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

Elena L. Luzina^a and Anatoliy V. Popov^{b,*}

^aInstitute of Physiologically Active Compounds, Severnyi pr. 1, Chernogolovka, Moscow region, 142432, Russia

^bUniversity of Pennsylvania, Perelman School of Medicine, Department of Radiology, 3620 Hamilton Walk, Philadelphia, PA 19104, USA

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 SN12C).

Keywords

trifluoromethylmaleic anhydride; trifluoromethyl succinimides; fluorinated heterocycles; cycloaddition; cyclocondensation; anticancer activity; synthesis

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 (CF₃) group [8]. The CF₃ 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

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*Corresponding author: Anatoliy V. Popov, Tel.: 1(215) 746-8761; Fax: 1(215) 746-8764, avpopov@mail.med.upenn.edu.

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metabolism of the drug [9–11]. The FDA-approved list of CF₃-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 trifluoromethyl-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 antiviral 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 CF₃-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-bicyclosubstituted succinimides have demonstrated cancer cell growth inhibition [36–38]. Recently, anticancer activity was demonstrated for cantharidin (**XIV**, Fig. 2) and its demethyl and dedimethyl (norcantharidin) derivatives, including *N*-substituted imides and mono *C*-fluorinated [39, 40]. High carcinogenic 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 isoindolones (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 in benzene at 10 °C, and then heated at 60 °C for 4 h producing imide **6a** with a good yield (see synthetic scheme in Fig. 4).

The products **3a,b** and **6a–c** were white crystals, and the imides **3** represent a mixture of enantiomers (Fig. 5). As for norbornenes **6**, four isomers are theoretically possible due to sterically non-specific Diels-Alder reactions with cyclopentadiene. England reported a highly exothermic neat reaction between trifluorocitraconic anhydride **1** and cyclopentadiene that yields a mixture of *exo*- and *endo*- products [43]. However, we have found when run at low/moderate temperature in solution this reaction results in only the *exo*-CF₃-cycloadducts (succinic anhydride/succinimide moieties are in *endo*-position). This was confirmed previously by X-ray analysis of imide **6a** (SI, Fig. S1) [25]. Thus, imides **6** represent the mixture of two *exo*-CF₃-enantiomers (Fig. 5).

2.2 Biology

Biological activity of the newly synthesized compounds was evaluated using a variety of prediction methods (Lipinski rules and Gelovani parameters [47–49], PASS Online [50–53] and PharmMapper programs [54–56] as well as experimental studies (NCI primary test for anticancer activity) and the COMPARE analysis [57–59]. The results of these analyses can be found in the SI in the biological activity evaluation section.

2.2.1. The Lipinski's and Gelovani's parameters—All 5 synthesized compounds **3a,b** and **6a–c** are in agreement with Lipinski's rules of five [47, 48] which establish criteria for new potential drug candidates (160 < MW < 500; –0.4 < CLogP < 5; number of H-bond donors < 5; number of H-bond acceptors < 10). A potential drug candidate should not violate more than one of the above rules. Gelovani's parameters were additionally considered (number of atoms from 20 to 70, molar refractivity (MR) from 40 to 130 cm³/mol, polar surface area (PSA) < 140 Å²) [49]. The results of these calculations are presented in SI Table S1.

2.2.2. Prediction prognosis by using the PharmMapper server (Target Fishing)

—PharmMapper Server: an updated integrated pharmacophore-matching platform with statistical methods for identifying potential drug targets [54–56]. Nine targets, involved in

cancer therapy, were found common between the synthesized compounds. The fit scores of the synthesized compounds with the top targets were illustrated in SI Table S2.

2.2.3. Prediction prognosis using PASS Online—To investigate the biological potential of our compounds, the PASS program was implemented. PASS (Prediction of Activity Spectra for Substances) is a software product designed as a tool for evaluating the general biological potential of an organic, drug-like molecule. PASS provides simultaneous predictions of many types of biological activity based on the structure of the organic compounds [50–53, 60, 61].

