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Synthesis of 3,3,3-trifluoroethyl isocyanate, carbamate and ureas. Anticancer activity evaluation of *N*-(3,3,3-trifluoroethyl)-*N*-substituted ureas

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

A new method is described for producing 3,3,3-trifluoroethyl isocyanate from perfluoroisobutene (PFIB). Isocyanate was used for synthesis of carbamates and ureas. A series of trifluoroethyl-substituted ureas has been tested in the National Cancer Institute (NCI, Bethesda, USA) by the NCI-60 DTP Human Tumor Cell Line Screening Program at a single high dose (10^{-5} M). The moderate anticancer activity was shown against some types of cancer on the individual human cell lines for leukemia, non-small cell lung cancer and renal cancer.

Graphical abstract

Keywords

perfluoroisobutene, 3,3,3-trifluoroethyl isocyanate; 3,3,3-trifluoroethyl ureas; anticancer activity; synthesis

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

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Introduction

The search for new effective drugs relies on the continued development of synthetic methodologies to address the many problems associated with the design of new pharmaceutical agents. One approach to new drugs is the incorporation of CF₃ groups into molecules of potential drug candidates (e.g. aromatic or heterocyclic systems) or synthesis of new drug candidate from highly-reactive fluorinated reagents [1–3]. Recently we have found that polyfluorinated ureas containing different substituents show anticancer activity [4–8], and we described ureas with two geminal CF₃ groups in polyfluoroalkyl moieties. It would therefore be interesting to synthesize previously-unexplored monotrifluoromethyl-containing compounds, trifluoromethyl-substituted ureas, and investigate their anticancer activity.

Herein, we report a new method of synthesizing 3,3,3-trifluoroethylisocyanate from perfluoroisobutene (PFIB) and the subsequent preparation of a number of *N*-(3,3,3-trifluoroethyl)-*N'*-substituted ureas and a carbamate. The anticancer activity of the ureas is also evaluated.

This article is an extension of our publications united by a common idea of developing new physiologically active fluorinated compounds from perfluoroisobutene **1**, a toxic by-product of tetrafluoroethene and hexafluoropropene manufacturing [9, 10]. Our work covering the development of new synthetic methods for preparing mono-, bis- and tris-trifluoromethyl(alkyl)-containing compounds and their precursors has spanned nearly 20 years [4–8, 11–17].

2. Results and discussion

2.1. Chemistry

The preparation of 3,3,3-trifluoroethyl isocyanate **8** is shown in Scheme 1. Isocyanate **8** was prepared starting from the key starting material perfluoroisobutene (PFIB) **1**. Hydrolysis of perfluoroisobutene **1** into hexafluoroisobutyric acid **2** [4, 9] followed by treatment with phosphorus pentachloride led to chloroanhydride **3** [4, 18]. The reaction of chloride **3** with ethanol led to ester **4** which was converted into ethyl 3,3,3-trifluoropropionate **5** by treatment with the mixture Et₃N/H₂O (triethylamine/water) [19]. An alternative multigram synthesis of this ester **5** involved the conversion of **4** by using of AcOK (potassium acetate) as a base [20]. 3,3,3-Trifluoropropionic acid **6** was obtained by sulfuric acid mediated hydrolysis of ester **5** (alternative preparative ways: hydrolysis of ester **5** in aq. HBr [21] or three stage synthesis from 1-chloro-3,3,3-trifluoropropene [22], see also references therein). Acid **6** was transformed into chloroanhydride **7** by the treatment with PCl₅ according to [23] that is a modified method reported in [24]. Previously, 3,3,3-trifluoroisocyanate **8** was synthesized from 3,3,3-trifluoroethylamine and phosgene [25–27], by thermal degradation of *N*-diphenyl-*N'*-(3,3,3-trifluoroethyl) urea [28, 29]. It was also synthesized using a Curtius reaction of chloroanhydride **7** and sodium azide [30], but isocyanate **8** was not isolated. We obtained isocyanate **8** with 60% yield using a Curtius reaction with sodium azide in the presence of catalytic amount of trimethylsilylazide ([NaN₃]₀: [Me₃SiN₃]₀ = 1:0.016, mol/mol), similar to our previously reported procedure for

preparation of bis(trifluoromethyl)alkyl azides [4]. Ureas **10a–u**, **12**, and carbamate **14** were synthesized by addition of primary aliphatic or aromatic amines **9a–u**, morpholine **11** or alcohol **12** to isocyanate **8**. Two methods were used for the preparation of the above ureas and carbamate. While the reactions of well soluble amines **9a–e**, **9h–u**, **11** or alcohol **13** with isocyanate **8** were carried out at rt (see Experimental 4.6.1), ureidation of poorly soluble amines **9f,g** demanded elevated temperature and a catalyst, trimethyl amine (Experimental 4.6.2).

The synthesized polyfluorinated carbamate **14** and ureas **10a–u** and **12** are solids, stable at rt for more than 2 years without noticeable changes and were obtained with high yields – 80–95%.

2.2. Biological activity

Biological activity of the newly synthesized compounds was evaluated using a variety of prediction methods (Lipinski rules and Gelovani parameters [31–33], PASS Online [34–38], experimental studies (NCI primary test for anticancer activity) and the COMPARE analysis [39–41]. The results of these analyses can be found in the SI in the biological activity evaluation section.

