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Short communication

Synthesis of novel 3-amino-2-(4-chloro-2-mercaptobenzenesulfonyl)-guanidine derivatives as potential antitumor agents

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Abstract

Novel 3-amino-2-(4-chloro-2-mercaptobenzenesulfonyl)guanidine derivatives have been synthesized as potential anticancer agents. The in vitro antitumor activity of these compounds has been evaluated in the US National Cancer Institute (NCI), and relationships between structure and antitumor activity are discussed. The prominent compound was 1-allyl-2-[4-chloro-5-(4-chlorophenylcarbamoyl)-2-methylthiobenzenesulfonyl]-3-(5-nitrofurfurylideneamino)guanidine (**8**) with remarkable activity against 21 human tumor cell lines representing leukemia, lung, colon, melanoma, ovarian, renal, prostate and breast ($GI_{50} = 0.3–3.0$ μM), and selectivity toward leukemia RPMI-8226 cell line ($GI_{50} = 0.3$ μM, $TGI = 1.4$ μM).

Keywords: 3-Amino-2-(4-chloro-2-mercaptobenzenesulfonyl)guanidines; Synthesis; Antitumor effect

1. Introduction

Sulfonamides are among a growing list of compounds with desirable anticancer activity [1–27]. Although they have a common chemical motif of aromatic/heterocyclic sulfonamide, there are a variety of mechanisms for their anticancer action, such as disruption of microtubule assembly, cell cycle arrest in the G1 phase, functional suppression of the transcriptional activator NF-Y, angiogenesis inhibition as well as carbonic anhydrase inhibition [1]. Aryl sulfonamides incorporating disulfide grouping have recently been found to act as hypoxia-activatable prodrugs of 2-mercaptobenzenesulfonamides [28] or 4-(2-mercaptophenylcarboxamido)benzenesulfonamides [29] that target the tumor-associated isoform IX of carbonic anhydrase.

On the other hand, aminoguanidine and related derivatives are effective in inhibiting nitric oxide production in cells expressing inducible nitric oxide synthase (NOS2) [30,31], and therefore, aminoguanidines exhibit protective effect against nephrotoxicity [32] and ototoxicity [33] induced by chemotherapeutic agents.

In view of the above findings one may conclude that the compounds incorporating both the benzenesulfonyl and aminoguanidine moieties present potential use as safe antitumor drugs. Indeed, we and others have already found that 3-amino-2-(2-mercaptobenzenesulfonyl)guanidine derivatives (Fig. 1, structures **I** [6] and **II** [10]) and 3-amino-2-(5-indanylsulfonyl)-guanidine (Fig. 1, structure **III** [34]) display remarkable anticancer properties. These results encouraged us to design compounds of type **IV** (Fig. 1) resulting from the replacement of C=C of **I** by a C≡C group. Moreover, following the finding that various heterocyclic Schiff bases of aminoguanidine may also act as antitumor agents [35–37], we have also synthesized novel compounds of general structure **V** (Fig. 1).

2. Results and discussion

2.1. Chemistry

In general, we synthesized two series of 2-mercaptobenzenesulfonamide derivatives: series **A** (compounds **1–9**)

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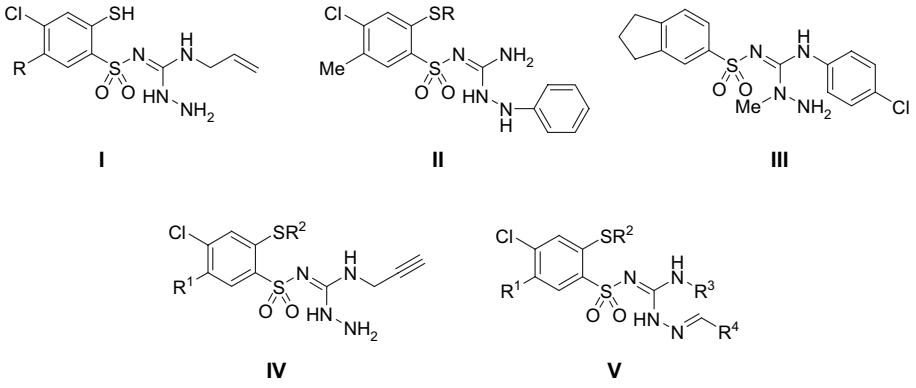


Fig. 1.

characterized by the presence of 1-allylguanidine group; series **B** (compounds **14**–**19**) containing 1-(2-propynyl)guanidine moiety.

