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Iodine catalyzed three component synthesis of 1-((2-hydroxy naphthalen-1-yl)(phenyl)(methyl))pyrrolidin-2-one derivatives: Rationale as potent PI3K inhibitors and anticancer agents

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ABSTRACT

A series of 1-((2-hydroxynaphthalen-1-yl)(phenyl)(methyl))pyrrolidin-2-one derivatives by an efficient iodine catalyzed domino reaction involving various aromatic aldehydes, 2-pyrrolidinone and β-naphthol was achieved and the structures were elucidated by FTIR ^{1}H NMR, ^{13}C NMR, and HRMS. Subsequently they were evaluated for cytotoxicity against breast cancer (MCF-7), colon cancer (HCT116) cell lines. In the cytotoxicity, the relative inhibition activity was remarkably found to be high in MCF-7 cell lines as 79% (**4c**), 83% (**4f**) and the IC_{50}values were 1.03 μM (**4c**), 0.98 μM (**4f**). Compounds **4a**, **4e**, **4k–m**, and **4q** were found to be inactive and rest showed a moderate activity. In order to get more insight into the binding mode and inhibitor binding affinity, compounds (**4a–q**) were docked into the active site phosphoinositide 3-kinase (PI3K) (PDB ID: 4JPS) which is a crucial regulator of apoptosis or programmed cell death. Results suggested that the hydrophobic interactions in the binding pockets of PI3K exploited affinity of the most favourable binding ligands (**4c** and **4f**: inhibitory constant (*ki*) = 66.22 nM and 107.39 nM). The SAR studies demonstrated that the most potent compounds are **4c** and 4f and can be developed into precise PI3K inhibitors with the capability to treat various cancers.

Because of the complication of the molecules that can be effortlessly attained from readily accessible starting materials in one reaction series, Multi-Component Reactions (MCRs) have attracted significant consideration.[1–5] MCRs yield a solitary product and are beneficial over linear stepwise synthesis with reduction in reaction time, operational simplicity, ecological friendliness, cost effectiveness and inexpensive purification.[6–9] In this regard, attention has already been focused on the synthesis of Mannich bases from 2-naphthol at room temperature using transition metal catalyst.[3] Synthesis of Mannich bases from 2-naphthol is one of the customized Mannich type reactions that yields capable synthetic building blocks, which have an extensive range of application such as: being a pioneer in the preparation of numerous nitrogen-containing heterocycles with numerous pharmacological properties[10–12], active drugs and key intermediates in several multistep organic syntheses. Presence of amino and oxygenated functional groups with 1,3 arrangements is often advantageous in a variety of biologically active natural products.[13]

Among the important class of compounds, 1-(α-aminoalkyl)-2-naphthols can be developed into derivatives which have antipain, antibacterial, hypotensive, and bradycardia activities.[14] Phenolic hydroxyl and amino groups can be readily employed in developing a number of synthetic building blocks. In addition, Betti bases are ligands in the enantioselective addition of diethylzinc to aromatic aldehydes and they exhibit extremely proficient asymmetric induction in this addition.[15] Betti bases, on reaction with aldehydes, produce 1,3-oxazines and bis oxazines and imperative biologically active scaffolds.[16] In recent times, several one-pot multi-component reactions have been reported for the development of new carbon–carbon, carbon–hetero atom and hetero-hetero atom bonds using different transition metal catalysts.[17] Due to innumerable uses in chemistry as well as in therapeutics, this expanded compound persuades us to develop a one pot, efficient synthetic route for their synthesis. β-Naphthol is a good nucleophile toward the imine. The generated *N*-acyliminium intermediate using pyrrolidinone and aromatic aldehyde was allowed to react with β-naphthol nucleophile.[18] Modified Betti reaction is efficient with good yields as shown in Scheme 1.

In cancer, Phosphoinositide 3-kinases (PI3Ks), are the crucial regulators of apoptosis and cellular functions concerned in the

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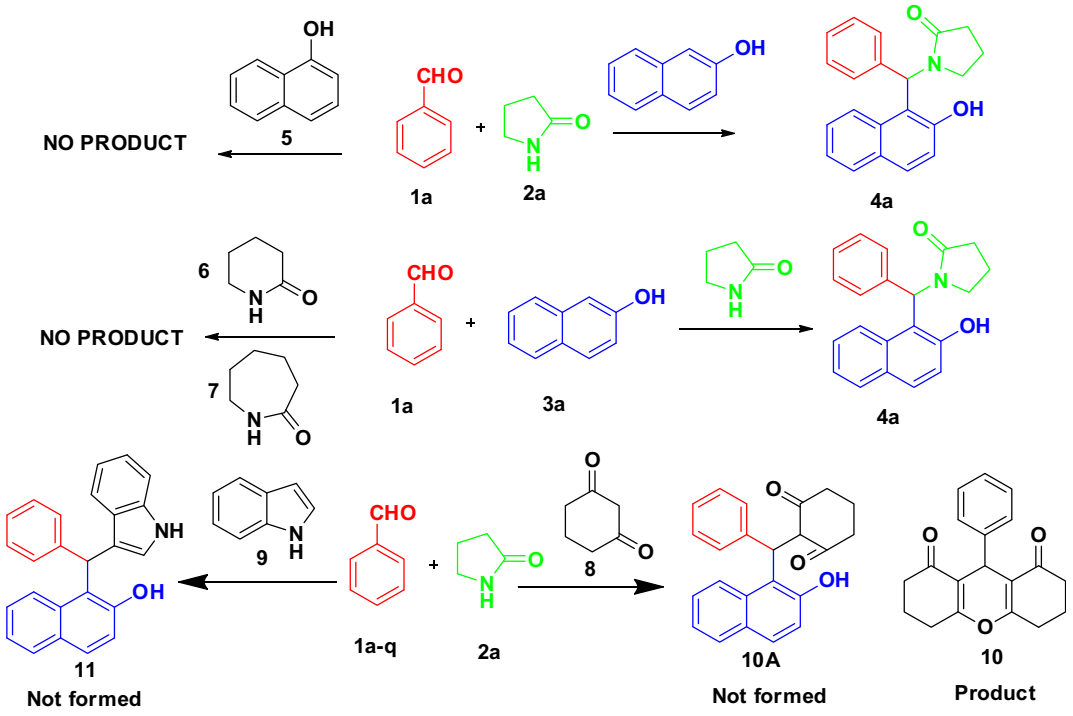