2.2.1. The Lipinski and Gelovani parameters—All 23 synthesized compounds **10a–u**, **12** and **14** are in agreement with Lipinski rules of five [31, 32], which establish criteria for new potential drug candidates (for our molecules $198 < MW < 378$; $0.42 < CLogP < 2.9$; 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 parameters were additionally considered (number of atoms from 20 to 70, molar refractivity (MR) from 40 to $130 \text{ cm}^3/\text{mol}$, polar surface area ($PSA < 140 \text{ Å}^2$) [33] (see also [42]). The results of these calculations are presented in Supplementary Information (SI) Table S1.

2.2.2. Prediction prognosis using PASS Online—To investigate the biological potential of compounds **10a–u**, **12** and **14**, 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 [34–38].

Predicted probability “to be active” (Pa) of different types of biological activity, pharmacological effects and mechanisms revealed from low to moderate Pa values. For a detailed analysis of the synthesized compounds, see SI Tables S2–S7.

2.2.3. Anticancer activity at one dose (10^{-5} M concentration)—Compounds **10a–r** were tested by the National Cancer Institute (NCI, Bethesda, USA) 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, at one dose (10^{-5} M concentration) in a primary anticancer assay [43–47].

The single-dose data is graphed as the mean of the percent growth of the treated cells, relative to the no-drug control, and relative to the time zero number of cells. This allows for detection of both growth inhibition (values between 0 and 100) and cytotoxicity (values less than 0). The screening begins with the evaluation of all compounds against the 60 cell lines at a single dose of 10^{-5} M (the methodology is presented in SI). The moderate anticancer activity was shown against some types of cancer on the individual human cell lines for leukemia, non-small cell lung cancer and renal cancer. The output from the single dose screen was used for the COMPARE analysis [39–41].

For a detailed analysis of NCI screening of the synthesized compounds **10a–r**, see SI Tables S8–S9.

2.2.4. COMPARE analysis—Since advanced target identification studies were beyond the scope of this article, for the first assumption of molecular mechanism we used an accessible on-line tool called the NCI COMPARE analysis [39–41]. This analysis has been performed for tested compounds **10a–10r** (see SI Tables S10–S12) in order to investigate whether there is a resemblance to the anticancer drugs from either the NCI standard agent database [39–41], or the NCI active synthetic and natural compounds (present in publicly-available databases). This is also used to predict putative mechanisms of action. The COMPARE analysis hypothesis is that compounds may have the same mechanism of action as known agents if the data pattern correlates well with the pattern of compounds belonging to the standard agent database.

The analysis revealed that possible mechanisms of action of these ureas include: alkylating agents (**10b**, **10f**, **10j**, **10n**, **10p**, **10r**), DNA antimetabolites (**10a–g**, **10i**, **10k**, **10m–o**, **10q**, **10r**), RNA/DNA antimetabolites (**10c**, **10h**, **10k**, **10o**), topoisomerase II inhibitor (**10m**) and antimitotic agents (**10o**, **10j**). Some compounds may exhibit several mechanisms of action (**10b**, **10c**, **10f**, **10j**, **10k**, **10m–o**, **10r**). For a detailed COMPARE analysis of synthesized compounds **10a–r**, see SI Tables S10–S12.

3. Conclusion

In this paper we reported a new preparative method of synthesis for 3,3,3-trifluoroethyl isocyanate from perfluoroisobutene (PFIB). 22 new trifluoromethyl-containing ureas and a carbamate were obtained. Their potential biological activity was predicted using the Lipinski rules, Gelovani parameters and the PASS program. The trifluoroethylsubstituted ureas **10a–r** were tested in the National Cancer Institute (NCI, Bethesda, USA) NCI-60 DTP Human Tumor Cell Line Screen Program at a single high dose (10^{-5} M) and the mechanism of action was evaluated with the COMPARE analysis. Synthesized compounds **10a–r** showed anticancer activity on individual cell lines. Activity was notable on individual cell lines against leukemia, non-small cell lung cancer and renal cancer.

4. Experimental

4.1. General

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. HPLC analysis was performed as described elsewhere [48]. Melting points were measured in open capillary tubes and are uncorrected. Perfluoroisobutene **1** was obtained by pyrolysis of octafluorocyclobutane [9]. The preparative procedures for the syntheses of 3,3,3-trifluoro-2-(trifluoromethyl)propanoic acid **2** and 3,3,3-trifluoro-2-(trifluoromethyl)propanoyl chloride **3** were published in our article [4].

4.2. Ethyl 3,3,3-trifluoro-2-(trifluoromethyl)propanoate **4**

610.2 g (2.84 mol) of chloroanhydride **3** was added, drop by drop, to boiling dry ethanol (196.59 g, 4.26 mol). After the addition the reaction mixture was refluxed for 1 h, then cooled until rt and washed with cold water several times until neutral pH. Organic layer was dried over MgSO_4 , and then distilled. Yield 87% (522.7 g), b.p. 100–102 °C. ^1H and ^{19}F NMR spectra correspond to the literature data.[49, 50].

4.3. Ethyl 3,3,3-trifluoropropanoate **5** (adopted from [19], scaled up)

A solution of Et_3N (708.4 g, 7 mol) and water (84 g, 4.67 mol) was added, drop by drop, to hot (~90 °C, water bath) ester **4** (522.2 g, 2.33 mol) under rigorous agitation with a mechanical stirrer. The reaction mixture was heated with water bath (100 °C) for additional 4 h, and then cooled to rt. Next, 1.5 L of cold water (4 °C) was added to the reaction flask. The obtained mixture was thoroughly agitated, then separated. Water fraction was extracted with Et_2O (3×450 ml). The combined organic fractions were washed with 5% HCl until acidic pH of water layer, dried over MgSO_4 , and distilled. Trifluoropropionate **5** was isolated with a high yield (82.7%, 301 g, b.p. 104–108 °C). ^1H and ^{19}F NMR spectra correspond to the literature data [51, 52].

