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Copper catalyzed 1,3-dipolar cycloaddition reaction of azides with *N*-(2-trifluoroacetylaryl)propargylamines A mild entry to novel 1,4-disubstituted-[1,2,3]-triazole derivatives

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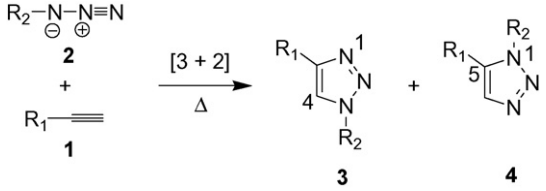
ABSTRACT

The synthesis of *N*-(2-trifluoroacetylaryl)propargylamines **10**–**14** and **17** is presented. The copper(I) catalyzed cycloaddition reaction of these propargylamines (dipolarophiles) with a series of azides (1,3-dipoles) **18**–**20**, **21** and **24** was found to proceed smoothly in dimethylsulfoxide at room temperature, to furnish the corresponding 1,4-disubstituted-[1,2,3]triazole derivatives **26**–**36** in moderate to good yields.

1. Introduction

[1,2,3]-Triazoles are an important class of five-membered nitrogen heterocycles, found in various therapeutic agents [1]. The well established approach utilized thus far for the synthesis of the [1,2,3]-triazole ring system relies on the thermal 1,3-dipolar Huisgen cycloaddition between alkynes **1** and azides **2** (Scheme 1) [2].

However, this strategy exhibits several disadvantages such as high temperature conditions with the potential for the decomposition of labile compounds and poor regioselectivity affording a mixture of 1,4 and 1,5-disubstituted triazoles (**3** and **4**), often difficult to separate. On the other hand the copper(I)-catalysis for the regioselective cycloaddition of terminal alkynes and azides originally developed by Sharpless and co-workers [3] and Meldal and co-workers [4] ('Click Chemistry') has become the most useful,



Scheme 1.

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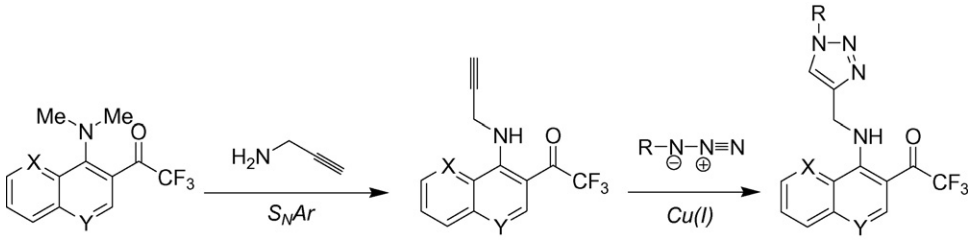
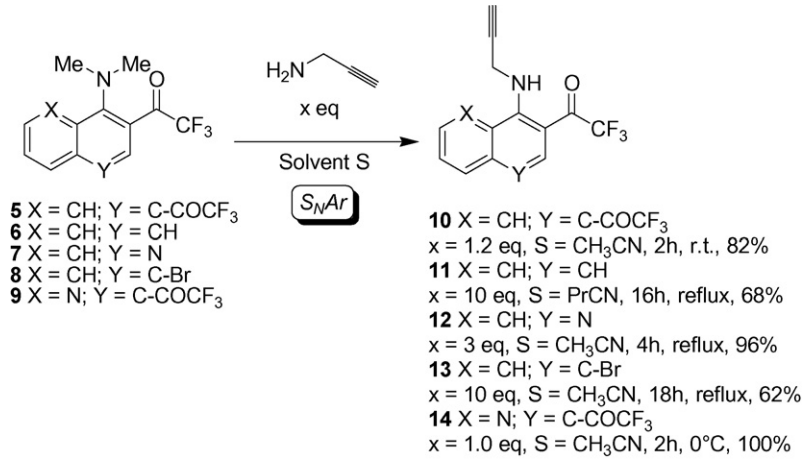
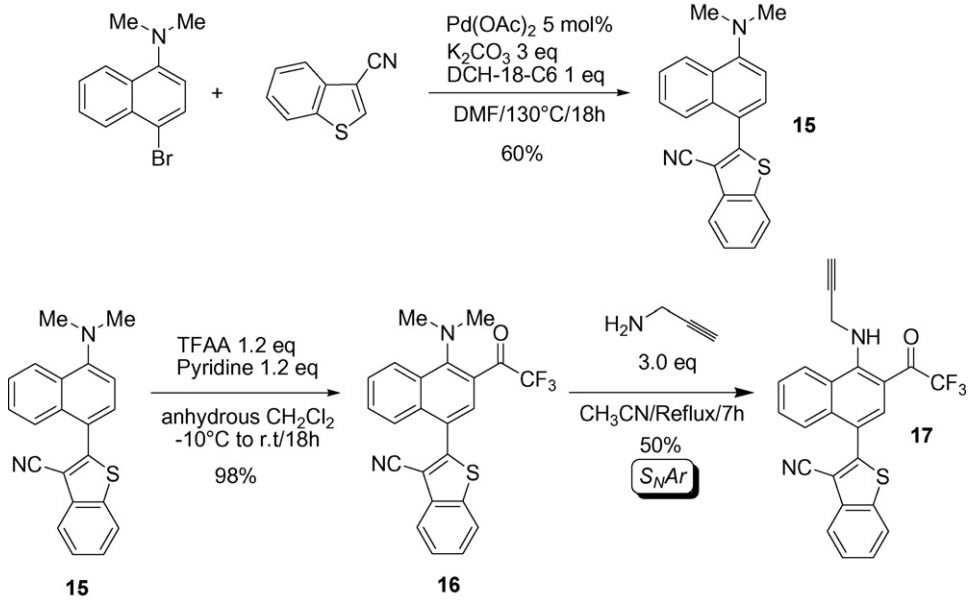


Scheme 2.



