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Convenient Synthesis and Biological Evaluation of Bis(indolyl)methane Alkaloid and Bis(aryl)alkanes Derivatives with Anti-cancer Properties

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Abstract

An efficient and metal free methodology for the synthesis of bis(indolyl)methanes (BIMs) and bis(aryl)alkanes derivatives in the presence of $B(C_6F_5)_3$ by the condensation of primary amines with pyruvates with good to high yields have been successfully developed. Some BIMs derivatives displayed good in vitro antitumor activity, screened by MTT assay. Compound **3b** show the best anti-cancer activity against lung carcinoma cell A549 cells with IC50 of 4.52 μM.

Keywords

bis(indolyl)methanes derivatives; metal free; primary amines; pyruvates; antitumor

Introduction

The indole scaffold and its derivatives are relevant and versatile structural nucleus in organic synthesis, in particular in many natural and biology medicine chemistry.[1-3] Bis(indolyl)methane derivatives (BIMs) are to be considered as very attractive motifs in numerous bioactive products, fine chemicals, especially in pharmaceutical chemistry (Figure 1).[4-5] BIMs as well as Bis(aryl)alkanes moieties show various types of biological and pharmacological activities, such as antibacterial, anti-inflammatory,[6] anti-infective,[7] and anti-cancer activities.[8] Because of their promising biological activities in medical chemistry, new drug discovery, and agrochemicals, the synthesis has attracted the attention of many chemists.[9] Subsequently, oceans of practical methods for the synthesis of BIMs have been reported, using Lewis acids,[10] heteropoly acids,[11] solid acids,[12] ionic liquids,[13] metal complexes [14] or biocatalysts [15] as catalysts. Even though these approaches have illustrated their convenience in the synthesis of BIMs, some drawbacks still limit their application, such as long reaction time, expensive or toxic metal ions, harsh acidity, high temperatures.[1,9] What's more, most of these synthetic accesses are the covalent C-C connection between Sp^2-C of indoles or pyrroles and the acceptors, while few catalytic protocols of activation of primary amine to form covalent C-N bonds have been reported (Scheme 1). Therefore, a demand of milder, wider application and metal-free catalytic methods for obtaining various BIMs or Bis(aryl)alkanes derivatives is of great interest and importance.

$B(C_6F_5)_3$, one component of FLPs (Frustrated Lewis Pairs, FLPs),[16] has been successfully applied to several important organic conversions as a Lewis acid catalyst without any metal ion, including hydrogenation,[17] hydrosilylation of unsaturated organic functional groups,[18] dehydrogenation,[19] polymerization[20] and other transformations.[21]

In general, $B(C_6F_5)_3$, as a strong Lewis acid, is able to activate the imine via π-coordination to the C-N double bonds. Accordingly, $B(C_6F_5)_3$ is used as a π-Lewis acid activating the imine to facilitate the addition of primary amine for the access of novel BIMs and Bis(aryl)alkanes derivatives. Herein we report, for the first time, the application of $B(C_6F_5)_3$ as an efficient metal-free catalyst to activate primary amine, provding diverse BIMs and Bis(aryl)alkanes derivatives (Scheme 1c).

