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Synthesis of 4-aryl-6-indolylpyridine-3-carbonitriles and evaluation of their antiproliferative activity

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ABSTRACT

A novel class of 6-indolypyridine-3-carbonitrile derivatives were synthesized and evaluated for antiproliferative activities to establish structure–activity relationship. The synthesis was carried out through one-pot multicomponent reaction of 3-acetylindole, aromatic aldehydes, ethyl cyanoacetate, and ammonium acetate in the presence of piperidine as a catalyst, using a microwave irradiation method or a traditional thermal method. This was followed by chlorination for compounds **13a–e** and subsequent nucleophilic substitution of the chlorine group by ethylenediamine at C_2 position of the pyridine ring. The antiproliferative activity of these new nicotinonitriles was evaluated against human ovarian adenocarcinoma (SK-OV-3), breast adenocarcinoma (MCF-7), and cervix adenocarcinoma (HeLa) cells. Among all compounds, 2-((2-aminoethyl)amino)-4-aryl-6-indolylnicotinonitriles series (**15a**, **15b**, **15d**, and **15e**) exhibited higher antiproliferative activity on the three cancer cell lines with IC_{50} values of 4.1–13.4 μM.

3-Substitued indolyl moiety is a basic constituent in numerous proteins, the neurotransmitter serotonin, and mammalian hormone melatonin as well as a large number of marketed available pharmaceutical drugs. For instance, indomethacin (**1**), naratriptan (**2**), tegaserod (**3**), ondansetron (**4**), zafirlukast (**5**), sunitinib (**6**), sertinole (**7**), and panobinostat (**8**) (Fig. 1) contain 3-substituted indole scaffold in their chemical structures.[1]

Additionally, several marine indole alkaloids have been isolated and evaluated for their anticancer, antiviral, and antiinflammatory activities. Meridianins A-E (**9**) were isolated from tunicate *Aplidium Meridianm*.[2,3] Bisindolyl alkaloids spaced by five or six membered heterocyclic moieties, such as piperazinone (Hamacanthin B, **10**), quinone (Asterriquinone, **11**), or imidazole (Nortopsentins A-C, **12**) (Fig. 1) have exhibited modest to high anticancer activities against a wide range of human cell lines at micromolar concentrations.[4–6]

Additionally, nicotinonitrile skeletons especially those with amino substituent at C_2 and/or 4,6-diaryl-substitutent have demonstrated broad range of biological activities, such as antibacterial,[7,8] antifungal,[9] antituberculosis,[10] antiviral,[11] antipyretic, analgesic, and antiinflammatory[12–14] effects.

Furthermore, they have been used as inhibitors for protein kinase, topoisomerase,[15,16] phosphodiesterase[17,18] as well as antiproliferative agents for the treatment of a number of human cancer cell lines.[19–21]

The application of one-pot multicomponent reactions (MCRs) and microwave-assisted have been demonstrated to offer smooth reaction conditions and higher overall yield when compared to classical synthesis methodologies.[22–28] Bis(3′-indolyl)pyridine and indol-3-yl pyrazolopyridine derivatives have been previously synthesized through MCR and/or microwave assisted reactions[29a,29b] according to the previously reported procedure.[29c]

In continuation of our efforts to synthesize and evaluate new indole derivatives as antiproliferative agents,[30] we designed novel indole-3-cyanopyridine hybrid structures to determine the substituent effects at C_2 and C_4 on the cytotoxic potency of this scaffold. Although other heterocyclic indolyl derivatives have been previously synthesized,[29] to the best of our knowledge this is the first microwave-assisted synthesis of hybrid indole and 3-cyano-4-aryl-substituted pyridine compounds and evaluation of their antiproliferative activities.

Considering the advantages of MCRs approach and microwave irradiation, 3-acetyl indole reacted with ethyl cyanoacetate and a series of aromatic aldehydes with an excess of ammonium acetate under microwave irradiation for 15–20 min affording novel 4-aryl-6-indolyl-nicotinonitrile-2-one derivatives (**13a–e**) (Scheme 1). All compounds were characterized by mass and NMR spectroscopy (Supplementary material).