4.4. 3,3,3-Trifluoropropionic acid **6**

301 g (1.93 mol) of ester **5** and 2.0 L of 50% sulfuric acid were stirring at 90 °C during 20 h. 400 g of NaCl was added and dissolved, then acid **6** was extracted from the resulted mixture with diethyl ether (3 × 900 ml). The ether solution was dried over MgSO_4 , concentrated and the residue was distilled. Yield 150.2 g (61%) of acid **6**. B.p. 142–145 °C (literature data 153 °C [53]). ^1H NMR (CDCl_3): δ 3.76 (q, 2H, $^3J_{\text{HF}} = 9.8$ Hz, CH_2), 11.75 (s, 1H, OH). ^{19}F NMR (CDCl_3): δ -63.88 (t, $^3J_{\text{FH}} = 9.8$ Hz).

4.5. 3,3,3-Trifluoropropionyl chloride **7**

76.6 g (0.6 mol) of acid **6** was added slowly dropwise to 125 g (0.6 mol) of phosphorus pentachloride (PCl_5) under cooling with an ice bath. Then the mixture was warmed on a water bath (65 °C) until complete dissolution of PCl_5 and very slowly distilled. Yield 86.7 g

(99%) of chloroanhydride **7**. B.p. 70–75 °C. ^1H NMR (CDCl_3): δ 3.84 (q, $^3J_{\text{HF}} = 9.2$ Hz). ^{19}F NMR (CDCl_3): δ –64.02 (t, $^3J_{\text{FH}} = 9.2$ Hz).

4.6. 3,3,3-Trifluoroethyl isocyanate **8**

In 3-necked flask equipped with a dropping funnel, a thermometer and an effective condenser, 112.3 g (0.77 mol) of chloroanhydride **7** was added dropwise to a mixture of sodium azide (59.8 g, 0.92 mol), 2 ml trimethylsilylazide (0.015 mol), 1g triethylbenzylammonium chloride in 200 ml of dibutyl ether and 100 ml diglyme with intensive stirring at temperature no more 35 °C and stirred 3 h. Then the mixture was slowly heated to release a large amount of nitrogen. After complete nitrogen excretion the mixture was heated on a boiling water bath during 1 h and distilled with an effective deflegmator. Yield 57 g (60%) of isocyanate **8**. B.p. 58–63 °C. ^1H NMR (CDCl_3): δ 3.80 (q, $^3J_{\text{HF}} = 8.3$ Hz). ^{19}F NMR (CDCl_3): δ –73.82 (t, $^3J_{\text{FH}} = 8.3$ Hz).

4.6.1. General procedure for the synthesis of compounds **10a–e**, **10h–u**, **12**, **14**

—To a solution of 1 mmol of primary amine **9a–e, h–u**, morpholine **11** or alcohol **13** in 10 ml of dry diethyl ether or dry benzene 1 mmol of isocyanate **8** was added. The mixture was stirred during 4 h at rt and left overnight. The resulting precipitate was filtered and recrystallized from benzene. HPLC analysis revealed single peaks for all tested compounds.

4.6.1.1. 1-Phenyl-3-(2,2,2-trifluoroethyl)urea (10a): Yield 98 %, m.p. 151–153 °C. ^1H NMR (DMSO-d_6): δ 3.86 (dq, 2H, $^3J_{\text{HF}} = 10$ Hz, $^3J_{\text{HH}} = 6$ Hz, CF_3CH_2), 6.62 (t, 1H, $^3J_{\text{HH}} = 6$ Hz, CH_2NH), 6.90 (t, 1H, $^3J_{\text{HH}} = 7$ Hz, CH_{Ar}), 7.20 (t, 2H, $^3J_{\text{HH}} = 7$ Hz, CH_{Ar}), 7.38 (d, 2H, $^3J_{\text{HH}} = 7$ Hz, CH_{Ar}), 8.53 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ –71.48 (t, $^3J_{\text{FH}} = 10$ Hz). EI-MS (m/z): 218 (M^+). Anal. Calcd. for $\text{C}_9\text{H}_9\text{F}_3\text{N}_2\text{O}$: C, 49.55%; H, 4.16%; F, 26.12%; N, 12.84%; Found: C, 49.53%; H, 4.21%; F, 26.37%; N, 12.60%.

4.6.1.2. 1-(Pyridin-2-yl)-3-(2,2,2-trifluoroethyl)urea (10b): Yield 96 %, m.p. 160–161 °C. ^1H NMR (DMSO-d_6): δ 3.96 (dq, 2H, $^3J_{\text{HF}} = 10$ Hz, $^3J_{\text{HH}} = 7$ Hz, CF_3CH_2), 6.90 (t, 1H, $^3J_{\text{HH}} = 7$ Hz, CH_2NH), 7.20 (d, 1H, $^3J_{\text{HH}} = 7$ Hz, CH_{Ar}), 7.66 (t, 1H, $^3J_{\text{HH}} = 7$ Hz, CH_{Ar}), 8.14 (t, 1H, $^3J_{\text{HH}} = 7$ Hz, CH_{Ar}), 8.60 (d, 1H, $^3J_{\text{HH}} = 7$ Hz, CH_{Ar}), 9.50 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ –71.02 (t, $^3J_{\text{FH}} = 10$ Hz). EI-MS (m/z): 219 (M^+). Anal. Calcd. for $\text{C}_8\text{H}_8\text{F}_3\text{N}_3\text{O}$: C, 43.84%; H, 3.68%; F, 26.01%; N, 19.17%; Found: C, 43.68%; H, 3.55%; F, 26.12%; N, 19.29%.