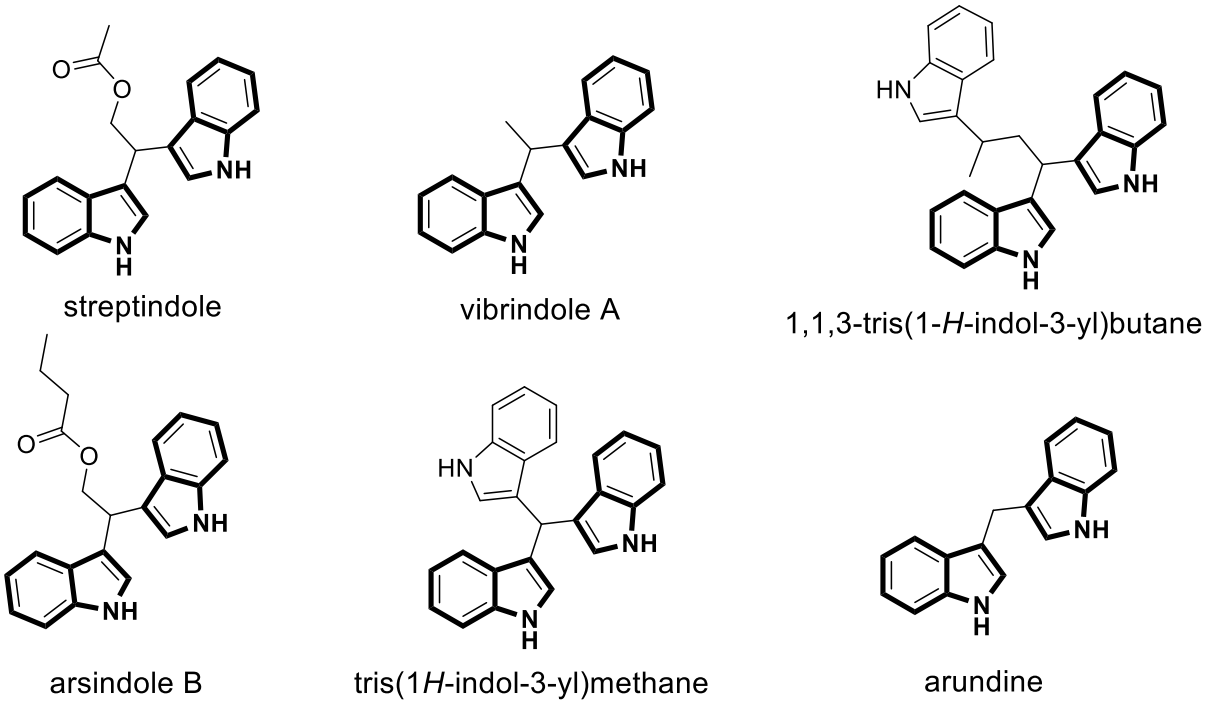
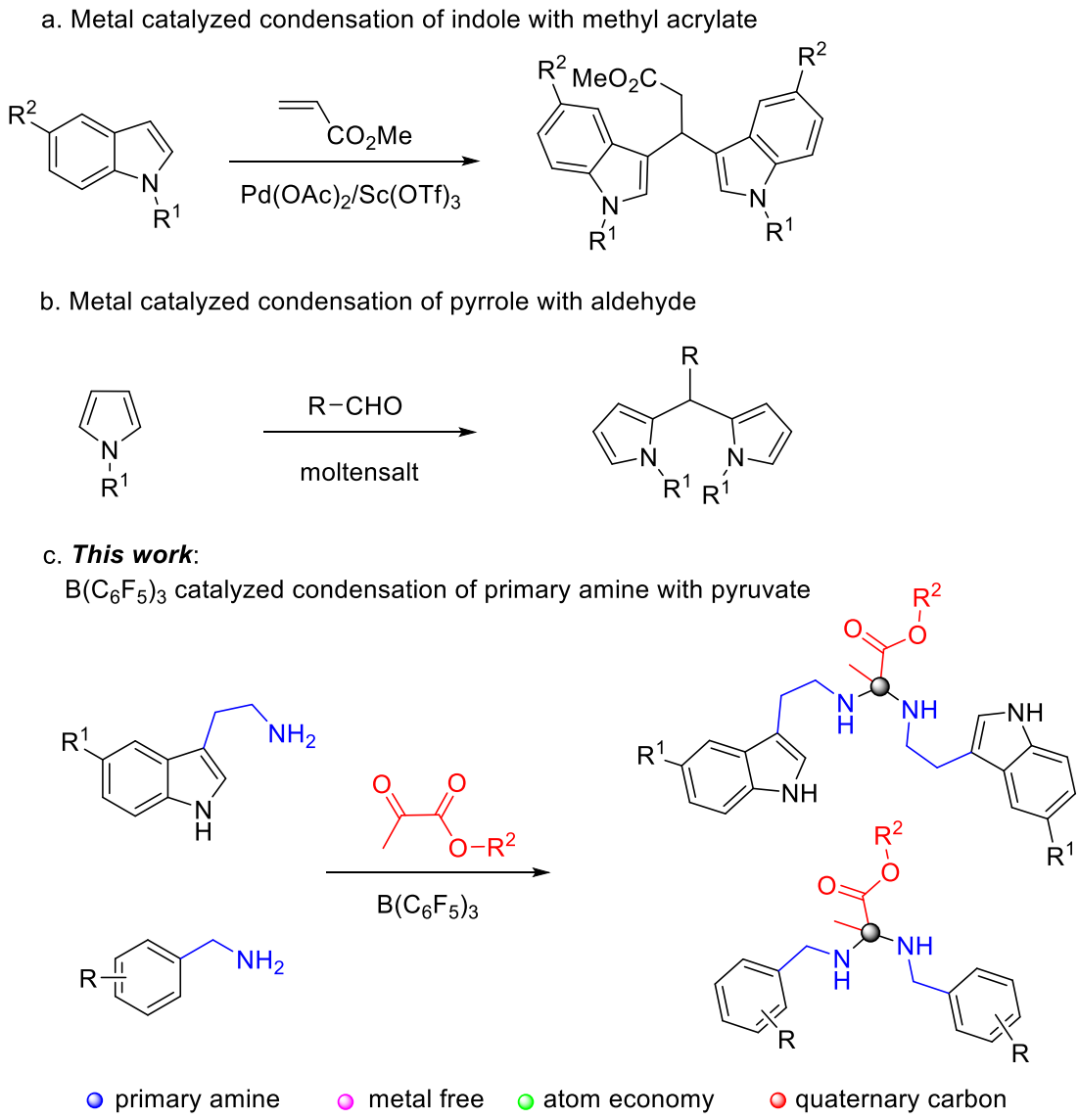