The results of the PASS prediction for the compounds **3a, b** and **6a–c** showed the following possible biological activity and pharmacological effects: dementia treatment (**3a,b** and **6a–c**), antineurotic (**3a,b** and **6a,b**) more likely for **6a,b**, phobic disorders treatment (**3a,b** and **6a–c**) more likely for **6a,b**, fibrinolytic (**3a,b** and **6a**) more likely for **3a**, antinociceptive (**3a, 6a,b**), antidyskinetic (**3a,b** and **6a–c**), insulysin inhibitor (**3a** and **6a–c**) more likely for **6a**, cancer associated disorders treatment, antineoplastic (**3a,b, 6a**), prostate disorders treatment (**3a,b** and **6a–c**), prostate cancer treatment (**3a, 6a**).

Some items among the predicted biological activity spectra identified by the PASS program, despite the low values of Pa (probability "to be active"), were also identified in the NCI screen. For a detailed analysis of the synthesized compounds, see SI Tables S3–S5.

Modern computational techniques can predict some of fluorine's effects on the host molecule's properties; however, in most cases the development of fluorine-containing (and especially trifluoromethyl-containing) drugs is a laborious trial-and-error process. For this reason, all new CF₃-bearing compounds are worth testing as potential drug candidates. Due to several structural similarities with known drugs (e.g. the 2-aminopyrimidine fragment in **X** and **3b** and **6b**, methyloxanorbornyl fragments in **XIV** and **XV** vs. trifluoromethylnorbornyl moieties in **6a–c**, as well as the 1,3-indanedione and anisole fragments in miradon **XIII** and anisylimides **3a** and **6a**), compounds **3a,b** and **6a–c** can be regarded as one of the most promising classes of biologically active compounds with a broad spectrum of action. We chose to focus on their *in vitro* anticancer activity, which was assessed by the standard NCI-60 anticancer test.

2.2.4. Anticancer activity at one dose (10^{−5} M concentration) and COMPARE analysis—Compounds **3a,b** and **6a–c** were tested by the National Cancer Institute (NCI, Bethesda, USA) at one dose (10^{−5} M) using the primary anticancer assay on 60 human cancer cell lines organized into subpanels derived from nine different human cancer types: leukemia, melanoma, lung, colon, renal, ovarian, breast, prostate and CNS [57, 62–65].

A summary of the antitumor activity of our compounds is presented in Table 1.

Compounds **3a, b** and **6a–c** showed selective activity (Growth Inhibition (%) > 10 – 20%) on the following cell lines: Leukemia RPMI-8226 (**6a–c**), Non-Small cell Lung cancer A549/ATCC (**3b, 6a, b**), Renal cancer A498 (**3a**) and SN12C (**6c**), and Melanoma UACC-257 (**6c**). For a detailed analysis of the synthesized compounds, see SI Table S6.

A COMPARE analysis [57–59] was performed for each compound to investigate possible resemblance to anticancer drugs from the NCI standard agent database [66]. NCI makes its active synthetic and natural compounds available in public databases to use for comparative prediction of new drug mechanism. The COMPARE analysis hypothesis states that a compound may have the same mechanism of action as an agent with a known mechanism if the data pattern of the two compounds. COMPARE analysis of trifluoromethylated mono- and bicyclic substituted succinimides showed low correlation coefficients (below 0.4) with the standard agents. Based on COMPARE analysis, we assume that the presented compounds **3a,b** and **6a–c** act mainly as alkylating agents (**3a,b** and **6a,c**), DNA antimetabolites (**3a,b**, **6b**), and antimitotic agent (**6a,c**) for which no specific mechanism of action are known.

For a detailed analysis of the synthesized compounds, see SI Tables S7–S9.

