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Discovery of indolizines containing triazine moiety as new leads for the development of antitumoral agents targeting mitotic events

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ABSTRACT

A new family of 3-aroylindolizines bearing a dimethoxytriazine unit in their position 1 was designed, synthesized and evaluated for their ability to inhibit tubulin polymerization and cellular growth in vitro. Compound **39** was the best candidate in the current study with a GI_{50} value of 870 nM on SNB-75 CNS cancer cells and of 920 nM on MDA-MB-231/ATCC breast cancer cells. The standard NCI Compare results indicated that indolizine **39** may target PLK1 (polo-like kinase 1).

Indolizines are important chemical structures having an important place both in organic synthesis and in biochemistry as they represent promising molecules with potential applications in the fields of pharmaceuticals,[1–3] total synthesis,[1] organic materials as novel fluorescent sensors[4] and as key intermediates in organic synthesis.[1–3] In particular, 3-aroylindolizine systems have attracted considerable interest from our research group in recent years for their antitumoral potential.[5,6] The reported biological activity for similar indolizines also highlights efficiency on cardiovascular disorders[7–10] or on degenerative joints diseases[11] as osteoarthritis or spondyloses. However, the existing literature on 3-aroylindolizines bearing a heterocyclic unit in their position 1 is extremely scarce and mainly concerns the synthetic procedures.[7,8,12–18] Only three of such indolizines have been reported and patented for their biological activity, particularly as potential antagonists of the binding of FGFs (fibroblast growth factors) to their receptors (compounds **I**–**III**, Fig. 1).[7,8]

Because of this limited number, the general development of new methodologies that can target these heterocycles and especially when they allow their diversification and discovery of new bioactive agents, is a valuable ambition. In this perspective, we propose in this manuscript the development of a new family of 3-aroylindolizines substituted by a dimethoxytriazine unit targeting mitotic events (target compounds **27**–**45**, Fig. 1). Tubulin is the structural protein of microtubules, a major component of the cytoskeleton. Since cancer cells divide more frequently than normal cells, and since mitotic microtubule dynamics is 4–100 times greater than that of microtubules during interphase, tubulin is a target for antitumor compounds.[19] Inhibitors of tubulin polymerization will therefore alter the cytoskeleton and inhibit the mitotic spindle formation, resulting in a high cytotoxic effect. Phenstatin (compound **IV**, Fig. 1) is one of the most potent tubulin polymerization inhibitor that binds to the colchicine site of the protein.[20] We have already obtained microtubule-interacting agents, phenstatin analogs, with indolizine skeleton as B-ring that showed excellent in vitro antiproliferative effect in the nanomolar range on MDA-MB-435 melanoma cell lines (GI_{50} = 30 nM) (e.g., compound **VI**, Fig. 1).[5] In order to develop new anti-cancer agents and enrich the structure–activity relationships in this field, we designed and synthesized new phenstatin analogs with dimethoxytriazine–indolizine core as B-ring and diversely substituted phenyl unit as A-ring (Fig. 1).

The chemical strategy started with the synthesis of the key dipolarophile **3**. In this light, propiolic acid **1**, after activation as acid chloride **2**, then treatment with zinc

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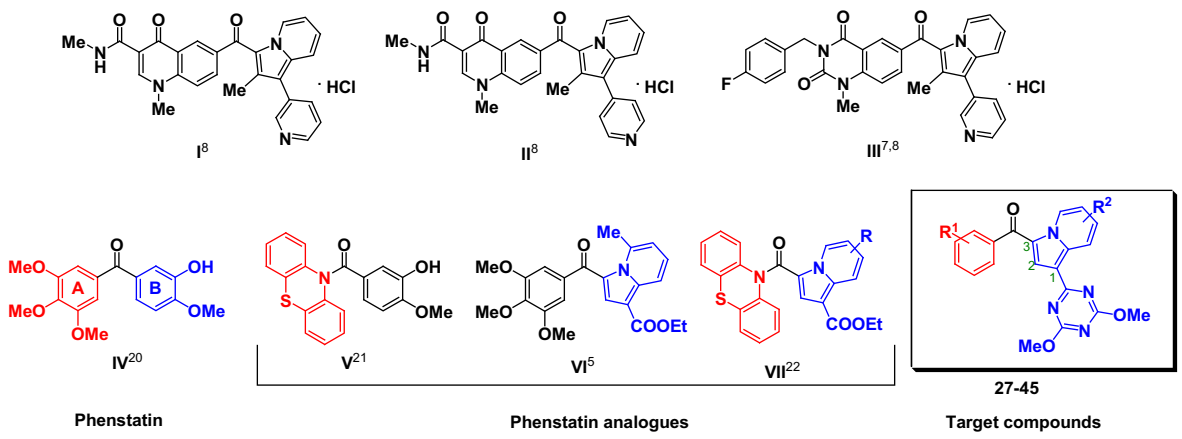
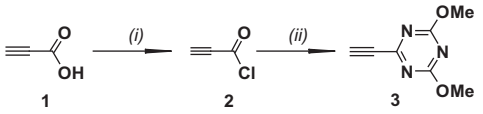