4.6.1.3. 1-(Pyridin-3-yl)-3-(2,2,2-trifluoroethyl)urea (10c): Yield 94 %, m.p. 197–199 °C. ^1H NMR (DMSO-d_6): δ 3.76 (dq, 2H, $^3J_{\text{HF}} = 10$ Hz, $^3J_{\text{HH}} = 7$ Hz, CF_3CH_2), 6.78 (t, 1H, $^3J_{\text{HH}} = 7$ Hz, CH_2NH), 7.20 (dd, 1H, $^3J_{\text{HH}} = 7$ Hz, $^4J_{\text{HH}} = 2$ Hz, CH_{Ar}), 7.92 (d, 1H, $^3J_{\text{HH}} = 7$ Hz, CH_{Ar}), 8.12 (d, 1H, $^4J_{\text{HH}} = 2$ Hz, CH_{Ar}), 8.48 (s, 1H, CH_{Ar}), 8.78 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ –71.10 (t, $^3J_{\text{FH}} = 10$ Hz). EI-MS (m/z): 219 (M^+). Anal. Calcd. for $\text{C}_8\text{H}_8\text{F}_3\text{N}_3\text{O}$: C, 43.84%; H, 3.68%; F, 26.01%; N, 19.17%; Found: C, 43.58%; H, 3.59%; F, 26.14%; N, 19.32%.

4.6.1.4. 1-(Pyridin-4-yl)-3-(2,2,2-trifluoroethyl)urea (10d): Yield 99 %, m.p. 150–151 °C. ^1H NMR (acetone-d_6): δ 4.02 (dq, 2H, $^3J_{\text{HF}} = 10$ Hz, $^3J_{\text{HH}} = 7$ Hz, CF_3CH_2), 6.70 (t,

1H, $^3J_{\text{HH}} = 7$ Hz, CH₂NH), 7.48 (d, 2H, $^3J_{\text{HH}} = 6$ Hz, CH_{Ar}), 8.36 (d, 2H, $^3J_{\text{HH}} = 6$ Hz, CH_{Ar}), 8.74 (s, 1H, NH). ^{19}F NMR (DMSO-*d*₆): δ -70.92 (t, $^3J_{\text{FH}} = 10$ Hz). EI-MS (*m/z*): 219 (*M*⁺). Anal. Calcd. for C₈H₈F₃N₃O: C, 43.84%; H, 3.68%; F, 26.01%; N, 19.17%; Found: C, 43.72%; H, 3.76%; F, 25.93%; N, 19.03%.

4.6.1.5. 1-(6-Methylpyridin-2-yl)-3-(2,2,2-trifluoroethyl)urea (10e): Yield 98 %, m.p. 145–147 °C. ^1H NMR (DMSO-*d*₆): δ 2.42 (s, 3H, CH₃), 3.98 (dq, 2H, $^3J_{\text{HF}} = 9$ Hz, $^3J_{\text{HH}} = 7$ Hz, CF₃CH₂), 6.94 (d, 1H, $^3J_{\text{HH}} = 7$ Hz, CH_{Ar}), 7.12 (d, 1H, $^3J_{\text{HH}} = 7$ Hz, CH_{Ar}), 7.52 (t, 1H, $^3J_{\text{HH}} = 7$ Hz, CH_{Ar}), 8.94 (br. s, 1H, CH₂NH), 9.38 (s, 1H, NH). ^{19}F NMR (DMSO-*d*₆): δ -71.04 (t, $^3J_{\text{FH}} = 9$ Hz). EI-MS (*m/z*): 234 (*M*⁺ + 1). Anal. Calcd. for C₉H₁₀F₃N₃O: C, 46.36%; H, 4.32%; F, 24.44%; N, 18.02%; Found: C, 46.22%; H, 4.38%; F, 24.62%; N, 17.88%.

4.6.1.6. 1-(5-Methylisoxazol-3-yl)-3-(2,2,2-trifluoroethyl)urea (10h): Yield 98%, m.p. 181–182 °C. ^1H NMR (DMSO-*d*₆): δ 2.30 (s, 3H, CH₃), 3.88 (dq, 2H, $^3J_{\text{HF}} = 9$ Hz, $^3J_{\text{HH}} = 6$ Hz, CF₃CH₂), 6.35 (s, 1H, =CH), 6.82 t (1H, $^3J_{\text{HH}} = 6$ Hz, CH₂NH), 9.38 (s, 1H, NH). ^{19}F NMR (DMSO-*d*₆): δ -70.90 (t, $^3J_{\text{FH}} = 9$ Hz). EI-MS (*m/z*): 223 (*M*⁺). Anal. Calcd. for C₇H₈F₃N₃O₂: C, 37.68%; H, 3.61%; F, 25.54%; N, 18.83%; Found: C, 37.70%; H, 3.45%; F, 25.64%; N, 18.96%.