Figure 1: Structures of bis(indolyl)methane derivatives in pharmaceutical chemistry.



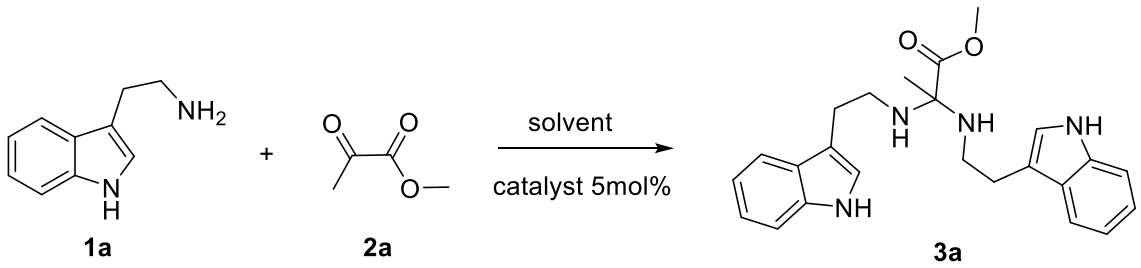
Scheme 1: Catalytic systems for BIMs derivatives.

Results and Discussion

Initially, model reactions were performed to optimize the reaction conditions of tryptamine and methyl pyruvate (Table 1). Some solvents were examined in the presence of 5 mol% of $B(C_6F_5)_3$, 1.0 mmol tryptamine **1a** and 0.6 mmol methyl pyruvate **2a**, it was found that 72% yield of **3a** was obtained in DCM at room temperature (Table 1, Entry 4). Surprisingly, when the same reaction was carried out in DCM at 40℃, the

desired product was synthesized in 81% yield at 6 h. Subsequently, a series of reactions was conducted for the synthesis of **3a** using some common metal catalysts. However, the yield was poor, even in a high temperature (Table 1, Entry 6-10). What's more, 79% yield of expected product could be obtained in the 2 mol% of $B(C_6F_5)_3$ in DCM at 40℃, while 61% yield of **3a** was obtained with 1mol% of catalyst (Table 1, Entry 11-12).

Table 1: Optimization of reaction condition [a]



