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Synthesis and biological evaluation of heteroaryl styryl sulfone derivatives as anticancer agents

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ABSTRACT

Herein we disclose a series of novel heteroaryl styryl sulfone derivatives as potential anticancer agents. Structure-activity relationships of these newly synthesised compounds were explored with respect to the significance of the position and number of nitrogen atom of the heteroaryl ring for anti-proliferative activity in human cancer cell lines. A lead compound **14f** was tested against a panel of cancerous and untransformed cell lines, and found to be highly potent against cancer cells with minimal toxicity in the untransformed cells. Further mechanistic studies uncovered that **14f** caused cell-cycle arrest at the G2/M phase and induced apoptosis by targeting CDC25C and Mcl-1 proteins in A2780 ovarian cells.

Rigosertib (ON01910.Na, Fig. 1) is a synthetic benzyl styryl sulfone that is currently in different phases of clinical trials for the treatment of myelodysplastic syndrome (MDS) and various other cancers [1–5]. It has shown efficacy with good tolerability through a range of dosing schedules by intravenous infusion [6,7]. However, it has poor oral bioavailability and ambiguous pharmacokinetics [8] We have identified a new series of (*E*)-2/3-((styrylsulfonyl)methyl)pyridine derivatives as mechanistic mimetics of rigosertib. The lead drug candidates **8** and **18** (Fig. 1) showed potent anti-proliferative activity against various cancer cell lines and significant efficacy in xenografted tumour models [9]. Both compounds **8** and **18** possess superior cell permeability, metabolic stability and pharmacokinetic properties with good oral bioavailability to rigosertib [9,10].

There are currently two plausible mechanisms of action proposed for rigosertib and its analogues. Firstly, rigosertib was found to target Polo-like kinase 1 (Plk1) in a substrate-dependent and ATP-independent manner [11,12]. Plk1 is an essential regulator of cell cycle progression as it regulates the activation of cyclin B1 and CDC25C phosphatase [11,13]. Secondly, rigosertib acts as a Ras mimetic. This is believed to be mediated by the binding of rigosertib to the Ras-binding domain (RBD) found in many Ras effector proteins, including the Raf and PI3K kinases [14,15]. As such, rigosertib can inhibit multiple Ras-driven signaling pathways. Previous data showed that rigosertib as well as its mechanistic mimetics **8** and **18** gave rise to three major effects on cancer cells: (1) abnormal cell division containing irregular chromosomal segregation and cytokinesis; (2) mitotic (G2/M phase) arrest and apoptosis; and (3) reduced expression levels of CDC25C and cyclin D1 [11,13].

In an attempt to further discover novel series of styryl sulfones for potential drug development, we designed and synthesised a series of styrylsulfonyl derivatives with different *N*-containing heteroaryl systems. Introduction of additional nitrogen atom(s) into the methylpyridinyl moiety of molecules may result in not only favourable pharmacological properties, but also new intellectual property. Herein, we report the synthesis of these novel compounds, their SAR analysis with respect to the alterations of heteroaryl rings and the adjacent methylene group, and insights into the mechanism of action. These data provide valuable clues for further optimising this class as potential anticancer agents.

The general synthetic route to designed derivatives is outlined in Scheme 1. The synthesis of **7** started with the reduction of ester **1**, and the subsequent chlorination gave 2-chloro-5-(chloromethyl) pyrazine **2**. Replacement of chlorine of the methyl group with methyl thioglycolate yielded thioether **3**, which was further oxidised to give sulfone **4**. After hydrolysis, Doebner modification of Knoevenagel condensation between **5** and 2,4,6-trimethoxybenzaldehyde was carried out to generate **6**, which was reacted with sodium alkoxide to yield **7a** and **7b**.