Figure 1. Structure of some biologically active 3-aroylindolizines **I–III**,[7,8] of phenstatin **IV**,[20] phenstatin analogs **V–VII**[5,21,22] and of target compounds **27–45**.

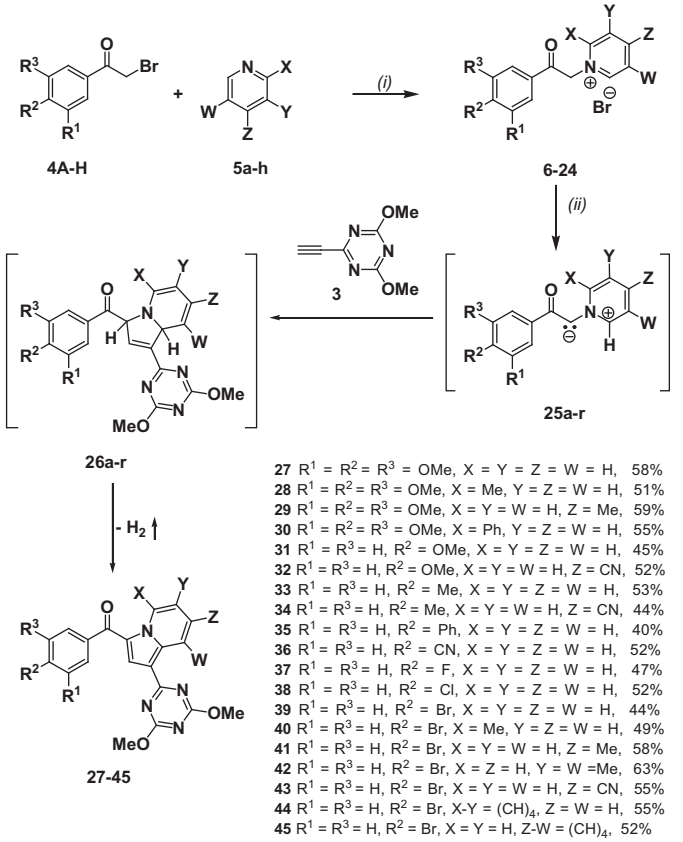


Scheme 1. Reagents and conditions: (i) 1 equiv PCl_5, dichloromethane, N_2, rt, 1 h, 90% yield; (ii) 0.7 equiv zinc dimethylimidodicarbonimidate, molecular sieves 4 Å, dichloromethane, N_2, rt, 24 h, 55% yield.[23]

dimethylimidodicarbonimidate salt,[23] furnished acetylenic derivative **3** (Scheme 1), used further for all the cycloaddition reactions.

Target indolizines containing triazine **27–45** were next obtained by [3+2] cycloaddition reaction of the corresponding ylide **25a–r**, generated in situ by triethylamine treatment of pyridinium salts **6–24**, with 2-ethynyl-4,6-dimethoxy-1,3,5-triazine **3**, followed by spontaneous aromatization of intermediates **26a–r** (Scheme 2). The cycloimonium salts **6–24** have been easily obtained in good yields by reacting commercially available pyridine derivatives **5a–h** with ω-bromoacetophenones **4A–H**.

In order to investigate the importance of the dimethoxytriazine ring of compound **39** on antitumoral activity, additional modulations have been envisaged and realized. In this light, we decided to use the chemical strategy discovered previously on *N*-substituted pyrrolidinones linked to a 4,6-dimethoxy-1,3,5-triazine[24] and transpose it to indolizines containing triazine developed in the current manuscript. Thus, refluxing indolizine **39** in 2% aqueous HCl for 24 h resulted in a total O-demethylation of methoxy groups and furnished triazinedione **46** in 94% yield. A mono