3. Conclusion

In this paper we reported the synthesis of trifluoromethylated mono- and bicyclic substituted succinimides. Their potential biological activity was predicted using the PharmMapper Server and the PASS program. The trifluoromethyl succinimides **3a,b** and **6a–c** were tested in 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) and the mechanism of action was evaluated with the COMPARE analysis. Imides **6a–c** revealed activity on Leukemia cell lines (RPMI-8226 - myeloma cell line), imides **3b** and **6a,b** demonstrated activity on Non-Small Cell Lung Cancer cell lines (A549/ATCC - lung carcinoma epithelial cells) and imides **3a** and **6c** demonstrated activity on A498 (**3a**) and SN12C (**6c**) Renal cancer cell lines. Further modifications of these compounds in order to improve their potency are currently under consideration.

4. Experimental

4.1. General

Hexafluoropropene oxide was purchased from Kirovo-Chepetsk Polymer Plant (Russia). Amines were purchased from Aldrich and sublimed in vacuum before use. Other chemicals and solvents were purchased from “Mosreaktiv” (Russia) and purified before use by standard procedures. The ^1H and ^{19}F NMR spectra were recorded on Bruker DXP at 200 and 188 MHz, respectively, in CDCl_3 , acetone- d_6 and $\text{Me}_2\text{SO}-d_6$ using tetramethylsilane (TMS) as an internal standard and CFCl_3 as an external standard. Chemical shifts are reported in ppm units with the use of δ scale. Mass-spectra were recorded on a Finnigan 4021 spectrometer. The elemental analyses (C, H, F, N) were performed in the laboratory of analytic chemistry of IPAC RAS. Melting points were measured in open capillary tubes and are uncorrected.

4.2. General procedure for the synthesis of compounds 3 and 6 (method A for 6a)

A solution of anhydride **1** (0.01 mol in 10 ml of anhydrous xylene) was added drop-by-drop to a solution of 2,3-dimethylbutadiene-1,3 or cyclopentadiene (0.01 mol in 10 ml of anhydrous xylene) at 0 °C, then the temperature was slowly increased to 60 °C and the

reaction mixture was kept for 1 h at this temperature. Next, 0.01 mol of aromatic amine was added and the reaction mixture was refluxed for an additional 8 h. The solvent was evaporated and residue was crystallized from heptane.

4.2.1. (3aRS,7aRS)-2-(4-methoxyphenyl)-5,6-dimethyl-3a-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione 3a—Yield 47%; mp 136–138 °C. ^1H NMR (200 MHz, acetone- d_6 , δ): 7.22 (AB, 4H, $\delta_{\text{A}} = 7.54$, $\delta_{\text{B}} = 6.91$, $J_{\text{AB}} = 8.8$ Hz, arom. H); 3.72 (s, 3H, CH_3O), 3.33 (t, 1H, $J_{\text{HH}} = 8$ Hz, 1H, CHCH_2), 2.59 (AB, 2H, $\delta_{\text{A}} = 2.86$, $\delta_{\text{B}} = 2.31$, $J_{\text{AB}} = 18$ Hz, CH_2); 2.56 (d, 2H, $J_{\text{HH}} = 8$ Hz, CHCH_2); 1.65 (s, 6H, CH_3). ^{19}F NMR (188.29 MHz, acetone- d_6 , δ): -69.32 (s, 3F, CF_3). EI-MS (m/z): 353 (M^+). Calc. for $\text{C}_{18}\text{H}_{18}\text{F}_3\text{NO}_3$: C, 61.19, H, 5.13, N, 3.96, F, 16.13%. Found: C, 61.28, H, 5.02, N, 3.78, F, 16.34%.