Above synthetic route was employed to prepare **10** and **16** following the bromination of the methyl group of **8** and **15** with

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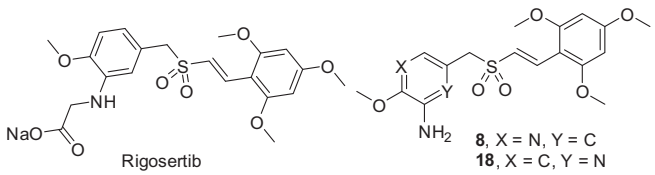
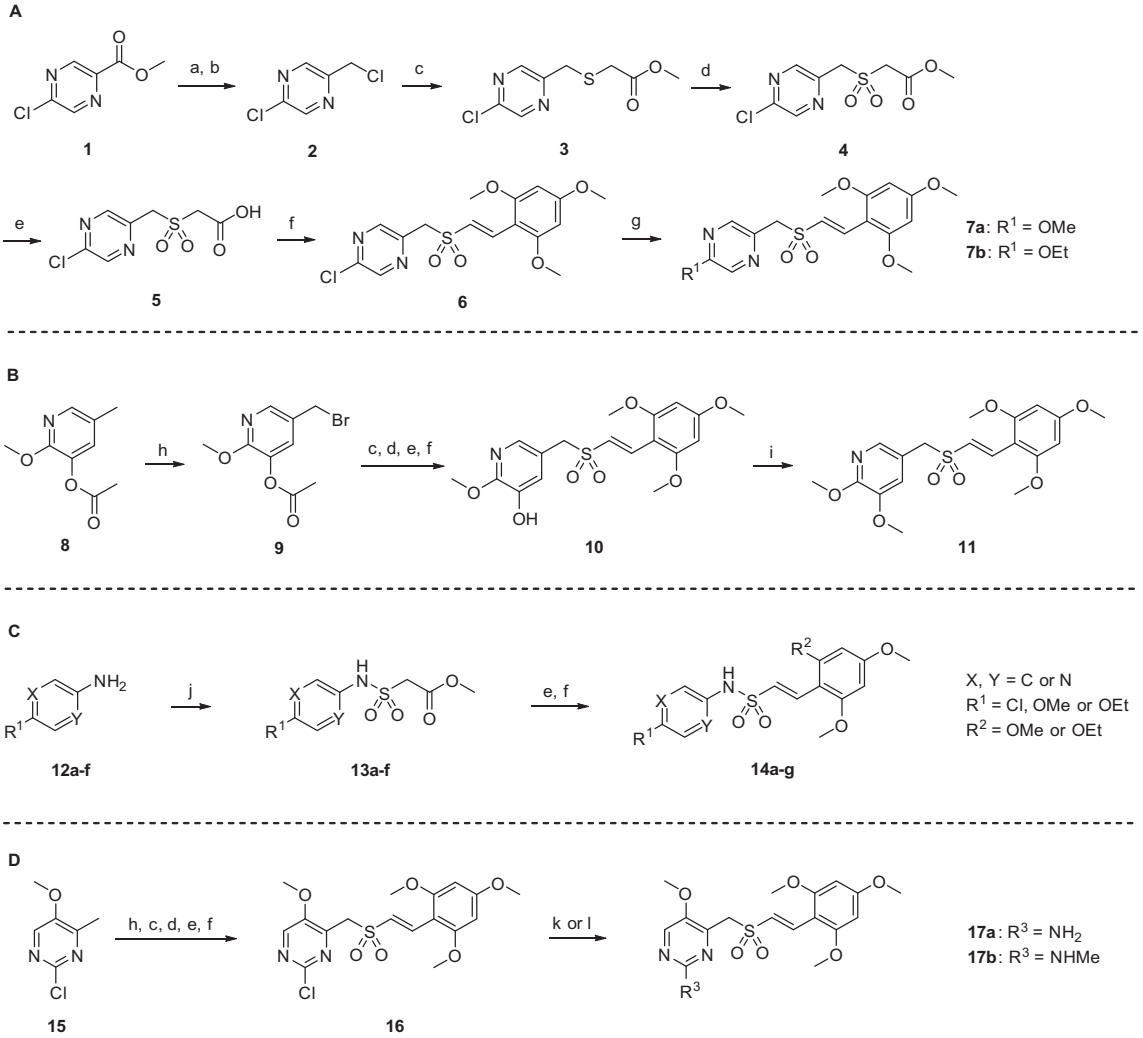


Fig. 1. Structures of rigosertib and (*E*)-2/3-((styrylsulfonyl)methyl) pyridines **8** and **18**.