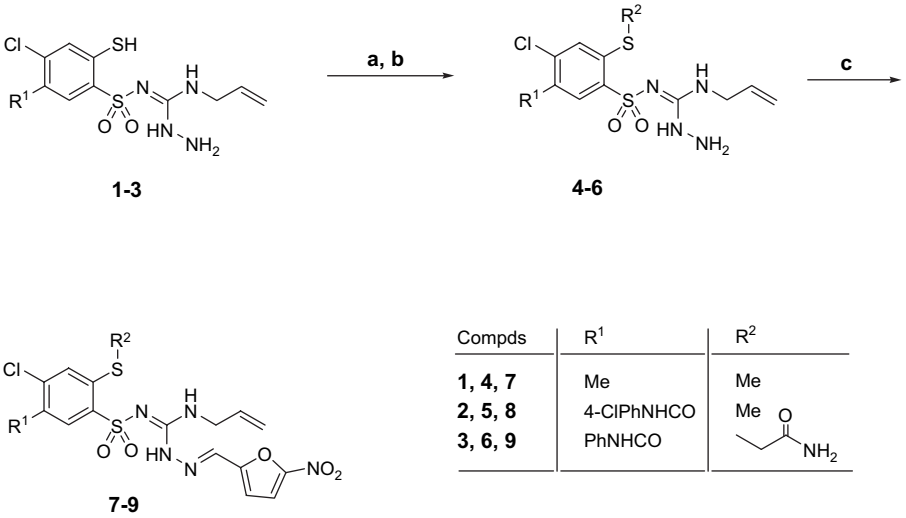
For the preparation of novel 3-amino-2-(4-chloro-2-mercaptobenzenesulfonyl)-1-allylguanidines **5**–**9** we made use of a two-step synthesis from the previously described aminoguanidines **2** and **3** [6] commencing with alkylation of the mercapto group with appropriate alkylating agents under alkaline conditions which gave the sulfides **5** and **6** in 94–96% yield. Subsequent treatment of **4** [6], **5** and **6** with 5-nitro-2-furaldehyde gave rise to the formation of the corresponding Schiff bases **7**–**9** in 83–92% yields (Scheme 1).

The syntheses of the compounds of series **B** were achieved by a convenient procedure depicted in Schemes 2 and 3. First, a readily available 3-methylthio-1,4,2-benzodithiazine 1,1-dioxides **10** [38] and **11** [39] were subjected to the reaction with 2-propynylamine in dry benzene to give the substitution products **12** and **13** in 89 and 96% yield, respectively. 3-(2-Propynylamino)-1,4,2-benzodithiazine 1,1-dioxides thus obtained were converted into the corresponding aminoguanidine derivatives **14** and **15** upon treatment with an excess of hydrazine hydrate in methanolic solution at room temperature (Scheme 2). Then, the reaction of **14** with appropriate alkylating agents under alkaline conditions furnished the expected sulfides **16**–**18** in 75–94% yields. The synthesis of the final Schiff base **19** was achieved by reacting aminoguanidine **16** with 5-nitro-2-furaldehyde in refluxing ethanol (Scheme 3).

The structures of all newly obtained compounds were confirmed by elemental analyses as well as by IR and NMR spectroscopy as shown in Section 4.

2.2. Biology

Three previously described compounds of series **A** (**1**–**3**) [6] and 11 newly prepared compounds of series **A** (**5**–**9**) and series **B** (**14**–**19**) were tested in the US National Cancer Institute (NCI, Bethesda, MD) for their in vitro anticancer activity. To facilitate the discussion of structure–activity relationships, the series **A** and **B** were further subdivided into three substructures according to substitution pattern: substructure **I** with $R^1 = H$ and unsubstituted NH_2 group; substructure **II** with $R^1 =$ alkyl and unsubstituted NH_2 group; substructure **III** with $R^1 =$ alkyl and NH_2 group involved in the formation of Schiff base (Table 1).



Compds	R^1	R^2
1, 4, 7	Me	Me
2, 5, 8	4-ClPhNHCO	Me
3, 6, 9	PhNHCO	

Scheme 1.