Scheme 3.



Scheme 4.

mild and efficient process to produce exclusively the 1,4-disubstituted triazoles. Trifluoromethyl moiety can greatly modify the physico-chemical features and thus the biological properties of a molecule [5], and there is an increasing demand to prepare such materials especially trifluoromethylated heterocycles because of their high value and pronouncing biological activity [6]. For some years we have been interested to develop new synthetic approaches to prepare fluorinated organic molecules. Among the recent studies developed in our laboratories, we have launched a program directed to the synthesis of novel trifluoromethylated heterocycles using aromatic nucleophilic substitution reactions of *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine [7], *N*,*N*-dimethyl-2-trifluoroacetyl-4-halo-1-naphthyl-amines [8], *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine [9], with amines, thiols and alcohols and we have shown that the corresponding exchanged products could be easily converted to various fluorinated fused-heterocycles of potential biological importance. Recently these aromatic nucleophilic substitution

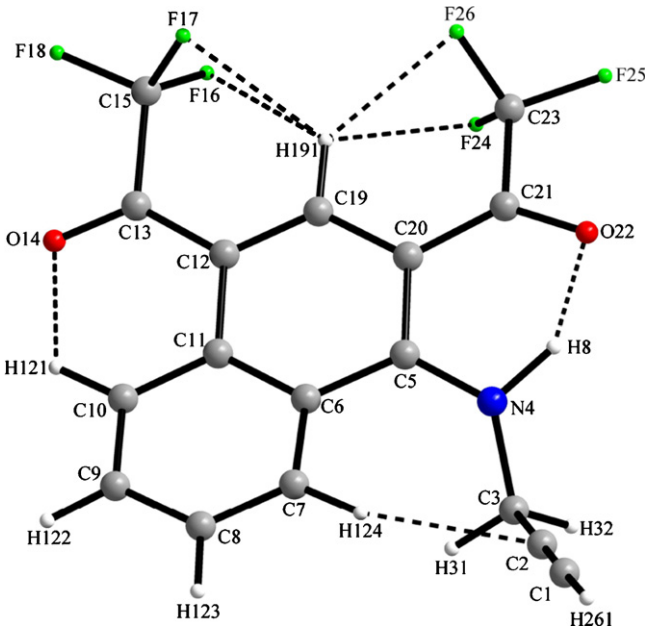


Fig. 1. Crystal structure of **10** with atomic labels. Hydrogen bonds and C–F···H interactions are also represented.

reactions were extended to 3-trifluoroacetyl-4-dimethylamino-quinoline [10] and *N*,*N*-dimethyl-2-trifluoroacetyl-1-naphthylamine [11]. Among the different nucleophiles used in these *N*–*N* exchanged reactions, propargylamine was found to be a good nucleophile giving access to novel *N*-(2-trifluoroacetylaryl)propargylamines. As part of a research program directed to the synthesis of novel trifluoromethylated aromatics and heterocycles using the peculiar reactivity of the propargylamine moiety [12], we envisaged to use the *N*-(2-trifluoroacetylaryl)propargylamines in the copper(I)-catalyzed 1,3-dipolar cycloaddition reactions with a series of benzylic azides, carbohydrate and nucleoside-derived azides that would give biologically relevant [1,2,3]-triazoles (Scheme 2); specifically the nucleosides derivatives that could be obtain are of significant importance because of the broad biological activity of natural and non-natural nucleosides, including some triazole nucleosides [13]. We wish to present herein our recent results.

2. Results and discussion

2.1. Syntheses of the dipolarophiles

1,3-Dipolarophiles **10**–**14** and **17** were prepared in moderate to quantitative yields (50–100%) through the *N*–*N* exchange reaction of the corresponding *N*,*N*-dimethylamino precursors with propargylamine (Schemes 3 and 4). Compound **10** was prepared as described in Ref. [12] in a 82% isolated yield from the *N*–*N* exchange reaction of *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine [7] with propargylamine (1.2 equivalent), in anhydrous acetonitrile at room temperature. The substrate **11** was obtained in 68% isolated yield from *N*,*N*-dimethyl-2-trifluoroacetyl-1-naphthylamine [11], but needed a large excess of propargylamine (10 equivalent) in refluxing propionitrile for 16 h for a complete conversion. 4-Amino quinoline derived substrate **12** was prepared as described in Ref. [10] and was obtained in a 96% isolated yield in acetonitrile under refluxing conditions for 4 h. The 4-bromo derivative **13** was prepared from *N*,*N*-dimethyl-2-trifluoroacetyl-4-bromo-1-naphthylamine [8] and needed as substrate **11**, a large excess of the amine (10 equivalent) in acetonitrile under refluxing conditions for 18 h. 8-Amino quinoline derived substrate **14** was prepared as described in Ref. [9] and was obtained in a quantitative yield; a temperature of 0 °C in acetonitrile for 2 h was crucial to get such high yield. *N*,*N*-dimethylamino precursors **5** and **9** were found to be the most reactive substrates, while **7** being the less reactive in this series. Benzo[*b*]thiophene is an important pharmacophore in medicinal chemistry [14] and therefore it was of interest to prepare derivative **17**; this substrate was prepared in two steps from the corresponding **15** (Scheme 4), which was in turn prepared in a 60% isolated yield from an original Heck reaction [16] developed in our laboratories, between *N*,*N*-dimethyl-4-bromo-1-naphthylamine [15] and benzo[*b*]thiophene-3-carbonitrile [16]. A moderate 50% isolated yield of **17** was obtained using an excess of propargylamine (3.0 equivalent) in refluxing acetonitrile for 7 h.

