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Synthesis and anticancer activity evaluation of 3,4-mono- and bicyclosubstituted *N*-(het)aryl trifluoromethyl succinimides

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ABSTRACT

Novel trifluoromethylated mono- and bicyclic succinimides derived from trifluoromethylmaleic anhydride were synthesized using cyclopentadiene or 2,3-dimethylbutadiene and (het)arylamines. The biological activity of these compounds was evaluated using prediction methods and experimental studies. This series of new trifluoromethyl succinimides (3a,b and 6a-c) were tested by the National Cancer Institute (NCI, Bethesda, USA) by Program NCI-60 DTP Human Tumor Cell Line Screen at a single high dose (10^{-5} M). Imides revealed activity on Leukemia cell lines (RPMI-8226 - myeloma cell line), Non-Small Cell Lung Cancer cell lines (A549/ATCC - lung carcinoma epithelial cells) and Renal cancer cell lines (A498 and SN12 C).

1. Introduction

Modern drug discovery is based on the continuous development of synthetic methods for the development of new pharmaceutical agents. Organofluorine compounds are gaining interest for a variety of medicinal applications [1–7]. Fluorine has become a precious tool for medicinal chemists due to the properties it imparts on the molecules it is attached to. A commonly used synthetic strategy to reduce *in vivo* metabolism of potential drugs involves the incorporation of electron-withdrawing functionality, such as the trifluoromethyl (CF_3) group [8]. The CF_3 group is important in medicinal chemistry because its incorporation into small molecules often enhances the effect of their interactions with cellular targets, improving cellular membrane permeability, and increases stability by minimizing oxidative metabolism of the drug [9–11]. The FDA-approved list of CF_3-containing drugs for human use consists of dozens of compounds [6–8]. Among them are antidepressants/serotonin reuptake inhibitors (Fluoxetine Hydrochloride (**I**)), Fluvoxamine Maleate (**II**)), anti-HIV agents (favirenz (**III**), tipranavir (**IV**)), antihypertensive agents (bendroflumethiazide (**V**), polythiazide (**VI**)), antimalarial agents (mefloquine hydrochloride (**VII**)), antidiabetics (sitagliptin (**VIII**)), etc. The trifluorometyl-containing anticancer agents include flutamide (**IX**) (an androgen receptor antagonist), nilotinib (**X**) (a tyrosine kinase inhibitor), trifluridine (**XI**) (an antimetabolite), a derivative of 5-trifluoromethyluracil (**XII**), etc (Fig. 1). 5-Trifluoromethyluracil **XII** [12–14], which was synthesized by our group using a novel synthetic pathway several years ago [15], and its derivatives have also showed antitumor activity [16–18] and antivirus activity as well [19,20].

Recently we have found that polyfluorinated ureas containing different substituents show anticancer activity [21–24] and we developed preparative methods for the synthesis of many CF_3-bearing molecules [15,25–30]. It was therefore intriguing to synthesize previously-unexplored trifluoromethyl-containing compounds and investigate their anticancer activity.

Substituted 1,3-cyclopentadiones, including 1,3-indanediones, phthalimides and substituted succinimides have been attracting the attention of pharmacologists and medicinal chemists for a long time. Succinimides represent an important class of organic compounds, both as synthetic intermediates and as biological agents with anticonvulsive [31–33], tranquilizing [34], and antiepileptic [35] activity. A 1,3-indanedione, miradon (anisindione, **XIII,** Fig. 2) is a known anticoagulant. Phthalimides and 3,4-bicyclosubtituted succinimides have demonstrated cancer cell growth inhibition [36–38]. Recently, anticancer activity was demonstrated for cantharidin (**XIV,** Fig. 2) and its demethyl and