4.6.1.7. 1-(2,2,2-Trifluoroethyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)urea (10i): Yield 90 %, m.p. 164–165 °C. ^1H NMR (DMSO-*d*₆): δ 4.02 (dq, 2H, $^3J_{\text{HF}} = 10$ Hz, $^3J_{\text{HH}} = 7$ Hz, CF₃CH₂), 7.55 (t, 1H, $^3J_{\text{HH}} = 7$ Hz, CH₂NH), 12.04 (s, 1H, NH). ^{19}F NMR (DMSO-*d*₆): δ -70.90 (t, 3F, $^3J_{\text{HF}} = 10$ Hz), 18.20 (s, 3F). EI-MS (*m/z*): 294 (*M*⁺). Anal. Calcd. for C₆H₄F₆N₄OS: C, 24.50%; H, 1.37%; F, 38.75%; N, 19.05%; Found: C, 24.29%; H, 1.28%; F, 38.62%; N, 19.15%.

4.6.1.8. 1-(5-(Ethylthio)-1,3,4-thiadiazol-2-yl)-3-(2,2,2-trifluoroethyl)urea (10j): Yield 95%, m.p. 215–216 °C. ^1H NMR (DMSO-*d*₆): δ 1.34 (t, 3H, CH₃, $^3J_{\text{HH}} = 7$ Hz), 3.30 (q, 2H, $^3J_{\text{HH}} = 7$ Hz, CH₂S), 4.02 (dq, 2H, $^3J_{\text{HF}} = 9$ Hz, $^3J_{\text{HH}} = 6$ Hz, CF₃CH₂), 6.85 (t, 1H, $^3J_{\text{HH}} = 6$ Hz, CH₂NH), 10.88 (br.s, 1H, NH). ^{19}F NMR (DMSO-*d*₆): δ -71.02 (t, $^3J_{\text{FH}} = 9$ Hz). EI-MS (*m/z*): 286 (*M*⁺). Anal. Calcd. for C₇H₉F₃N₄OS₂: C, 29.37%; H, 3.17%; F, 19.91%; N, 19.57%; Found: C, 29.56%; H, 3.45%; F, 19.82%; N, 19.76%.

4.6.1.9. 1-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-(2,2,2-trifluoroethyl)urea (10k): Yield 86 %, m.p. 231–233 °C. ^1H NMR (DMSO-*d*₆): δ 2.20 (s, 3H, CH₃C), 3.08 (s, 3H, CH₃N), 3.86 (dq, 2H, $^3J_{\text{HF}} = 9$ Hz, $^3J_{\text{HH}} = 6$ Hz, CF₃CH₂), 6.82 (t, 1H, $^3J_{\text{HH}} = 6$ Hz, CH₂NH), 7.28 (t, 1H, $^3J_{\text{HH}} = 7$ Hz, CH_{Ar}), 7.38 (d, 2H, $^3J_{\text{HH}} = 7$ Hz, CH_{Ar}), 7.40 (s, 1H, NH), 7.48 (m, 2H, CH_{Ar}). ^{19}F NMR (DMSO-*d*₆): δ -70.84 (t, $^3J_{\text{FH}} = 9$ Hz). EI-MS (*m/z*): 328 (*M*⁺). Anal. Calcd. for C₁₄H₁₅F₃N₄O₂: C, 51.22%; H, 4.61%; F, 17.36%; N, 17.07%; Found: C, 51.28%; H, 4.48%; F, 17.60%; N, 17.17%.

4.6.1.10. 1-(Benzo[d]thiazol-2-yl)-3-(2,2,2-trifluoroethyl)urea (10l): Yield 95%, m.p. 308–309 °C. ^1H NMR (DMSO-*d*₆): δ 3.95 (dq, 2H, $^3J_{\text{HF}} = 10$ Hz, $^3J_{\text{HH}} = 6$ Hz, CF₃CH₂), 7.15 (t, 1H, $^3J_{\text{HH}} = 7$ Hz, CH_{Ar}), 7.22 (t, 1H, $^3J_{\text{HH}} = 6$ Hz, CH₂NH), 7.30 (t, 1H, $^3J_{\text{HH}} = 8$ Hz, CH_{Ar}), 7.58 (d, 1H, $^3J_{\text{HH}} = 8$ Hz, CH_{Ar}), 7.74 (d, 1H, $^3J_{\text{HH}} = 7$ Hz, CH_{Ar}), 10.72 (s, 1H,

NH). ^{19}F NMR (DMSO- d_6): δ -70.93 (t, $^3J_{\text{FH}} = 10$ Hz). EI-MS (m/z): 275 (M^+). Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{F}_3\text{N}_3\text{OS}$: C, 43.64%; H, 2.93%; F, 20.71%; N, 15.27%; Found: C, 43.69%; H, 2.76%; F, 20.79%; N, 15.21%.