Table 1
F–H distances (Å) inside **10**

F16–H191	2.424 (6)
F25–H191	2.377 (5)
F17–H191	2.350 (6)
F24–H191	2.490 (6)

Table 2
Intra-hydrogen bonds inside **10**

D–H–A	D–H–A angle (°)	D–H bond length (Å)	H–A distance (Å)	D–A distance (Å)
N4–H8–O22	148	1.11	1.62	2.63 (2)
C10–H121–O14	124	1.06	2.14	2.87 (2)
C7–H124–C2	156	1.06	2.43	3.43 (2)

D: donor; A: acceptor.

All the substrates **10**–**14** and **17** were obtained with a free NH with a noticeable deshielded peak of the amino proton ($\delta_H > 9.0$ ppm) in the proton NMR, due to hydrogen bonding between NH and C=O. All compounds were obtained as solids after evaporation of the solvent and recrystallization (**12** and **14**) or after silica gel chromatography purification and recrystallization (**10**, **11**, **13** and **17**). The crystal structure of substrate **10** [17][1] has been also confirmed by X-ray analysis (Fig. 1) and all the refined bond lengths of this molecule are in good agreement with those previously reported in the literature [18]. This structure shows clearly two intra-molecular hydrogen bonds (O14···H121 and O22···H8, Table 1) forcing both the position of C=O groups on a particular orientation. It has to be noted that four intra-molecule C–F···H–C distances in the structure are significantly shorter than the sum of the van der Waals radii of fluorine and hydrogen atoms (2.55 Å) [19] showing the presence of F···H weak bonds (F16, F17, F26 and F24 with H191, Table 2). These later block then the two CF_3 groups in one configuration without any disorder on fluorine atoms (in the opposite of what can be usually found in other similar structures). In that sense, it is very important to investigate the presence or not of F···H bonds because of their influence on the structure of the molecule and then on the reactivity of this later and because little is known about hydrogen bonds containing fluorine as one of the acting atoms [20].

The whole packing can be viewed like pseudo columns running along the *a*-axis of the unit-cell (Fig. 2). Inside these columns (Fig. 3), the packing is assumed by Π–Π interactions between phenyl rings of two consecutive **10** molecules (shortest distance between centres of two consecutive phenyl rings is 3.89 Å). Then

[1] CCDC 684268 reference contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

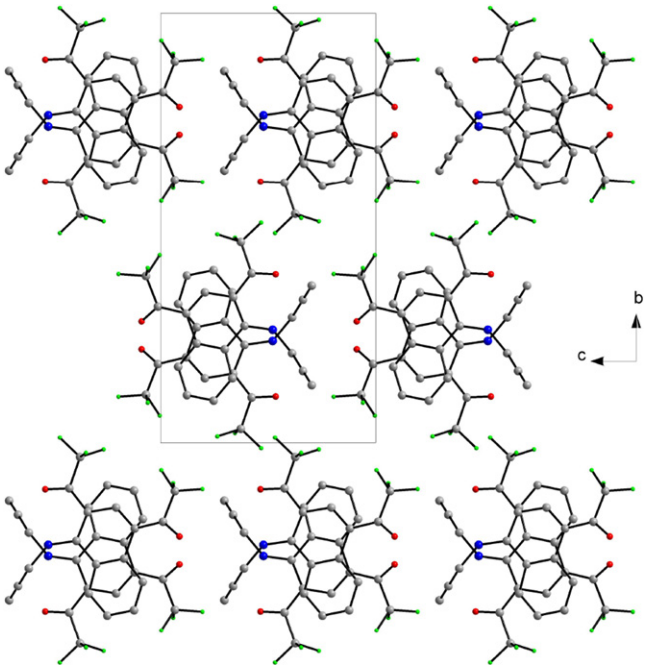


Fig. 2. Structural packing along *a*-axis of the unit-cell. For the clarity of the picture, hydrogen atoms have been omitted.

substrate **10** molecules stack one on the other one to form infinite columns. As no inter-molecule hydrogen bond has been found during the refinement, the structural cohesion between columns is assumed by van der Waals interactions.

2.2. Synthesis of the 1,3-dipoles

The benzylic azides **18**–**20** (Scheme 5) were conveniently prepared (71–91%) from known literature procedures using sodium azide (1.05 equivalent) and the corresponding benzylic bromides in acetonitrile at room temperature for 90 h [21].

5′-Azido-5′-deoxy-2′,3′-*O*-isopropylidene uridine **21** was prepared in three steps from commercially available uridine (Scheme 6). 2′,3′-*O*-Isopropylidene uridine **22** [22] and 5′-deoxy-2′,3′-*O*-isopropylidene-5′-*O*-methanesuflonyle uridine **23** [23] were obtained in respectively 88% and 63% isolated yields following literature procedures. Uridine derivative **21** [24] was then obtained in a 70% isolated yield through nucleophilic displacement of the –OMs using sodium azide (3 equivalent) in anhydrous DMF at 70 °C for 12 h. All the steps were completely stereoselective as evidenced by 1D and 2D NMR analysis.

2,3,5-Tri-*O*-benzoyl-*β*-D-ribofuranosyl azide **24** was obtained from commercially available 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose **25** in 95% isolated yield through the reaction of trimethylsilyl azide (1.1 equivalent) in the presence of $SnCl_4$ (5 mol%) according to [25] (Scheme 7). The reaction was completely stereoselective since only the *β*-anomer was obtained as already described in Ref. [25].