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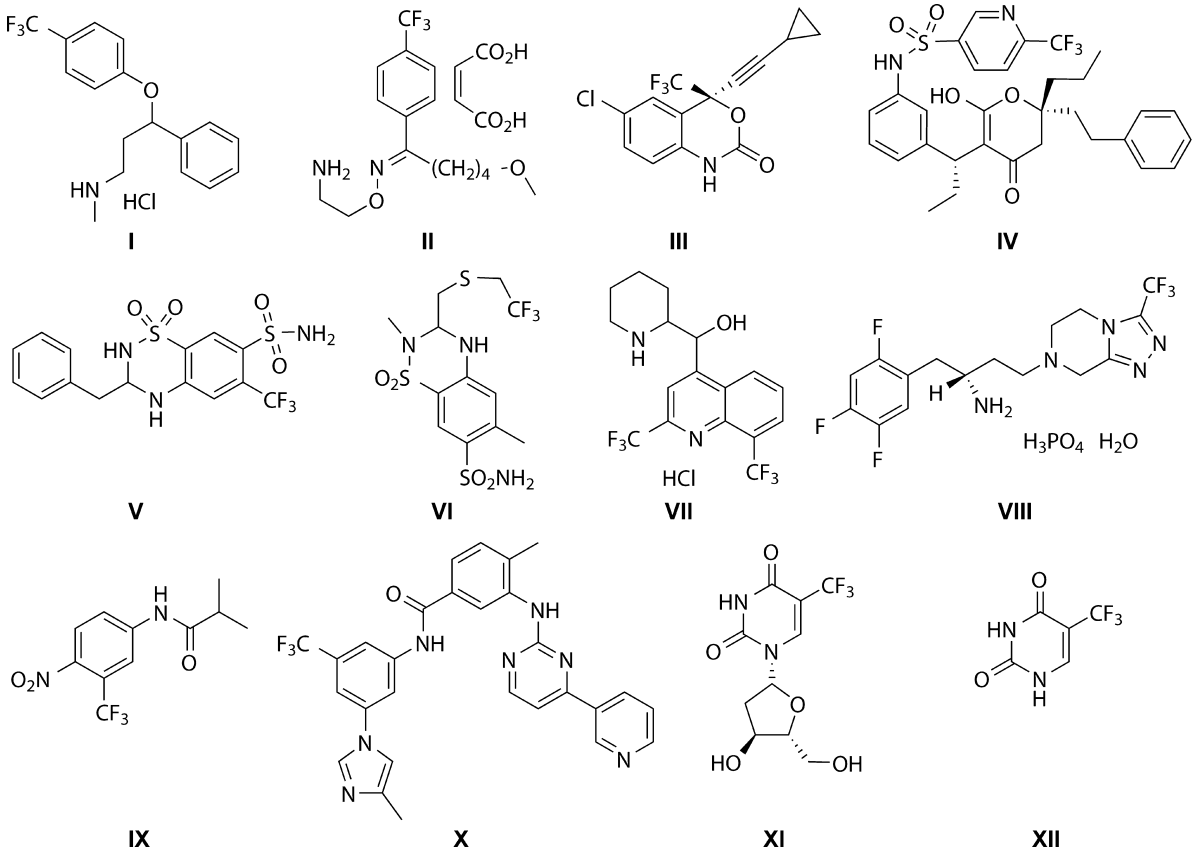

Figure 1. Trifluoromethyl-containing drugs **I-XII**.

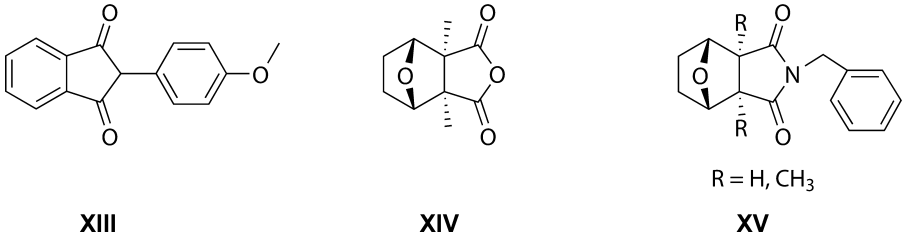

Figure 2. Structural analogs–physiologically active cyclic 1,3-diones XIII-XV.

dedimetyl (norcantharidin) derivatives, including *N*-substituted imides and mono *C*-fluorinated [39,40]. High carcinolitic activity was additionally reported for *N*-benzyl (nor)cantharidinimides (**XV,** Fig. 2) [41].

Taking into account the above information we decided to explore the synthesis of cyclosubstituted *N*-(het)aryl trifluoromethyl succinimides. We have previously reported the crystal and molecular structure of 4-(4-methoxyphenyl)-2-(trifluoromethyl)-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (**6a**, synthetic scheme in Fig. 4, see Supplementary Information (SI), **Fig. S1**), the first representative of (trifluoromethyl)-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-diones [25]. In this work we synthesized a number of isoindolediones (derivatives of fluorinated succinimides) and evaluated their anticancer activity.

2. Results and discussion

2.1. Chemistry

The starting trifluoromethylmaleic anhydride **1** [42,43] was obtained from hexafluoropropylene oxide (**XVI**) and acetic anhydride (**XVII**) as described by England [43] (Fig. 3). An alternative multistep-synthesis reported by Soloshonok et al. involved methyl trifluoropyruvate as a starting compound [42] which, in turn, was obtained from oxide **XVI** [44], that is why we preferred the direct synthesis of anhydride **1**. 2,3-Dimethylbutadiene (**XVIII**) was prepared from pinacone hexahydrate (**XIX**) [45] (Fig. 3**)**. Cyclopentadiene was prepared by thermal decomposition of dicyclopentadiene [46] and was immediately used in reactions. The imides **3** and **6** were prepared by one-pot reactions according to the following procedure: equimolar quantities of anhydride **1** and 2,3-dimethylbutadiene-1,3 or cyclopentadiene in anhydrous xylene were mixed at 0 °C, then the temperature was slowly increased to 60 °C. Thus, cyclic anhydrides **2** or **4** were formed (not isolated). Next, aromatic amine was added and the reaction mixture was refluxed for 8 h. After evaporating the solvent, the remaining residue was crystallized from heptane.

Compound **6a** was synthesized both by the above procedure (method A) and by an alternative pathway (method B). For the latter, trifluoromethylmaleic anhydride **1** and *p*-anisidine were condensed in boiling xylene. Isolated trifluoromethylmaleic imide **5** was introduced in a cycloaddition reaction with cyclopentadiene