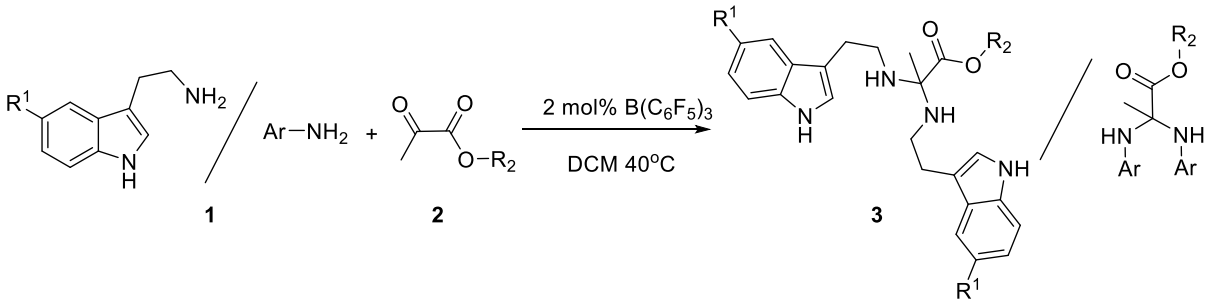
Entry	Solvent	Catalyst(mol%)	Time (h)	Temperature(℃)	Yield(%)[b]
1	Toluene	$B(C_6F_5)_3$	7	60	42
2	MeCN	$B(C_6F_5)_3$	6	60	54
3	$CHCl_3$	$B(C_6F_5)_3$	8	80	33
4	DCM	$B(C_6F_5)_3$	8	r.t.	72
5	DCM	$B(C_6F_5)_3$	6	40	81
6	DCM	$ZnCl_2$	12	40	16
7	DCM	$AlCl_3$	10	40	32
8	DCM	$FeCl_3$	12	40	18

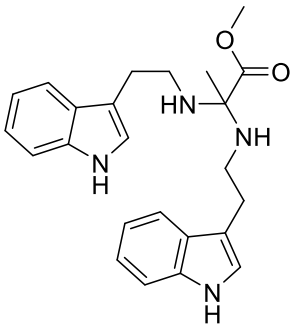
9	DCM	$Cu(OAc)_2$	12	40	17
10	DCM	$CuCl_2$	12	40	10
11[c]	**DCM**	**$B(C_6F_5)_3$**	**8**	**40**	**79**
12[d]	DCM	$B(C_6F_5)_3$	6	40	61

[a] The reaction was performed with tryptamine(1.0 mmol) and methyl pyruvate(0.6 mmol) in 2 mL solvent. [b] Isolated yield. [c] 2mol% of catalyst. [d] 1mol% of catalyst.

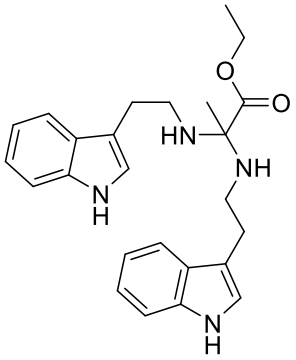
With the optimized reaction conditions in hand, other substrates were selected to explore the scope and limitations of the developed methodology using this catalytic system. Under this condition, BIMs and Bis(aryl)alkanes derivatives were obtained in good to excellent yields (Scheme 2, **3a-3k**). In addition, the reaction with methoxy group in tryptamine afforded the desired products in 86% yield and 82% yield respectively (**3c**, **3d**). To further broaden the scope of the reaction, we tried to explore the condensation reaction of aromatic primary amines with pyruvate under optimum condition. The length of aromatic primary amine side chain has slight impact on the yield of product. For example, benzylamine and methyl pyruvate (**3e**) got a slight higher yield than phenylethylamine (**3h**). Additionly, α-methylbenzylamine and pyruvate could not proceed smoothly due to the steric effect, probably (**3l**). Furthermore, heterocyclic primary amine, such as thiopheneamine and methyl pyruvate gave expected product with good yield (**3i**). Above reuslts shown that the protocol of $B(C_6F_5)_3$ catalyzed condensation reaction between primary amine and pyruvate provided an effective and convenient approach toward BIMs and Bis(aryl)alkanes derivatives.

Scheme 2: Synthesis of BIMs or Bis(aryl)alkanes derivatives under $B(C_6F_5)_3$ catalysis [a]