2.3. Coupling reactions

Substrate **10** and benzylic azide **18** were chosen as a model partners in the copper(I) catalyzed 1,3-dipolar cycloaddition; stoichiometric amount of CuI in the presence of *i*-Pr_2NEt in anhydrous THF as well as a stoichiometric combination of sodium ascorbate/$CuSO_4{\cdot}5H_2O$ [26] [to pre-form the copper(I) species] in

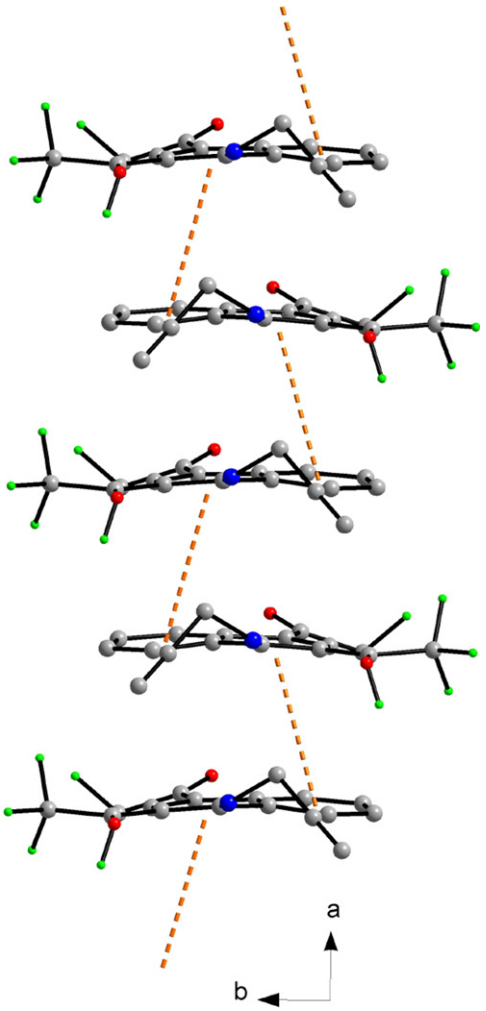
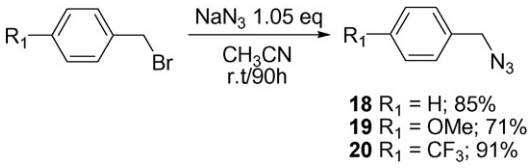


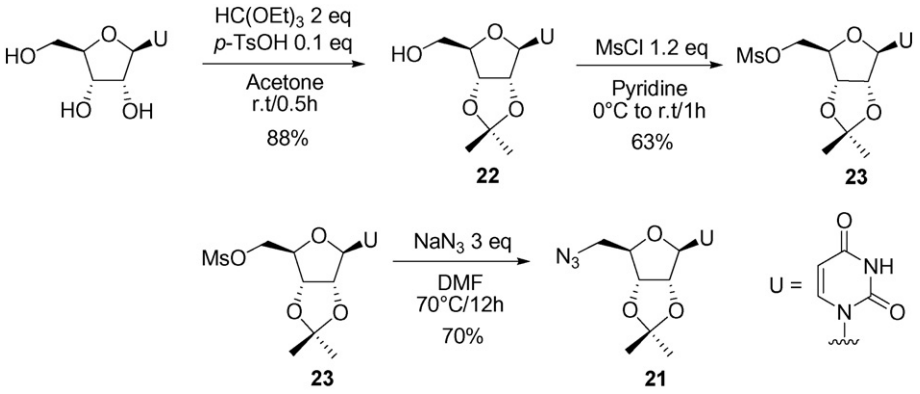
Fig. 3. Illustration of columns running along the *a*-axis of the unit-cell. Π–Π interactions between phenyl rings are represented as orange dash bonds. For clarity of the picture, hydrogen atoms have been omitted.



Scheme 5.

dimethylsulfoxide, afforded the desired [1,2,3]-triazole **26** in a 62–64% isolated yields (Scheme 8).

Although both conditions worked well with substrate **10**, it was then found that for other dipolarophiles, DMSO was a better solvent in order to improve the yields due to a better solubility of all reagents; in addition as already observed in the literature catalytical amount of Cu(I) was enough to achieve complete conversion. Under these mild conditions (room temperature for 24 h), [1,2,3]-triazoles **26**–**36** were obtained in good yields (Schemes 9–11). Classical *t*-BuOH/H_2O solvent combination [26] could not be used with our substrates as side-reactions were observed giving complex mixtures. In addition [1,2,3]-triazole **29** could not be obtained using **18** as 1,3-dipole despite many attempts and different conditions [increasing amount of Cu(I), increasing temperature] probably due to a competitive coordina-



Scheme 6.

Scheme 7.

tion between the –NH of the propargylamine moiety and the nitrogen of the quinoline.

As expected, the new triazoles were formed in a completely regioselective manner, with no contamination by the 1,5-regioisomer as highlighted from NOE experiments (Fig. 4): in the case of **26** irradiation of the resonance arising from H_b (triazole proton) resulted in the observation of strong NOE in the resonance arising from H_c and H_a. In carbohydrate and nucleoside series the reaction was found to be not only regioselective but also stereoselective.