4.6.1.11. 1-(4-Methylbenzo[d]thiazol-2-yl)-3-(2,2,2-trifluoroethyl)urea: Yield 70%, m.p. 185–186 °C. ^1H NMR (DMSO- d_6): δ 2.27 (s, 3H, CH_3), 3.88 (dq, 2H, $^3J_{\text{HF}} = 9$ Hz, $^3J_{\text{HH}} = 6$ Hz, CF_3CH_2), 7.21 (t, 1H, $^3J_{\text{HH}} = 6$ Hz, CH_2NH), 7.32 (d, 1H, $^3J_{\text{HH}} = 6$ Hz, CH_{Ar}), 7.35 (s, 1H, CH_{Ar}), 7.93 (s, 1H, NH). 8.15 (d, 1H, $^3J_{\text{HH}} = 6$ Hz, CH_{Ar}). ^{19}F NMR (DMSO- d_6): δ -70.98 (t, $^3J_{\text{FH}} = 9$ Hz). EI-MS (m/z): 289 (M^+). Anal. Calcd. for $\text{C}_{11}\text{H}_{10}\text{F}_3\text{N}_3\text{OS}$: C, 45.67%; H, 3.48%; F, 19.70%; N, 14.53%; Found: C, 45.46%; H, 3.54%; F, 19.92%; N, 14.69%.

4.6.1.12. 1-(4,6-Dimethylbenzo[d]thiazol-2-yl)-3-(2,2,2-trifluoroethyl)urea (10n): Yield 94 %, m.p. 291–293 °C. ^1H NMR (DMSO- d_6): δ 2.35 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.77 (dq, 2H, $^3J_{\text{HF}} = 9$ Hz, $^3J_{\text{HH}} = 6$ Hz, CF_3CH_2), 6.84 (s, 1H, CH_{Ar}), 7.15 (t, 1H, $^3J_{\text{HH}} = 6$ Hz, CH_2NH), 7.35 (s, 1H, CH_{Ar}), 10.80 (s, 1H, NH). ^{19}F NMR (DMSO- d_6): δ -70.99 (t, $^3J_{\text{FH}} = 9$ Hz). EI-MS (m/z): 303 (M^+). Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{F}_3\text{N}_3\text{OS}$: C, 47.52%; H, 3.99%; F, 18.79%; N, 13.85%; Found: C, 47.36%; H, 3.74%; F, 18.92%; N, 13.69%.

4.6.1.13. 1-(4-Chlorobenzo[d]thiazol-2-yl)-3-(2,2,2-trifluoroethyl)urea (10o): Yield 54%, m.p. 245–246 °C. ^1H NMR (DMSO- d_6): δ 3.87 (dq, 2H, CF_3CH_2 , $^3J_{\text{HF}} = 9$ Hz, $^3J_{\text{HH}} = 6$ Hz), 7.29 (dd, 1H, $^3J_{\text{HH}} = 9$ Hz, $^4J_{\text{HH}} = 2$ Hz, CH_{Ar}), 7.42 (d, 1H, $^4J_{\text{HH}} = 2$ Hz, CH_{Ar}), 7.60 (t, 1H, $^3J_{\text{HH}} = 6$ Hz, CH_2NH), 8.21 (s, 1H, NH), 8.25 (d, 1H, $^3J_{\text{HH}} = 9$ Hz, CH_{Ar}). ^{19}F NMR (DMSO- d_6): δ -70.99 (t, $^3J_{\text{FH}} = 9$ Hz). EI-MS (m/z): 309 (M^+). Anal. Calcd. for $\text{C}_{10}\text{H}_7\text{ClF}_3\text{N}_3\text{OS}$: C, 38.78%; H, 2.28%; F, 18.40%; N, 13.57%; Found: C, 38.66%; H, 2.44%; F, 18.62%; N, 13.39%.

4.6.1.14. 1-(Furan-2-ylmethyl)-3-(2,2,2-trifluoroethyl)urea (10p): Yield 90 %, m.p. 120–122 °C. ^1H NMR (DMSO- d_6): δ 3.70 (dq, 2H, $^3J_{\text{HF}} = 10$ Hz, $^3J_{\text{HH}} = 7$ Hz, CF_3CH_2), 4.24 (d, 2H, $^3J_{\text{HH}} = 6$ Hz, CH_2N), 6.10 (d, 1H, $^3J_{\text{HH}} = 4$ Hz, CH_{Ar}), 6.30–6.50 (m, 3H, $2\text{CH}_{\text{Ar}} + \text{CF}_3\text{CH}_2\text{NH}$), 7.36 (s, 1H, NH). ^{19}F NMR (DMSO- d_6): δ -70.96 (t, $^3J_{\text{FH}} = 10$ Hz). EI-MS (m/z): 222 (M^+). Anal. Calcd. for $\text{C}_8\text{H}_9\text{F}_3\text{N}_2\text{O}_2$: C, 43.25%; H, 4.08%; F, 25.65%; N, 12.61%; Found: C, 43.50%; H, 4.35%; F, 25.78%; N, 12.42%.

4.6.1.15. 1-(3,4-Dimethoxyphenethyl)-3-(2,2,2-trifluoroethyl)urea (10q): Yield 84 %, m.p. 135–136 °C. ^1H NMR (DMSO- d_6): δ 2.67 (t, 2H, $^3J_{\text{HH}} = 7$ Hz, CH_2Ar), 3.29 (q, 2H, $^3J_{\text{HH}} = 7$ Hz, $\text{CH}_2\text{CH}_2\text{N}$), 3.70 (m + 2s, 8H, $\text{CF}_3\text{CH}_2 + \text{CH}_3\text{O}$), 5.83 (t, 1H, $^3J_{\text{HH}} = 7$ Hz, $\text{CH}_2\text{CH}_2\text{NH}$), 6.35 (t, 1H, $^3J_{\text{HH}} = 6$ Hz, $\text{CF}_3\text{CH}_2\text{NH}$), 6.70 (m, 3H, CH_{Ar}). ^{19}F NMR (DMSO- d_6): δ -71.35 (t, $^3J_{\text{FH}} = 9$ Hz). EI-MS (m/z): 306 (M^+). Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_3$: C, 50.98%; H, 5.68%; F, 18.61%; N, 9.15%; Found: C, 50.76%; H, 3.76%; F, 18.87%; N, 9.04%.