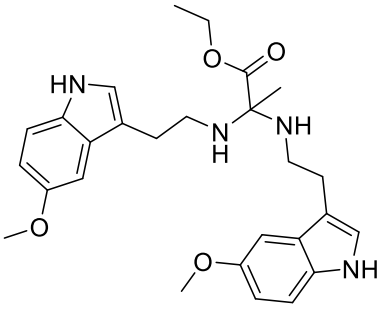




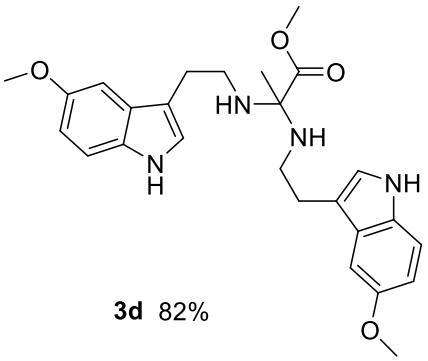
3a 79%



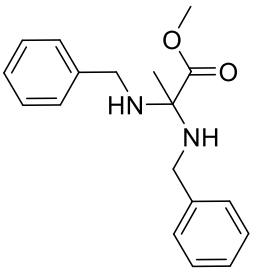
3b 81%



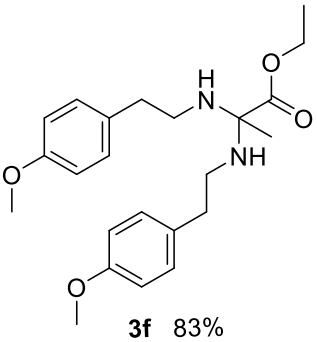
3c 86%



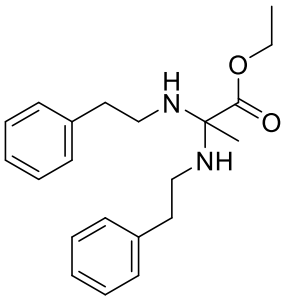
3d 82%



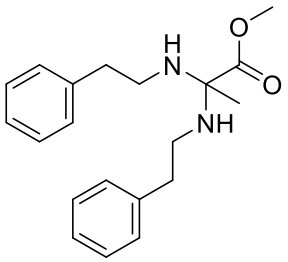
3e 87%



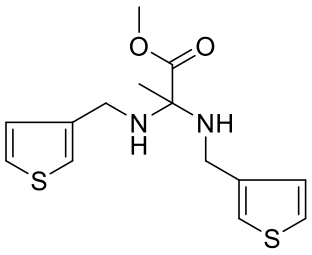
3f 83%



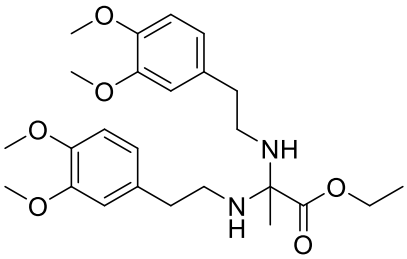
3g 89%



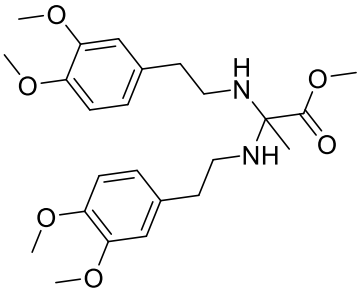
3h 83%



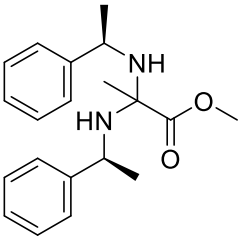
3i 67%



3j 91%



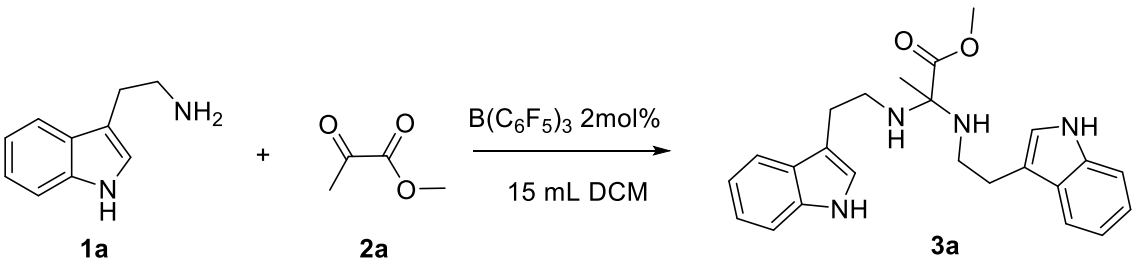
3k 89%



3l <5%

[a] The reaction was performed with **1**(1.0 mmol) and **2**(0.6 mmol) in 2 mL DCM. Isolated yield. Reaction time: 6-12h. Monitored by TLC.

In order to demonstrate the protocol of $B(C_6F_5)_3$ catalyzed condensation reaction, a scale-up reaction at 5 mmol was carried out between tryptamine **1a** and methyl pyruvate **2a** under optimized conditions, affording **3a** with a slight increase in yield (Scheme 3), thus indicating that this catalytic system could be applied as a environmentally friendly and effective method for the larger scale synthesis of BIMs derivatives.