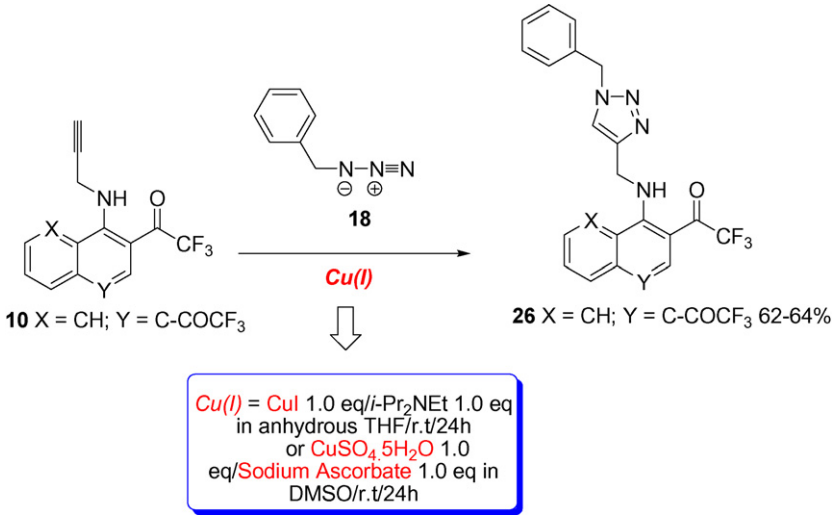
3. Conclusions

In this study we demonstrated that *N*-(2-trifluoroacetylaryl)-propargylamines **10**–**14** and **17** are good partners in copper(I) catalyzed 1,3-dipolar cycloaddition with a series of azides. The corresponding 1,4-disubstituted-[1,2,3]-triazole derivatives are novel compounds and were obtained in moderate to good yields under mild conditions. However the 8-amino quinoline substrate **14** failed to react under various conditions. We are currently extending this efficient approach to new substrates and more complex azides, especially in nucleoside series, as well as studying the "classical" thermal Huisgen 1,3-dipolar cycloaddition with the substrates presented in this study; in addition deprotection of the nucleosides is now actively pursued. We made significant progress in this area and the results will be presented in our forthcoming papers. Biological testings of all the triazole derivatives is currently under way.

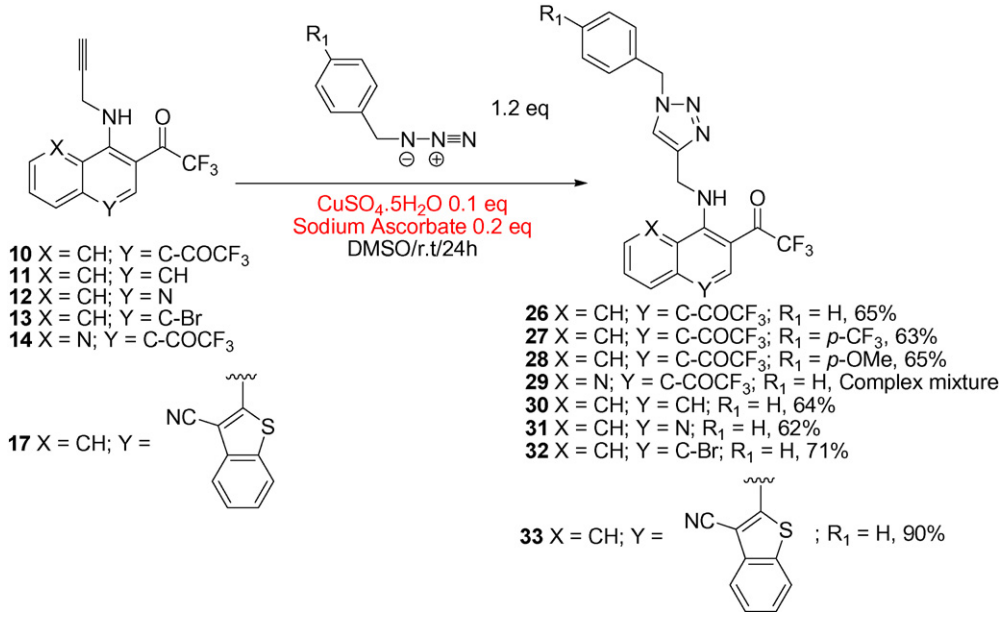
4. Experimental

4.1. General comments

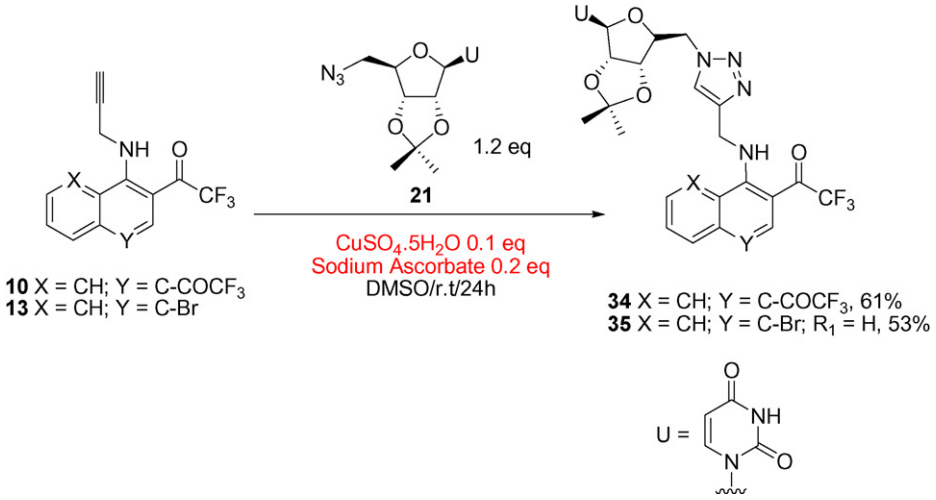
Solvents were distilled before use. Reagents were obtained commercially and used without further purification. Compounds **10** and **14** were already described in Refs. [12,9]. Benzo[*b*]thiophene-3-carbonitrile was prepared as described in Ref. [16]. Azides **18**–**20** were prepared as described in Ref. [21]. **21** and **22** were prepared as described in Ref. [18] and **23** as in Ref. [19]. **25** was prepared as described in Ref. [21]. ^{1}H, ^{19}F and ^{13}C NMR were recorded with a Bruker Avance 300 spectrometer (in $CDCl_3$) at 300, 282 and 75 MHz, respectively. Chemical shifts are given in ppm relative to residual peak of solvent (δ_H = 7.26 ppm for $CHCl_3$, δ_C = 77.0 ppm for $CDCl_3$) or $CFCl_3$ (^{19}F). Coupling constants are given in Hertz. Silica gel chromatography was performed on



Scheme 8.



