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The synthesis and biological evaluation of unsymmetrical 2,2-di(1*H*-indol-3-yl)-*N*-phenylacetamide derivatives

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ABSTRACT

A mild and highly efficient method has been developed for the synthesis of unsymmetrical 2,2-di(1*H*-indol-3-yl)-*N*-phenylacetamide derivatives by the regioselective Friedel–Crafts alkylation of 2-hydroxy-2-(1*H*-indol-3-yl)-*N*-phenylacetamide derivatives with various indoles catalyzed by $AlCl_3$ at room temperature in a short reaction time in high yields (up to 96%). All these compounds were screened for their antiproliferative activity against human colorectal carcinoma HCT116 cell line. The preliminary biological study showed that some of them exhibited moderate to good antiproliferative activity in vitro. Especially, compound **3e** exerted the most powerful antiproliferative activity even better than the positive control MDM-2/p53 antagonist Nutlin-3a.

Introduction

Previous studies have demonstrated the potential of bisindolylmethanes (BIMS) derivatives that contain two indoles or substituted indole units in a molecule feature exhibiting a wide range of biological and pharmacological activities such as antibacterial,[1] antimicrobial,[2] antifungal,[3] antiparkinsonian,[4] immunomodulator,[5] antidiabetic,[5] antiobesity,[6] lipoprotein disorder,[6] apoptosis in acute myelogenous leukemia (AML),[7] and vaginal spermicide.[8] Some of the bisindolylmethane derivatives are used for estrogen metabolism in humans,[9] in the treatment of fibromyalgia, chronic fatigue, and irritable bowel syndrome.[10] (Fig. 1) In addition to this, diheteroarylmethanes are also used in the food industry,[11] while triheteroarylmethanes are applied in non-linear optics and conducting polymers.[12] Particularly, the bisindolylmethane derivatives also appear to have anti-tumor properties,[13] although the exact mechanisms remain unclear. These observations suggest that additional BIMS derivatives may possess antiproliferative functions capable of therapeutic applications, and are worthy of further development.

Due to their wide range of biological and pharmacological activities, industrial and synthetic applications, a number of methods have been reported for the synthesis of symmetrical bisindolylmethanes, whereas the highly efficient synthesis of unsymmetrical bisindolylmethanes derivatives remains a challenge and has received the renewed attention of researchers interested in the discovery of improved protocols. Various groups have reported the synthesis of unsymmetrical bisindolylmethanes (BIMS) derivatives using either Lewis acids or protic acids, such as Me_3SiCl,[14] CAN,[15] *p*-TsOH,[16] $FeCl_3$,[17] chiral phosphoric acid,[18] HBF_4-SiO_2,[19] $InBr_3$,[20] and chiral imidodiphosphoric acids,[21] as well as a leaving group strategy[22] is employed. Though the reported methods are satisfactory, some of the methods suffer from certain drawbacks such as need of expensive catalysts,[18,20,21] longer reaction time,[14–16,18] harsh reaction conditions (e.g., high temperatures),[20,22] cumbersome work-up procedures,[17,19,22] and poor yield[16] of the desired product. In this context the development of an efficient and rapid method for the synthesis of bisindolylmethanes under mild reaction conditions is highly desirable.

In our initial research, we have shown efficient Brønsted acid-catalyzed regioselective Friedel–Crafts hydroxyalkylation of *N*-substituted glyoxylamide with indoles to afford the 2-hydroxy-2-(1*H*-indol-3-yl)-*N*-substituted acetamide and the symmetrical bisindole.[23] In the present Letter, we report a facile route using $AlCl_3$ as an efficient catalyst and 2-hydroxy-2-(1*H*-indol-3-yl)-*N*-substituted acetamide as the substance for the synthesis of a wide range of unsymmetrical 2,2-di(1*H*-indol-3-yl)-*N*-phenylacetamide derivatives. The main objective of this work thus comprised the synthesis of novel 2,2-di(1*H*-indol-3-yl)-*N*-phenylacetamide derivatives and their preliminary antiproliferative activity to assess the potential of these new scaffolds as they are the open chain analogues of trisindoline[13c] for more elaborate studies in future (Fig. 2).

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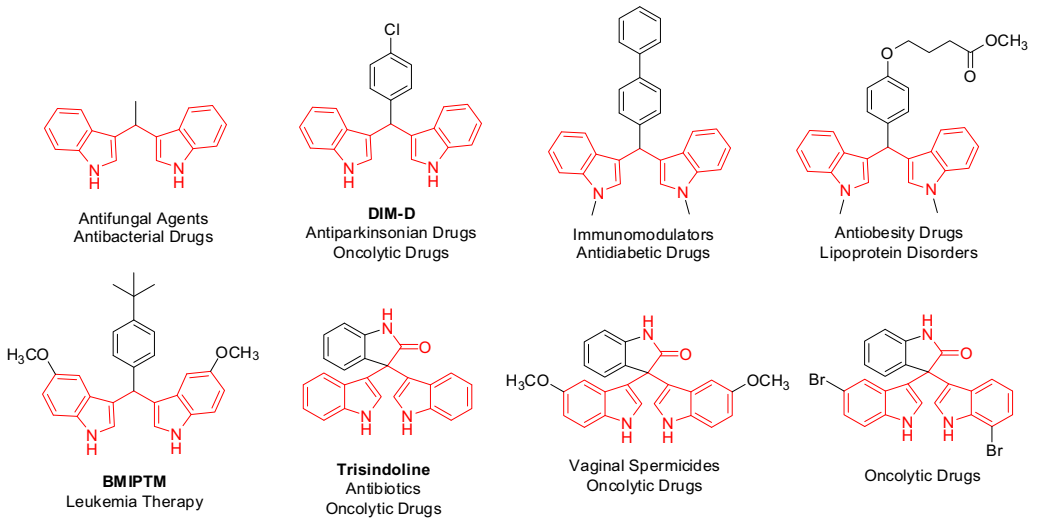

Figure 1. Selected biologically active molecules containing bisindolylmethanes (BIMS) moiety.