6 $R^1 = R^2 = R^3$ = OMe, X = Y = Z = W = H, 70%
7 $R^1 = R^2 = R^3$ = OMe, X = Me, Y = Z = W = H, 96%
8 $R^1 = R^2 = R^3$ = OMe, X = Y = W = H, Z = Me, 65%
9 $R^1 = R^2 = R^3$ = OMe, X = Ph, Y = Z = W = H, 20%
10 $R^1 = R^3$ = H, R^2 = OMe, X = Y = Z = W = H, 93%
11 $R^1 = R^3$ = H, R^2 = OMe, X = Y = W = H, Z = CN, 23%
12 $R^1 = R^3$ = H, R^2 = Me, X = Y = Z = W = H, 94%
13 $R^1 = R^3$ = H, R^2 = Me, X = Y = W = H, Z = CN, 84%
14 $R^1 = R^3$ = H, R^2 = Ph, X = Y = Z = W = H, 70%
15 $R^1 = R^3$ = H, R^2 = CN, X = Y = Z = W = H, 93%
16 $R^1 = R^3$ = H, R^2 = F, X = Y = Z = W = H, 70%
17 $R^1 = R^3$ = H, R^2 = Cl, X = Y = Z = W = H, 92%
18 $R^1 = R^3$ = H, R^2 = Br, X = Y = Z = W = H, 99%
19 $R^1 = R^3$ = H, R^2 = Br, X = Me, Y = Z = W = H, 89%
20 $R^1 = R^3$ = H, R^2 = Br, X = Y = W = H, Z = Me, 97%
21 $R^1 = R^3$= H, R^2 = Br, X = Z = H, Y = W =Me, 96%
22 $R^1 = R^3$ = H, R^2 = Br, X = Y = W = H, Z = CN, 56%
23 $R^1 = R^3$ = H, R^2 = Br, X-Y = $(CH)_4$, Z = W = H, 97%
24 $R^1 = R^3$ = H, R^2 = Br, X = Y = H, Z-W = $(CH)_4$, 89%

27 $R^1 = R^2 = R^3$ = OMe, X = Y = Z = W = H, 58%
28 $R^1 = R^2 = R^3$ = OMe, X = Me, Y = Z = W = H, 51%
29 $R^1 = R^2 = R^3$ = OMe, X = Y = W = H, Z = Me, 59%
30 $R^1 = R^2 = R^3$ = OMe, X = Ph, Y = Z = W = H, 55%
31 $R^1 = R^3$ = H, R^2 = OMe, X = Y = Z = W = H, 45%
32 $R^1 = R^3$ = H, R^2 = OMe, X = Y = W = H, Z = CN, 52%
33 $R^1 = R^3$ = H, R^2 = Me, X = Y = Z = W = H, 53%
34 $R^1 = R^3$ = H, R^2 = Me, X = Y = W = H, Z = CN, 44%
35 $R^1 = R^3$ = H, R^2 = Ph, X = Y = Z = W = H, 40%
36 $R^1 = R^3$ = H, R^2 = CN, X = Y = Z = W = H, 52%
37 $R^1 = R^3$ = H, R^2 = F, X = Y = Z = W = H, 47%
38 $R^1 = R^3$ = H, R^2 = Cl, X = Y = Z = W = H, 52%
39 $R^1 = R^3$ = H, R^2 = Br, X = Y = Z = W = H, 44%
40 $R^1 = R^3$ = H, R^2 = Br, X = Me, Y = Z = W = H, 49%
41 $R^1 = R^3$ = H, R^2 = Br, X = Y = W = H, Z = Me, 58%
42 $R^1 = R^3$ = H, R^2 = Br, X = Z = H, Y = W =Me, 63%
43 $R^1 = R^3$ = H, R^2 = Br, X = Y = W = H, Z = CN, 55%
44 $R^1 = R^3$ = H, R^2 = Br, X-Y = $(CH)_4$, Z = W = H, 55%
45 $R^1 = R^3$ = H, R^2 = Br, X = Y = H, Z-W = $(CH)_4$, 52%

4A $R^1 = R^2 = R^3$ = OMe
4B $R^1 = R^3$ = H, R^2 = OMe
4C $R^1 = R^3$ = H, R^2 = Me
4D $R^1 = R^3$ = H, R^2 = Ph
4E $R^1 = R^3$ = H, R^2 = CN
4F $R^1 = R^3$ = H, R^2 = F
4G $R^1 = R^3$ = H, R^2 = Cl
4H $R^1 = R^3$ = H, R^2 = Br

5a X = Y = Z = W = H
5b X = Me, Y = Z = W = H
5c X = Y = W = H, Z = Me
5d X = Ph, Y = Z = W = H
5e X = Z = H, Y = W =Me
5f X = Y = W = H, Z = CN
5g X-Y = $(CH)_4$, Z = W = H
5h X = Y = H, Z-W = $(CH)_4$

Scheme 2. Reagents and conditions: (i) EtOAc, reflux, 24 h; (ii) 1.5 equiv TEA, acetonitrile, rt, 24 h.