Scheme 9.



Scheme 10.

Macherey–Nagel silica gel 60 M (0.04–0.063 mm). Solvents for chromatography and work-up are: benzene (BE), dichloromethane (DCM), ethyl acetate (EA), *n*-hexane (Hx), methanol (MET) and petroleum ether (PE). Mass spectra were recorded using a FINIGAN MAT 95 [EI, CI (CH_4 or NH_3) and ESI]. Melting points (uncorrected) were determined in capillary tubes on a Buchi apparatus.

4.2. X-ray characterization

4.2.1. Data collection

The data were processed using the KappaCCD analysis programs [27]. The lattice constants were refined by least-squares refinements. No absorption correction was applied to the data set and the data collection has been performed at 293 K.

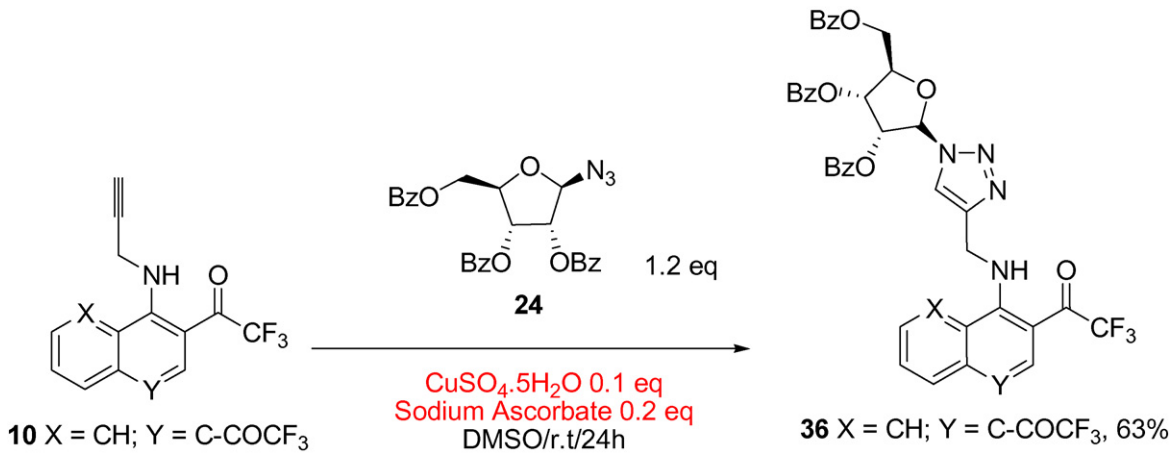
4.2.2. Structure solution and refinement

Complexes of **10** crystallizes in the monoclinic system. According to the observed systematic extinctions, its structure has been solved and refined in the $P2_1/a$ space group.

Structure of **10** has been solved by direct methods using the SIR97 program [28] combined with Fourier difference syntheses and refined against F using CRYSTALS program [29]. The hydrogen atoms have been either found by Fourier difference and located theoretically based on the conformation and environment of the supporting atom. Then, the positions and the isotropic displacement factors of these hydrogen atoms have been refined keeping some restraints with the supporting atom. All the atomic displacement parameters for non-hydrogen atoms have been refined anisotropically.

4.3. Synthesis of 15 and 16

In a 1 M solution of the benzo[*b*]thiophene-3-carbonitrile (0.24 g, 1.51 mmol) in DMF were successively added DCH-18-C-6 (1 eq, 0.562 g, 1.51 mmol), K_2CO_3 (3 eq, 0.626 g, 4.53 mmol) and the 4-bromo-*N*,*N*-dimethylnaphthalen-1-amine (1.1 equiv). The mixture was heated at 100 °C for 5 min and $Pd(OAc)_2$ (5 mol%, 0.017 g, 0.076 mmol) was added. The resulting mixture was then heated at 130 °C overnight. After cooling to room temperature, the



Scheme 11.

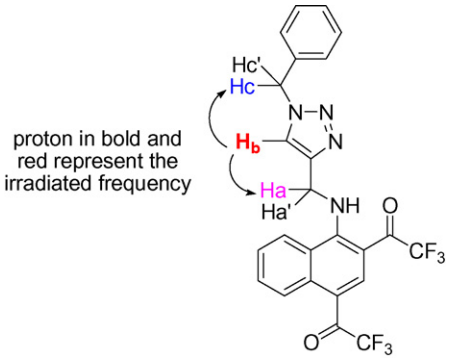
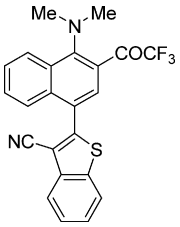


Fig. 4.

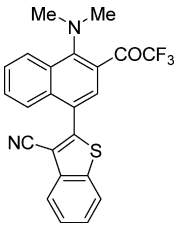
mixture was filtered over celite which was rinsed with CH_2Cl_2. The resulting organic layer was successively washed with water and brine, dried over $MgSO_4$, filtered and solvents were removed under reduced pressure. The crude product was purified by flash chromatography (DCM/PE = 5/5).

4.3.1. 2-(4-(Dimethylamino)naphthalen-1-yl)benzo[b]thiophene-3-carbonitrile, **15**



Yield: 60%, yellow solid, m.p.: 172–176 °C. ^{13}C NMR ($CDCl_3$): δ 45.0 ($2CH_3$), 106.1 (C), 113.0 (CH), 114.7 (C), 122.3 (CH), 122.5 (CH), 122.6 (C), 125.0 (CH), 125.6 (CH), 125.7 (CH), 126.0 (CH), 126.1 (CH), 127.0 (CH), 128.6 (C), 129.5 (CH), 132.7 (C), 138.3 (C), 138.6 (C), 153.3 (C), 154.9 (C). ^1H NMR ($CDCl_3$): δ 8.35 (1H, d, J = 9.2 Hz), 8.02–8.07 (2H, m), 7.89 (1H, d, J = 7.9 Hz), 7.47–7.65 (5H, m), 7.14 (1H, d, J = 7.7 Hz), 3.00 (6H, s, CH_3). HRMS (EI): m/z calcd for $C_{21}H_{16}N_2S$ 328.1034; found: 328.1048.