4.6.1.16. 2-(3,4-Dimethoxybenzoyl)-N-(2,2,2-trifluoroethyl)hydrazine-1-carboxamide (10r): Yield 77%, m.p. 198–199 °C. ^1H NMR (DMSO- d_6): δ 4.85 (s+m, 8H, $\text{CH}_3\text{O} + \text{CF}_3\text{CH}_2$), 7.02 (d, 1H, $^3J_{\text{HH}} = 7$ Hz, CH_{Ar}), 7.16 (t, 1H, $^3J_{\text{HH}} = 6$ Hz, CH_2NH), 7.56 (s+d, 2H, $^3J_{\text{HH}} = 7$ Hz, CH_{Ar}), 8.28 (s, 1H, NH), 10.14 (s, 1H, NH). ^{19}F NMR (DMSO- d_6): δ

–70.13 (t, $^3J_{\text{FH}} = 9$ Hz). EI-MS (m/z): 322 ($\text{M}^+ + 1$). Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_4$: C, 44.86%; H, 4.39%; F, 17.74%; N, 13.08%; Found: C, 44.72%; H, 4.44%; F, 17.62%; N, 17.15%.

4.6.1.17. 2-(2-Bromobenzoyl)-N-(2,2,2-trifluoroethyl)hydrazine-1-carboxamide (10s):

Yield 73%, m.p. 148–150 °C. ^1H NMR ($\text{DMSO}-d_6$): δ 3.86 (dq, 2H, CF_3CH_2 , $^3J_{\text{HF}} = 9$ Hz, $^3J_{\text{HH}} = 6$ Hz), 6.82 t (1H, CH_2NH , $^3J_{\text{HH}} = 6$ Hz), 7.24–7.45 (m, 2H, CH_{Ar}), 7.46–7.70 (m, 2H, CH_{Ar}), 8.48 (s, 1H, NH), 10.08 (s, 1H, NH). ^{19}F NMR ($\text{DMSO}-d_6$): δ –70.96 (t, $^3J_{\text{FH}} = 9$ Hz). EI-MS (m/z): 399 (M^+). Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{BrF}_3\text{N}_3\text{O}_2$: C, 35.32%; H, 2.67%; F, 16.76%; N, 12.36%; Found: C, 35.60%; H, 2.41%; F, 16.74%; N, 12.22%.

4.6.1.18. 1-Isobutyl-3-(2,2,2-trifluoroethyl)urea (10t): Yield 99 %, m.p. 103–105 °C. ^1H NMR ($\text{DMSO}-d_6$): δ 0.86 (d, 6H, CH_3 , $^3J_{\text{HH}} = 7$ Hz), 1.63 (sept, 1H, CH, $^3J_{\text{HH}} = 7$ Hz), 2.86 (t, 2H, CHCH_2 , $^3J_{\text{HH}} = 7$ Hz), 3.76 dq (2H, CF_3CH_2 , $^3J_{\text{HF}} = 10$ Hz, $^3J_{\text{HH}} = 7$ Hz), 5.98 (t, 1H, NH, $^3J_{\text{HH}} = 7$ Hz), 6.28 (t, 1H, NH, $^3J_{\text{HH}} = 7$ Hz). ^{19}F NMR ($\text{DMSO}-d_6$): δ –71.16 (t, $^3J_{\text{FH}} = 10$ Hz). EI-MS (m/z): 199 ($\text{M}^+ + 1$). Anal. Calcd. for $\text{C}_7\text{H}_{13}\text{F}_3\text{N}_2\text{O}$: C, 42.42%; H, 6.61%; F, 28.76%; N, 14.13%; Found: C, 42.50%; H, 6.49%; F, 28.57%; N, 14.30%.

4.6.1.19. 1-(4-Chlorobenzyl)-3-(2,2,2-trifluoroethyl)urea (10u): Yield 97%, m.p. 158–159 °C. ^1H NMR (acetone- d_6): δ 3.77 (dq, 2H, CF_3CH_2 , $^3J_{\text{HF}} = 9$ Hz, $^3J_{\text{HH}} = 6$ Hz), 4.25 (d, 2H, CH_2Ar , $^3J_{\text{HH}} = 6$ Hz), 6.43 (br. s, 2H, CH_2NH), 7.26 (s, 4H, CH_{Ar}). ^{19}F NMR (acetone- d_6): δ –71.29 (t, $^3J_{\text{FH}} = 9$ Hz). EI-MS (m/z): 267 (M^+). Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{ClF}_3\text{N}_2\text{O}$: C, 45.04%; H, 3.78%; F, 13.30%; N, 10.51%; Found: C, 45.16%; H, 3.72%; F, 13.82%; N, 10.27%.