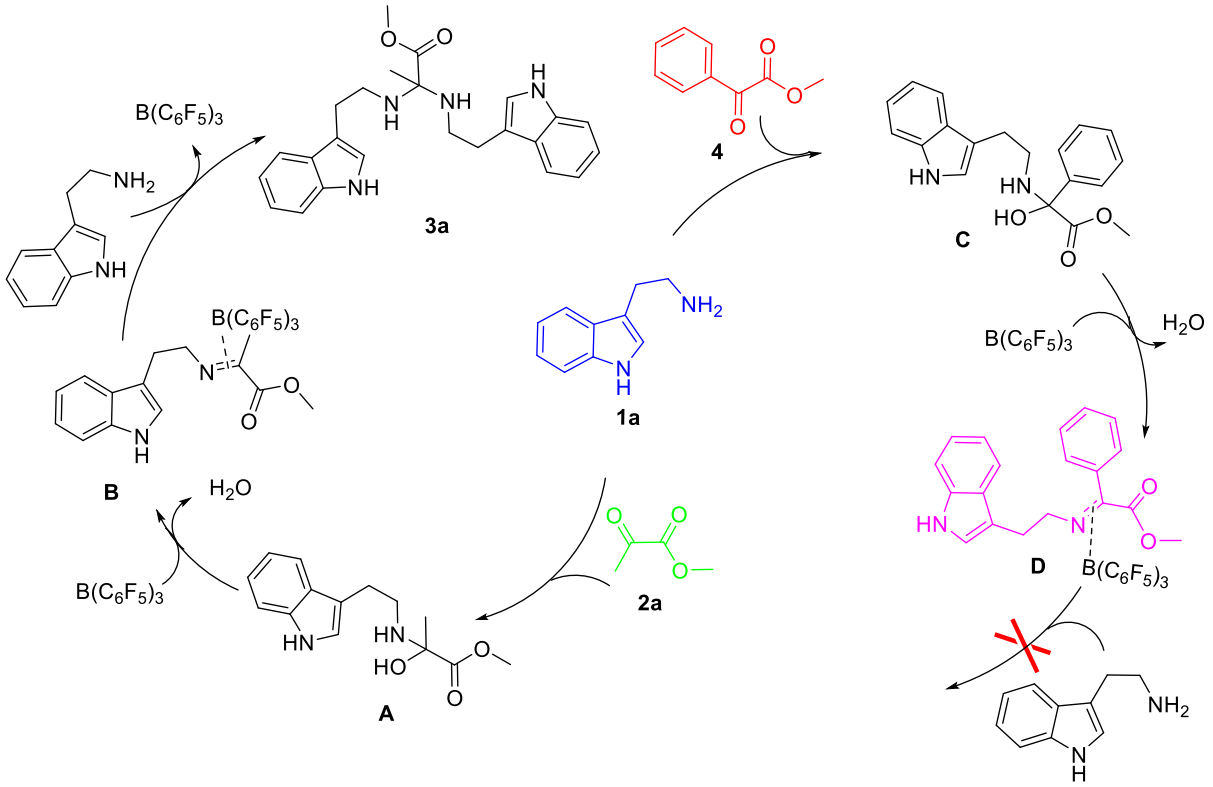


1a **2a** **3a**

83% (5 mmol scale)

Scheme 3: Gram-scale synthesis of **3a**.

Based on our results and the previous work on $B(C_6F_5)_3$ catalyzed reactions,[22-23] a proposed mechanism for this reaction is described in Scheme 4 using tryptamine **1a** and methyl pyruvate **2a** as template substrates. Firstly, nucleophilic attack of **1a** on the ketocarbonyl of **2a** results in the intermediate **A**. Subsequently, remove one molecule of water to form **B** in the presence of $B(C_6F_5)_3$. Coordination of $B(C_6F_5)_3$ with amine could activate the C-N double bonds, then another nucleophilic attack formed between tryptamine and intermediate **B**, resulting the desired product **3a** along with the release of catalyst. However, the condensation reaction could not occur between **1a** and methyl 2-oxo-2-phenylacetate **4**. Probably because the large conjugate system cause intermediate **D** stable and can not be activated by $B(C_6F_5)_3$. Fortunately, **D** could be obtained very shortly after being isolated by column chromatography (^{1}H NMR see Supporting Information).