4.3.2. 2-(4-(Dimethylamino)-3-(2,2,2-trifluoroacetyl)naphthalen-1-yl)benzo[b]thiophene-3-carbonitrile, **16**

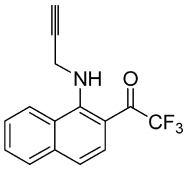


To a stirred solution of **15** (0.328 g, 1.0 mmol) and pyridine (1.2 mmol) in anhydrous dichloromethane (5 mL), was added dropwise an anhydrous dichloromethane solution (10 mL) containing trifluororoacetic anhydride (1.2 mmol) with cooling (−10 °C). When the addition was finished (30 min), the reaction mixture was slowly warmed-up to room temperature and stirred at this temperature for 18 h. The solution was quenched with H_2O (20 mL) and extracted with dichloromethane (2× 20 mL). The combined organic layers were washed with an aqueous solution of 1N HCl (2× 20 mL) and water (2× 20 mL) and dried over Na_2SO_4. Evaporation of the solvent left a yellowish oil (0.416 g, 0.98 mmol, 98%) as crude product of enough purity (>95%) for the next step. ^1H NMR ($CDCl_3$): δ 8.34–8.37 (1H, m, H_{arom}), 8.04 (1H, dd, J = 12.2, 1.5 Hz, H_{arom}), 7.92–8.06 (2H, m, H_{arom}), 7.76 (1H, s, H_{arom}), 7.51–7.67 (4H, m, H_{arom}), 3.08 (6H, s, CH_3). ^{19}F NMR ($CDCl_3$): δ −72.53. HRMS (EI): m/z calcd for $C_{23}H_{15}F_3N_2OS$ 424.0857; found: 424.0892.

4.4. General procedure for the synthesis of **10**–**14** *and* **17**

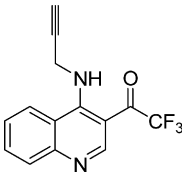
To a solution of **5**–**9** and **16** in acetonitrile (8 mL/1 mmol) were added propargylamine (1–10 equivalent) and the mixture was stirred at 0 °C-reflux temperature for 2–18 h. The solvent was evaporated to dryness to give the practically pure products **12** and **14**. In the case of **10**, **11**, **13** and **17** the crude product was purified by silica gel chromatography using Hx/BE (7/3) for **10**, Hx/EA (24/1) for **11**, Hx/EA (49/1) for **13** and PE/EA (98/2) for **17**, as eluent. In the case of **11**, propionitrile was used as a solvent.

4.4.1. 2,2,2-Trifluoro-1-(1-(propyl-2-ynylamino)naphthalen-2-yl)ethanone, **11**



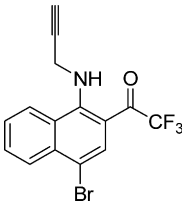
Yield: 68%, m.p.: 59–60 °C (Hx). ^{1}H NMR ($CDCl_3$): δ 9.83–9.07 (1H, br s, NH), 8.27–8.12 (1H, m, H_{arom}), 7.75–7.28 (4H, m, H_{arom}), 7.07 (1H, d, J = 9.0 Hz, H_{arom}), 4.32 (2H, dd, J = 6.0, 2.5 Hz, CH_2), 2.37 (1H, t, J = 2.5 Hz, ≡CH). ^{19}F NMR ($CDCl_3$): δ −69.08. IR (KBr): ν (cm^{-1}) 3321, 3052, 1621, 1584, 1532. HRMS (EI): m/z calcd for $C_{15}H_{10}F_3NO$ 277.0714; found: 277.0725.

4.4.2. 2,2,2-Trifluoro-1-(4-(prop-2-ynylamino)quinolin-3-yl)ethanone, **12**



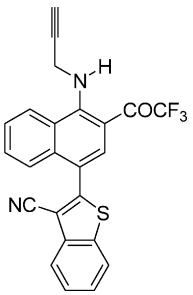
Yield: 96%, m.p.: 167–168 °C (Hx/EA). ^{1}H NMR ($CDCl_3$): δ 10.93–10.05 (1H, br s, NH), 8.97 (1H, q, J_{HF} = 2.0 Hz, H-2), 8.37 (1H, d, J = 8.0 Hz, H_{arom}), 8.10–7.30 (3H, m, H_{arom}), 4.63 (2H, dd, J = 6.0, 2.0 Hz, CH_2), 2.55 (1H, t, J = 2.0 Hz, ≡CH). ^{19}F NMR ($CDCl_3$): δ −68.85. IR (KBr): ν (cm^{-1}) 3183, 3068, 2103, 1635, 1575, 1530. HRMS (EI): m/z calcd for $C_{14}H_9F_3N_2O$ 278.0667; found: 278.0671.

4.4.3. 1-(4-Bromo-1-(prop-2-ynylamino)naphthalen-2-yl)-2,2,2-trifluoroethanone, **13**



Yield: 62%, m.p.: 105–106 °C (Hx/EA). ^{1}H NMR ($CDCl_3$): δ 9.80–9.27 (1H, br s, NH), 8.48–7.48 (5H, m, H_{arom}), 4.40 (2H, dd, J = 6.0, 2.2 Hz, CH_2), 2.44 (1H, t, J = 2.2 Hz, ≡CH). ^{19}F NMR ($CDCl_3$): δ −68.25. IR (KBr): ν (cm^{-1}) 3301, 3289, 3269, 2126, 1624, 1613, 1603, 1578, 1528. HRMS (EI): m/z calcd for $C_{15}H_9BrF_3NO$ 354.982; found: 354.984.