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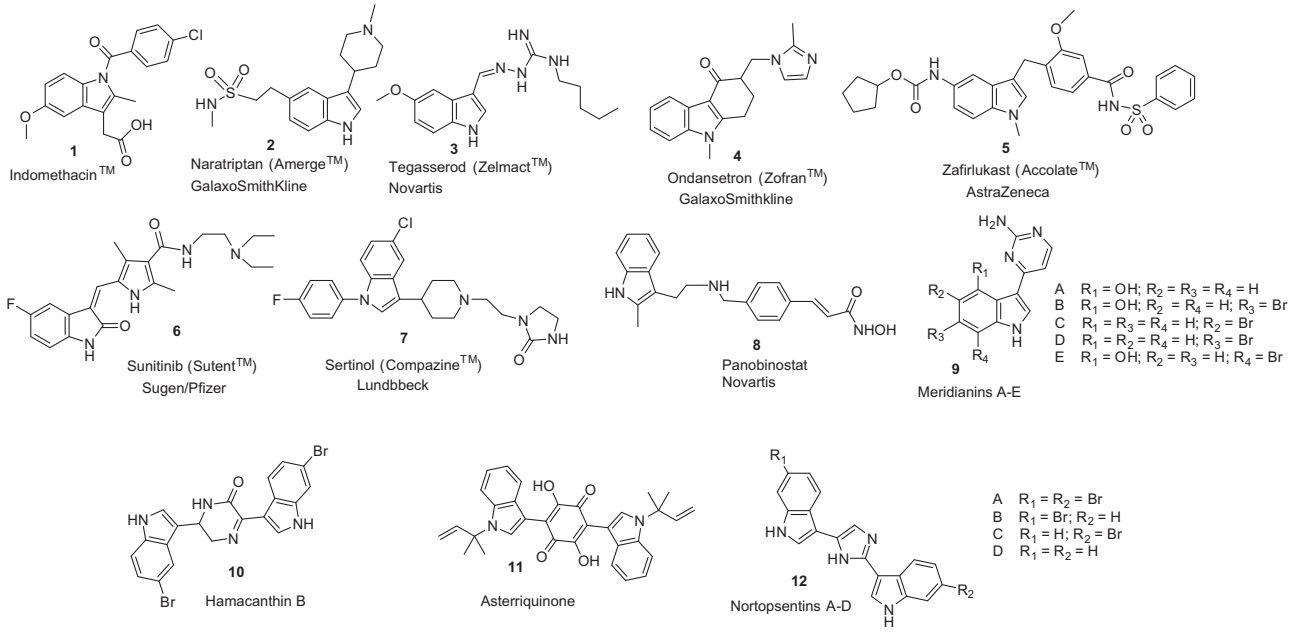
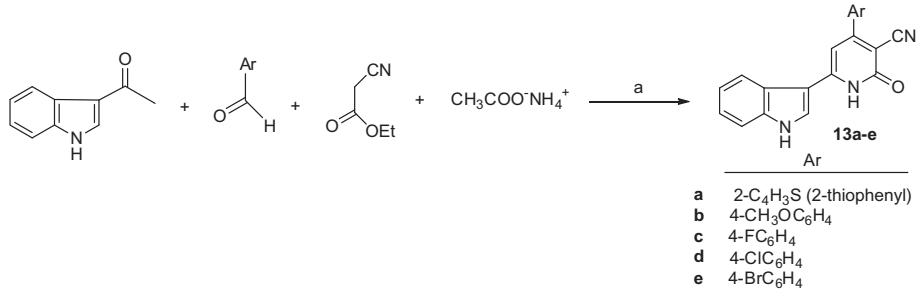


Figure 1. Common biologically active 3-substituted indolyl derivatives.



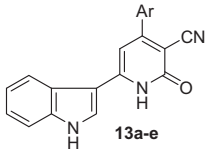
Scheme 1. Synthesis of indolylnicotinonitriles (**13a**–**e**). Reagents and conditions: (a) piperidine (1 mL), ethylene glycol (1 mL), MW irradiation (W 250 and T 150 °C).

Ethylene glycol and piperidine were used as a solvent and a catalyst, respectively, during the microwave reaction at a power of 250 W and 150 °C for a given time. The reactions were successful in achieving the benefits of both utilizing microwave irradiation and the one-pot MCRs. Compared to the traditional thermal method, the reaction time was shortened from hours to minutes with improvement in both the target product purity and overall product yield (77–87%) in case of microwave method. The results for each entry are summarized in (Table 1).

The mechanism of one pot syntheses of nicotinonitrile derivatives is known to be through the formation of α,β-unsaturated ketones intermediate via the Claisen–Schimdt reaction between active methylene containing ketones and aromatic aldehydes using catalytic amount of strong bases like sodium hydroxide, triethylamine, or piperidine (10%). This reaction is followed by condensation with nitrile containing active methylene compounds (e.g., ethyl cyanoacetate or malononitrile) through the Michael addition reaction in the presence of ammonium acetate, cyclization, and aromatization to afford the corresponding 4-aryl-2-oxo-1*H*-pyridine-3-carbonitrile derivatives[31] (Scheme 2).

Results in Table 1 showed that, the electronic effect and the nature of the substituent on the aromatic aldehyde ring played a critical effect in terms of reaction time and product yield under similar reaction conditions. When aromatic aldehydes bearing a strong electron withdrawing group (e.g., 4-fluorine, 4-chloro, 4-bromo) in *para* positions were used, the yield of the products was increased in a shorter reaction time compared to those carrying electron donating groups (e.g., 4-methoxy group) in *para* position under a similar reaction condition.

Table 1
Comparative synthesis of 2-oxo-1,2-dihydropyridine-3-carbonitrile derivatives (**13a**–**e**) by microwave irradiation and thermal heating



Product	Ar	Time		Yield[c] (%)		mp (°C)
		MW[a] (min)	Th[b] (h)	MW[a]	Th[b]	
13a	2-C_4H_3S	20	17	77	44	>300
13b	4-$OCH_3C_6H_4$	20	18	79	45	>300
13c	4-FC_6H_4	15	10	87	56	>300
13d	4-ClC_6H_4	17	15	82	63	>300
13e	4-BrC_6H_4	17	14	83	61	>300

[a] The reaction was carried out by microwave irradiation at 250 W and 150 °C.
[b] The reaction was carried out by thermal heating at 150 °C in oil bath.
[c] Isolated yields.

Moreover, the reaction of compounds **13a**–**e** with phosphoryl chloride for 18–24 h afforded the corresponding 2-chloropyridine derivatives (**14a**–**e**) after thermal heating at 80 °C as shown in