4.6.1.20. N-(2,2,2-trifluoroethyl)morpholine-4-carboxamide (12): Yield 99%, m.p. 118–119 °C. ^1H NMR ($\text{DMSO}-d_6$): δ 3.34 (m, 4H, CH_2N), 3.60 (m, 4H, CH_2O), 3.92 (dq, 2H, CF_3CH_2 , $^3J_{\text{HF}} = 9$ Hz, $^3J_{\text{HH}} = 6$ Hz), 6.60 (br. s, 1H, NH). ^{19}F NMR ($\text{DMSO}-d_6$): δ –71.03 (t, $^3J_{\text{FH}} = 9$ Hz). EI-MS (m/z): 212 (M^+). Anal. Calcd. for $\text{C}_7\text{H}_{11}\text{F}_3\text{N}_2\text{O}_2$: C, 39.63%; H, 5.23%; F, 26.86%; N, 13.20%; Found: C, 39.56%; H, 3.45%; F, 26.78%; N, 13.16%.

4.6.1.21. 4-Fluorobenzyl (2,2,2-trifluoroethyl)carbamate (14): Yield 98 %, m.p. 58–60 °C. ^1H NMR (acetone- d_6): δ 3.83 (dq, 2H, CF_3CH_2 , $^3J_{\text{HF}} = 9$ Hz, $^3J_{\text{HH}} = 6$ Hz), 5.10 (s, 3H, CH_2NH), 7.02 (t, 2H, CH_{Ar} , $^3J_{\text{HF}} = 9$ Hz), 7.46 (m, 2H, CH_{Ar}). ^{19}F NMR (acetone- d_6): δ –113.08 (s, 1F), –71.36 (t, 3F, $^3J_{\text{FH}} = 9$ Hz). EI-MS (m/z): 251 ($\text{M}^+ + 1$). Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{F}_4\text{NO}_2$: C, 47.82%; H, 3.61%; F, 30.25%; N, 5.58%; Found: C, 47.65%; H, 3.43%; F, 30.29%; N, 5.64%.

4.6.2. General procedure for the synthesis of compounds 10f, 10g—A solution of 1 mmol of isocyanate **8** in 5 ml of benzene was added to 1 mmol of amine **9f,g** in 10 ml of dry benzene and 0.2 ml of saturated ether solution of catalyst trimethylamine in a 50 ml glass ampoule. This ampoule was sealed and heated at 100 °C for 1.5–2 h. The ampoule was opened, the solvent was evaporated, and the residue was recrystallized from benzene.

4.6.2.1. 1-(Pyrimidin-2-yl)-3-(2,2,2-trifluoroethyl)urea (10f): Yield 86 %, m.p. 190–191 °C. ^1H NMR ($\text{DMSO}-d_6$): δ 3.96 (dq, 2H, $^3J_{\text{HF}} = 9$ Hz, $^3J_{\text{HH}} = 7$ Hz, CF_3CH_2), 7.05 (t,

^1H , $^3J_{\text{HH}} = 7 \text{ Hz}$, CH_{Ar}), 8.58 (d, 2H, $^3J_{\text{HH}} = 7 \text{ Hz}$, CH_{Ar}), 9.50 (t, 1H, $^3J_{\text{HH}} = 7 \text{ Hz}$, CH_2NH), 10.05 (s, 1H, NH). ^{19}F NMR (DMSO- d_6): δ -70.74 (t, $^3J_{\text{FH}} = 9 \text{ Hz}$). EI-MS (m/z): 221 ($\text{M}^+ + 1$). Anal. Calcd. for $\text{C}_7\text{H}_7\text{F}_3\text{N}_4\text{O}$: C, 38.19%; H, 3.20%; F, 25.89%; N, 25.45%; Found: C, 38.02%; H, 3.38%; F, 25.72%; N, 25.28%.

4.6.2.2. N-(5-Methylisoxazol-3-yl)-4-(3-(2,2,2-trifluoroethyl)ureido)benzenesulfonamide (10g): Yield 86 %, m.p. 247–248 °C. ^1H NMR (DMSO- d_6): δ 2.20 (s, 3H, CH_3), 3.85 (dq, 2H, $^3J_{\text{HF}} = 9 \text{ Hz}$, $^3J_{\text{HH}} = 6 \text{ Hz}$, CF_3CH_2), 6.04 (s, 1H, =CH), 6.82 t (1H, $^3J_{\text{HH}} = 6 \text{ Hz}$, CH_2NH), 7.66 (d, 2H, $^3J_{\text{HH}} = 7 \text{ Hz}$, CH_{Ar}), 7.76 (d, 2H, $^3J_{\text{HH}} = 7 \text{ Hz}$, CH_{Ar}), 9.08 (s, 1H, NH), 11.08 (br. s, 1H, NH). ^{19}F NMR (DMSO- d_6): δ -71.01 (t, $^3J_{\text{FH}} = 9 \text{ Hz}$). EI-MS (m/z): 378 (M^+). Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{F}_3\text{N}_4\text{O}_4\text{S}$: C, 41.27%; H, 3.46%; F, 15.07%; N, 14.81%; Found: C, 41.36%; H, 3.24%; F, 15.22%; N, 14.62%.

Supplementary Material

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Highlights

- 3,3,3-Trifluoroethyl isocyanate was synthesized by a preparative pathway.
- Novel *N*-3,3,3-trifluoroethyl-substituted ureas and a carbamate were obtained.
- Anticancer activity of the synthesized ureas was evaluated by the NCI.
- The activity was demonstrated against individual cancer cell lines.

Scheme 1.

Synthesis of 3,3,3-trifluoroethyl- isocyanate **8**, carbamate **14** and ureas **10a-u** starting from perfluoroisobutene **1**.