N-bromosuccinimide. 3-Pyridinol **10** was methylated with iodomethane to give **11**; chloride **16** was reacted with aqueous ammonia or methylamine hydrochloride to produce **17a** and **17b** respectively. Preparation of **14a–g** started with the coupling of an appropriate amine **12** with methyl 2-(chlorosulfonyl)acetate to give the corresponding sulfonamide **13**, which was followed by saponification and condensation to yield **14**.

These newly synthesised molecules were tested for their anti-proliferative activity against two tumour cell lines derived from ovarian carcinoma A2780 and colorectal carcinoma HCT-116 using a 72 h MTT cell viability assay. Rigosertib served as a positive control, and the results are presented in Table 1.

Pyrazine derivative **6** displayed moderate to weak anti-proliferative activity against A2780 and HCT-116 cells (GI_{50} = 4.76 μM and >10 μM, respectively). Replacement of the bridging methylene between the pyrazine and sulfone moieties of **6** (Z = CH_2) with a secondary amino group (**14g**, Z = NH) abolished the activity (GI_{50} > 10 μM for both cell lines), while conversion of the chloride on **6** (R^1 = Cl) into an alkyloxy group (**7a**, R^1 = OMe; **7b**, R^1 = OEt) dramatically boosted the potency against both cell lines with the GI_{50} values in the range of 0.49–1.28 μM. Replacement of the pyrazine ring of **7a** (Y = N) with a pyridine ring (**11**, Y = CH) reduced the potency by approximately 2 folds against both cell lines. On the other hand, replacement of the R^3 of the comparator **8** (R^3 = NH_2) with methoxy (**11**, R^3 = OMe) significantly decreased anti-proliferative activity by ~100 folds, indicating the vital role of the amino group. These results indicate that the position and number of the heteroaryl nitrogen atom significantly affect the anti-proliferative activities, and that alkyloxy substitutions at R^1



Scheme 1. General synthetic routes to (*E*)-2-(((2,4,6-trimethoxystyryl)sulfonyl)methyl)pyrazine derivatives (**A**), (*E*)-2,3-dimethoxy-5-(((2,4,6-trimethoxystyryl) sulfonyl) methyl)pyridine (**B**), (*E*)-*N*-(hetero)aryl-2-(2,4,6-trialkoxyphenyl)ethene-1-sulfonamide derivatives (**C**) and (*E*)-5-methoxy-4-(((2,4,6-trimethoxystyryl) sulfonyl)methyl) pyrimidine derivatives (**D**). Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, o/n, 66%; (b) $SOCl_2$, DCM, rt, 1 h, 81%; (c) methyl thioglycolate, Na_2CO_3, MeOH, rt, 12 h, 62–87%; (d) H_2O_2, acetic acid, 60 °C, 12 h, 78–93%; (e) Na_2CO_3, H_2O/MeOH (1:1), rt, 12 h, 61–94%; (f) 2,4,6-trimethoxybenzaldehyde or 2-ethoxy-4,6-dimethoxybenzaldehyde, benzoic acid, piperidine, toluene, reflux, 3 h, 38–47%; (g) MeONa (or EtONa), MeOH (or EtOH), 90 °C, 2 h, 68–72%; (h) NBS, AIBN, CH_2Cl_2, reflux, 18 h, 36–47%; (i) MeI, K_2CO_3, DMF, rt, 12 h, 65%; (j) methyl 2-(chlorosulfonyl)acetate, Et_3N, DCM, rt, 3 h, 74–82%; (k) 32% aqueous ammonia, reflux, o/n, 10%; (l) $MeNH_2HCl$, Et_3N, 2-methoxyethanol, microwave, 150 °C, 1 h, 79%.