4.2.2. (3aRS,7aRS)-5,6-dimethyl-2-(pyrimidin-2-yl)-3a-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione 3b—Yield 51%; mp 150–151 °C. ^1H NMR (200 MHz, $\text{Me}_2\text{SO}-\text{d}_6$, δ): 8.15 (d, 2H, $J_{\text{HH}} = 4.7$ Hz, pyrimidin-2-yl 4- H , 6- H); 6.47 (t, 1H, $J_{\text{HH}} = 4.7$ Hz, pyrimidin-2-yl 5- H); 3.26 (t, 1H, $J_{\text{HH}} = 4.2$ Hz, CHCH_2); 2.51 (AB, 2H, $\delta_{\text{A}} = 2.86$, $\delta_{\text{B}} = 2.5$, $J_{\text{AB}} = 18$ Hz, CH_2), 2.38 (bs, 2H, CHCH_2); 1.64 (s, 6H, CH_3). ^{19}F NMR (188.29 MHz, $\text{Me}_2\text{SO}-\text{d}_6$, δ): -69.73 (s, 3F, CF_3). EI-MS (m/z): 325 (M^+). Calc. for $\text{C}_{15}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_2$: C, 55.39, H, 4.34, N, 12.92, F, 17.52%. Found: C, 55.24, H, 4.45, N, 12.82, F, 17.68%.

4.2.3. (3aRS,4RS,7SR,7aRS)-2-(4-methoxyphenyl)-3a-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione 6a (method B)—3.7 mmol of imide **5** and 3.7 mmol of cyclopentadiene were mixed in 20 ml of anhydrous benzene at 10 °C. Then the temperature was slowly increased and the reaction mixture was refluxed for 1 h. The solvent was evaporated and residue was crystallized from heptane.

Yield 59% relative to **1** (method A), 72% relative to **5** (method B); mp 80–81 °C. ^1H NMR (200 MHz, CDCl_3 , δ): 7.00 (AB, 4H, $\delta_{\text{A}} = 7.10$, $\delta_{\text{B}} = 6.95$, $J_{\text{AB}} = 9$ Hz, arom. H); 6.41 (m, 2H, $\text{CH}=\text{CH}$); 3.85 (s, 3H, OCH_3); 3.65–3.53 (3m, 3H, 3 CH); 1.94 (AB, 2H, $\delta_{\text{A}} = 2.06$, $\delta_{\text{B}} = 1.84$, $J_{\text{AB}} = 8$ Hz, CH_2). ^{19}F NMR (188.29 MHz, CDCl_3 , δ): -68.02 (s, 3F, CF_3). EI-MS (m/z): 337 (M^+). Calc. for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{NO}_3$: C, 60.54, H, 4.18, N, 4.15, F, 16.90%. Found: C, 60.65, H, 4.12, N, 4.27, F, 16.82%.

4.2.4. (3aRS,4RS,7SR,7aRS)-2-(pyrimidin-2-yl)-3a-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione 6b—Yield 46%; mp 120–121 °C. ^1H NMR (200 MHz, $\text{Me}_2\text{SO}-\text{d}_6$, δ): 8.15, (d, 2H, $J_{\text{HH}} = 4.7$ Hz, pyrimidin-2-yl 4- H , 6- H); 6.47 (t, 1H, $J_{\text{HH}} = 4.7$ Hz, pyrimidin-2-yl 5- H); 6.20 (bs, 1H, $\text{CH}=\text{}$); 6.11 (m, 1H, $\text{CH}=\text{}$); 3.28 (bs 1H, CH); 3.11 (m 1H, CH); 3.28 (bs 1H, CH); 1.51 (AB, 2H, $\delta_{\text{A}} = 1.67$, $\delta_{\text{B}} = 1.35$, $J_{\text{AB}} = 8.8$ Hz, CH_2). ^{19}F NMR (188.29 MHz, $\text{Me}_2\text{SO}-\text{d}_6$, δ): -64.68 (s, 3F, CF_3). EI-MS (m/z): 309 (M^+). Calc. for $\text{C}_{14}\text{H}_{10}\text{F}_3\text{N}_3\text{O}_2$: C, 54.38, H, 3.36, N, 13.59, F, 18.43%. Found: C, 54.44, H, 3.46, N, 13.72, F, 18.64%.