Scheme 4: Proposed mechanism.

BIMs derivatives can be found in a variety of bioactive products and displayed good in vitro antitumor activity.[2] Therefore, the desired compounds were screened for their anticancer activity using MTT assay.[24] In order to validate the assay, standard anticancer drug camptothecin was used as positive control. According to the result, six most active compounds (**3a, 3b, 3c, 3d, 3j, 3k**) were filtered by measuring their IC50 values against lung carcinoma cell A549 cells (Figure 2). The IC50 of **3b** was 4.52μM and **3a** with a similar IC50 of 6.03 μM (Figure 2). Generally, BIMs derivatives show better anti-cancer activities than bis(aryl)alkanes derivatives. However, most of them have less effective activities against HCT 116 cells, the best IC50 of **3b** was only 17.14μM. The compound **3b** shows the optimum structural requirement for anticancer activity. These experimental data indicated that the BIMs nucleus as an important

structural feature possess good anticancer activity. Therefore, this compound will be further modified to discover more potent molecules.

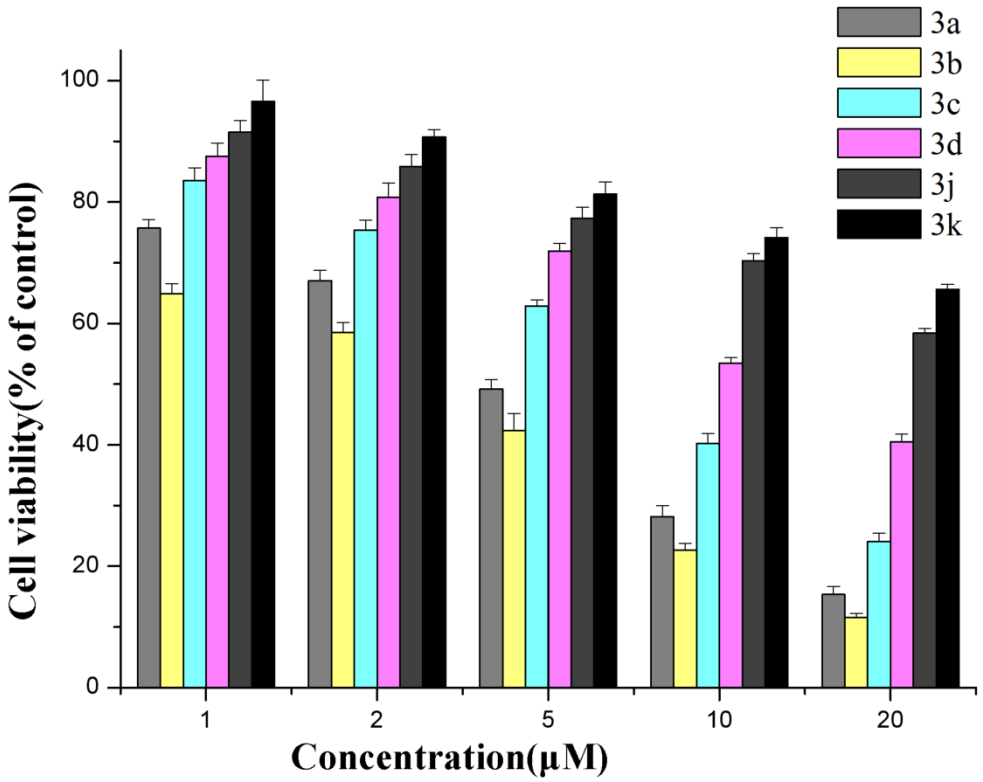


Figure 2: Anti-cancer activity against A549 cells.

Conclusion

In conclusion, an efficient and metal free methodology for the synthesis of BIMs and bis(aryl)alkanes derivatives in the presence of $B(C_6F_5)_3$ by the condensation of primary amines with pyruvates with good to high yields have been successfully developed. Various BIMs and bis(aryl)alkanes derivatives have been synthesized by the exploring

protocol and evaluated their anti-cancer activities by MTT assay. Some display significant antitumor activity, thus indicate the scope for screening the relatively unexplored BIMs derivatives in potential anticancer compounds.

Acknowledgements

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Funding

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