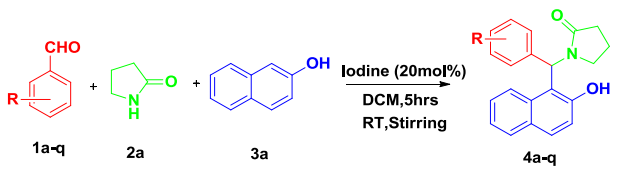
Scheme 1. Betti reaction of β-naphthol, aldehyde and amine.

cancer-like cell growth, proliferation, differentiation, motility, survival and intracellular trafficking.[19,20] PI3Ks are the signal transducer enzymes proficient with phosphorylating the 3 position hydroxyl group of the inositol ring of phosphatidylinositol (PtdIns).[21] Different cancers are rebellious to apoptosis owing to greater expression of these protein family members.[22,23] As a result of these substantiations, currently, PI3 Kinases are being thoroughly investigated as the cancer medications.[20,21,24,25] In this note, we are reporting the iodine catalyzed synthesis of 1-((2-hydroxynaphthalen-1-yl)(phenyl)(methyl))pyrrolidin-2-ones and their cytotoxicity on human breast (MCF-7) and colon cancer (HCT-116) cell lines by pertaining molecular docking as a tool to find the ligand protein interaction analysis of the synthesized compounds **4a–q**.

Based on our previous efforts in iodine-mediated domino reactions,[26] trial experiments were carried out to determine the optimum reaction conditions. The suitable reaction conditions for the synthesis of 1-((2-hydroxynaphthalen-1-yl)(phenyl)(methyl)) pyrrolidin-2-one **4a** via three component one-pot manner were optimized by screening various reaction parameters such as catalysts, solvents and different reaction conditions (Table 1). The first set of reactions was examined using various transition metal catalysts such as $ZnCl_2$, $HgCl_2$, CAN, $AlCl_3$ (entries 2–5, Table 1) for 5 h at room temperature using the catalysts up to 25 mol% and no progress was observed in the reaction. The reaction did not proceed in the absence of catalyst.

It was noteworthy to establish that molecular iodine played a considerable role in our domino reaction. Thus, to investigate the effective molar percentage of catalyst required to initiate the reaction with tremendous yields, we conducted the reaction with 1 mol% and increased this up to 25 mol% of catalyst. Moderate to exceptional yields were observed when using 20 mol% of iodine as the catalyst whereas the use of increased quantities of catalyst and temperature did not furnish improvement in the yields significantly. Hence we carried out all the reactions with 20 mol% of iodine. In order to optimize best solvent, the reactions were carried out in different solvents (DCM, *n*-BtOH, THF, i-PrOH, EtOH, CH_3CN, hexane, benzene, pentane and no solvent); they were catalyzed by 20 mol% of iodine (entries 14–22, Table 1). The best yields for the three-component reactions were achieved in DCM solvent (entry 15, Table 1). The other solvents gave low to moderate yields. The

Table 1
Screening of optimized reaction conditions for the synthesis of **4a**.[a]



Entry	Catalyst (mol%)	Solvent	% Yield (rt)[b]
1	None	DCM	–
2	$ZnCl_2$ (25)	DCM	–
3	$HgCl_2$ (25)	DCM	–
4	CAN (25)	DCM	–
5	$AlCl_3$ (25)	DCM	–
6	Iodine (25)	DCM	90
8	Iodine (20)	DCM	90
9	Iodine (15)	DCM	80
10	Iodine (10)	DCM	72
11	Iodine (5)	DCM	60
12	Iodine (1)	DCM	50
13	Iodine (20)	None	–
14	Iodine (20)	CH_3CN	63
15	Iodine (20)	DCM	90
16	Iodine (20)	THF	65
17	Iodine (20)	Ethanol	51
18	Iodine (20)	*n*-Butanol	16
19	Iodine (20)	IPA	12
20	Iodine (20)	Hexane	11
21	Iodine (20)	Benzene	28

[a] Unless otherwise noted, all the reactions were carried out with 10 mmol of **1a**, 10 mmol of **2a** and 10 mmol **3a**.
[b] Isolated yield.