate/hexane as eluents to yield a pure product (**4a-r**). All the compounds were characterized by ESI-MS, ¹H NMR and ¹³C NMR spectroscopic data.
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