4.2.5. (3aRS,4RS,7SR,7aRS)-2-(6-methylpyridin-2-yl)-3a-(trifluoromethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione 6c—Yield 40%; mp

136–138 °C. ^1H NMR (200 MHz, $\text{Me}_2\text{SO}-d_6$, δ): 7.77 (d, 1H, $J = 8$ Hz, arom. H); 7.38 (t, 1H, $J = 8$ Hz, arom. H); 6.46 (d, 1H, $J = 8$ Hz arom. H); 6.12 (m, 2H, $\text{CH}=\text{CH}$), 3.38 (m, 1h, CH); 3.25 (bs, 1h, CH); 3.02 (bs, 1h, CH); 2.33 (s, 3H, CH_3); 1.48 (AB, 2H, $\delta_A = 1.65$, $\delta_B = 1.30$, $J_{AB} = 8.8$ Hz, CH_2). ^{19}F NMR (188.29 MHz, $\text{Me}_2\text{SO}-d_6$, δ): -64.96 (s, 3F, CF_3). EI-MS (m/z): 322 (M^+). Calc. for $\text{C}_{16}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_2$: C, 59.63, H, 4.07, N, 8.69, F, 17.68%. Found: C, 59.48, H, 4.22, N, 8.77, F, 17.54%.

4.3. 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrrole-2,5-dione 5

9.2 mmol of anhydride **1** and 10.6 mmol of *p*-anisidine in 20 ml of anhydrous xylene were stirred 1 h at room temperature, then were refluxed for 8 h. The solvent was distilled out and the residue was crystallized from heptane.

Yield 68%; mp 80–81 °C. ^1H NMR (200 MHz, CDCl_3 , δ): 7.65 (q, 1H, $J_{\text{HF}} = 1.8$ Hz, $\text{CH}=\text{}$); 7.23 (AB, 4H, $\delta_A = 7.45$, $\delta_B = 7.08$, $J_{AB} = 7$ Hz, arom. H); 3.84 (s, 3H CH_3O). ^{19}F NMR (188.29 MHz, CDCl_3 , δ): -62.44 (d, $J_{\text{FH}} = 1.8$ Hz, 3F, CF_3). EI-MS (m/z): 337 (M^+). Calc. for $\text{C}_{12}\text{H}_8\text{F}_3\text{NO}_3$: C, 53.15, H, 2.97, N, 5.16, F, 21.02%. Found: C, 53.25, H, 2.83, N, 5.27, F, 21.26%.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- A series of trifluoromethyl succinimides was synthesized and subjected to anticancer screening by NCI.
- The synthesized compounds showed observed activity against Leukemia (RPMI-8226), Non-Small cell Lung cancer (A549/ATCC), and Renal cancer cell lines (A498 and SN12C).

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

XIII **XIV**

R = H, CH₃

XV

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

Figure 3. Synthetic schemes of trifluoromethylmaleic anhydride (**1**) and 2,3-dimethylbuta-1,3-diene (**XVIII**).

Figure 4.
Synthetic scheme of imides **3a,b** and **6a-c**.

Figure 5.
Enantiomers of imides **3** and **6**.

Table 1

Evaluation of antitumor activity (Percentage of Growth inhibition for most sensitive cell lines) of the compounds **3a**, **b** and **6a–c**.

Comp.	NSC number	Number of tested cell lines	Range	Panel	Most sensitive cell lines (Growth inhibition percent)
3a	758735	55	41.21 81.43 – 122.64	Renal cancer	A498 (18.57)
3b	758736	52	38.06 87.83 – 125.89	Non-Small cell Lung cancer	A549/ATCC (12.17)
6a	758737	56	43.93 77.49 – 121.42	Leukemia	RPMI-8226 (22.51)
6b	758738	56	68.41 71.84 – 140.25	Leukemia	RPMI-8226 (28.16)
6c	758739	55	51.64 77.49 – 129.13	Leukemia	RPMI-8226 (22.51)
				Melanoma	UACC-257 (10.22)
				Renal cancer	SN12C (10.11)

Range- Difference in value of the most sensitive cell lines and the most inactive value