Results and discussion

At the beginning of our study, the screening of reaction conditions was focused on a variety of reaction parameters by using a model reaction of *N*-(4-chlorophenyl)-2-hydroxy-2-(1*H*-indol-3-yl)acetamide (**1a**) with 5-bromine indole (**2a**). The results are summarized in Table 1. Various Lewis acids such as $SnCl_2$, $FeCl_3$, $AlCl_3$, $CuCl_2$, $Cu(CF_3SO_3)_2$, $Fe(CF_3CO_2)_3$, $SnCl_4$, $NiCl_2$, $ZnCl_2$, $FeSO_4$, $CoCl_2$, $AgSbF_6$, $Ce(NO_3)_3$, and $MnCl_2$ were used. Among these catalysts, $AlCl_3$ exhibited the higher activity (Table 1, entry 3, 87% yield). Furthermore, other aluminum salts such as $Al(NO_3)_3$ (Table 1, entry 15, 84% yield) and $Al_2(SO_4)_3$ (Table 1, entry 16, 83% yield) were used, forming the desired product **3a** in a nearly high level of yield as catalyzed by $AlCl_3$. In terms of the optimal amount of $AlCl_3$ needed in the model reaction, it was found that the yield of desired product **3a** increased to 96% (Table 1, entry 17) when 50 mmol % $AlCl_3$ was used, while the yield of **3a** increased to nearly 92% when 100 mmol % $AlCl_3$ was used (Table 1, entry 18). Therefore, using 50 mmol % $AlCl_3$ was found to be more effective.

Further investigation indicated that temperature was important for this transformation. An excellent yield had been obtained when the reaction was carried out at 25 °C (Table 1, entry 17). However, when the reaction temperature increased to 50 °C and even higher to 80 °C, the yield of the desired product **3a** dropped to 74% and 57% (Table 1, entries 19–20). Among various solvents examined, C_2H_5OH turned out to be the best choice, while others such as THF, CH_3CN, DMF, dioxane, acetone, toluene, CH_2Cl_2, and $CH_3COOC_2H_5$ were less effective (Table 1, entries 17 and 21–28). We did not find the desired increment of product **3a** when the reaction time was extended to 24 h (Table 1, entry 29) or 2 equiv of **2a** was added (Table 1, entry 30).

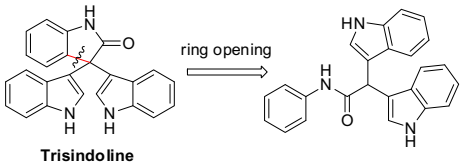

Figure 2. The template of trisindoline used for structural modification.

Therefore, in concerns of catalytic selectivity and level of yield, we could obtain the product **3a** with 96% yield by using 50 mmol % $AlCl_3$ as catalyst and C_2H_5OH as the solvent.

With the optimized conditions in hand, a series of unsymmetrical 2,2-di(1*H*-indol-3-yl)-*N*-phenylacetamide derivatives resulting from the regioselective Friedel–Crafts alkylation were thus carried out. The results are summarized in Table 2. Among the tested substrates, a variety of 2-hydroxy-2-(1*H*-indol-3-yl)-*N*-phenylacetamide derivatives with indoles owning different substituents bearing either the electron-donating groups such as methyl, isopropyl, and alkoxy at the 1- and 6-positions, or electron-withdrawing groups such as bromo and cyano at the 5-position, were well tolerated during the course of the reaction providing the desired products **3a**–**3r** in moderate to good yields.

The 17 novel 2,2-di(1*H*-indol-3-yl)-*N*-phenylacetamide derivatives were then evaluated for their in vitro antiproliferative activity using MTT assay on human HCT116 colorectal carcinoma cell line. The preliminary biological study showed that seven of the prepared 2,2-di(1*H*-indol-3-yl)-*N*-phenylacetamide derivatives displayed antiproliferative activity against the HCT116 colorectal carcinoma cell (**3e**, **3l**, **3n**, **3o**, **3p**, **3q**, **3r**). Furthermore, among all the screened compounds, the compound **3e** containing 5-hydroxyindole and 6-chloroindole moieties exhibited better antiproliferative activity as compared to the positive control MDM-2/p53 antagonist Nutlin-3a[24] (the IC_{50} value described in the literature was 0.09 μM) at the screening concentration of 10 μM (see the SM for full details).

Conclusion

In conclusion, we have developed a mild and highly efficient method for the synthesis of unsymmetrical 2,2-di(1*H*-indol-3-yl)-*N*-phenylacetamide derivatives from various indoles and 2-hydroxy-2-(1*H*-indol-3-yl)-*N*-phenylacetamide derivatives using 50 mol % of $AlCl_3$ in C_2H_5OH. The advantages of this method include its simplicity, clean reactions, high yields, short reaction time, and use of inexpensive catalyst. The simple catalytic system worked well with a broad range of indoles and allowed the facile synthesis of appropriately substituted unsymmetrical 2,2-di(1*H*-indol-3-yl)-*N*-phenylacetamide derivatives. All these compounds were screened for their antiproliferative activity against human colorectal carcinoma HCT116 cell line. The preliminary biological study showed that some of them exhibited moderate to good