4.4.4. 2-(4-(Prop-2-ynylamino)-3-(2,2,2-trifluoroacetyl)naphthalen-1-yl)benzo[b]thiophene-3-carbonitrile, **17**

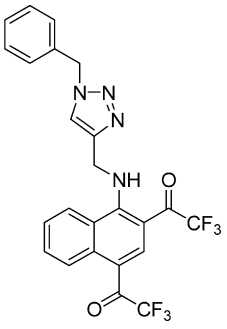


Yield: 50%, m.p.: 145 °C. ^{1}H NMR ($CDCl_3$): δ 10.09–10.12 (1H, br s, NH), 8.44 (1H, d, J = 8.2 Hz, H_{arom}), 8.01 (1H, d, J = 6.9 Hz, H_{arom}), 8.01 (1H, d, J = 7.7 Hz, H_{arom}), 7.90 (2H, m, H_{arom}), 7.59 (4H, m, H_{arom}), 4.52 (2H, dd, J = 2.4, 2.2 Hz, CH_2), 2.50 (1H, t, J = 2.1 Hz, ≡CH). ^{19}F NMR ($CDCl_3$): δ −69.14. HRMS (ESI): m/z calcd for $C_{24}H_{13}F_3N_2OS$ 434.0701; found: 434.0713.

4.5. General procedure for the synthesis of **26–35**

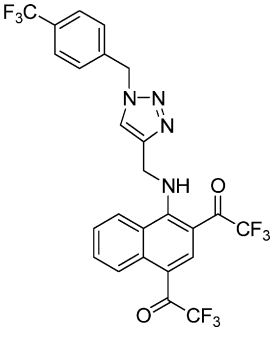
To a solution of dipolarophile **10**–**14** and **17** in dimethylsulfoxide (1 mL/1 mmol), 0.1 mmol of $CuSO_4{\cdot}5H_2O$ followed by 0.2 mmol of sodium ascorbate and 1.2 mmol of 1,3-dipole **18**–**21** and **24** were added. 1 mL of additional dimethylsulfoxide was then added in order to dissolve all materials. After 24 h of vigorous stirring, 2 mL of a saturated aqueous solution of ammonium chloride was then added and the organic phase extracted with EA (3× 10 mL). The combined organic phases were washed with brine (3× 10 mL), water (3× 10 mL), dried over Na_2SO_4, filtered and concentrated to yield a crude product which was purified by silica gel chromatography.

4.5.1. 1-[4-[(1-Benzyl-1H-[1,2,3]triazol-4-ylmethyl)-amino]-3-(2,2,2-trifluoro-acetyl)-naphthalen-1-yl]-2,2,2-trifluoro-ethanone, **26**



Yield: 65%, silica gel chromatography (PE/EA = 8/2 → 6/4), yellow solid, m.p.: 123 °C. ^{1}H NMR ($CDCl_3$): δ 11.02 (1H, br s, NH), 9.09 (1H, dd, J = 8.5, 0.8 Hz, H_{arom}), 8.59 (1H, s, H-3), 8.35 (1H, d, J = 8.3 Hz, H_{arom}), 7.69 (2H, m, H_{arom}), 7.57 (1H, s, $H_{triazole}$), 7.54 (1H, ddd, J = 8.5, 7.2, 1.1 Hz, H_{arom}), 7.35 (1H, m, H_{arom}), 7.25–7.29 (3H, m, H_{arom}), 5.56 (2H, s, –CH_2Ph), 5.19 (2H, d, J = 5.3 Hz, –CH_2NH). ^{19}F NMR ($CDCl_3$): δ −69.12, −69.16. HRMS (ESI): m/z calcd for $C_{24}H_{16}F_6N_4O_2$ 506.1177; found: 506.1182.

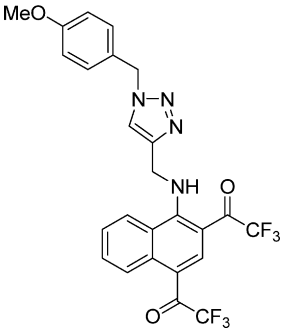
4.5.2. 2,2,2-Trifluoro-1-(3-(2,2,2-trifluoro-acetyl)-4-{[1-(4-trifluoromethyl-benzyl)-1H-[1,2,3]triazol-4-ylmethyl]-amino}-naphtalen-1-yl)-ethanone, **27**



Yield: 63%, silica gel chromatography (PE/EA = 9/1), yellow solid, m.p.: 125 °C. ^{1}H NMR ($CDCl_3$): δ 11.00 (1H, d, J = 4.8 Hz, NH), 9.08 (1H, dd, J = 8.5, 0.8 Hz, H_{arom}), 8.59 (1H, s, $H_{triazole}$), 8.33 (1H, d, J = 8.5 Hz, H_{arom}), 7.79 (1H, m, H_{arom}), 7.55 (2H, m, H_{arom}), 7.36 (2H,

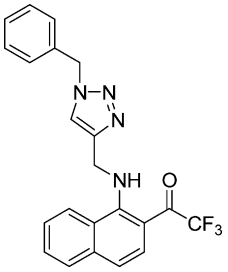
d, J = 8.1 Hz, H_{arom}), 6.89 (2H, d, J = 8.6 Hz, H_{arom}), 5.63 (2H, s, –CH_2Ph), 5.21 (2H, d, J = 5.5 Hz, –CH_2NH). ^{19}F NMR ($CDCl_3$): δ −69.29 (CF_3), −69.13 (2× $COCF_3$). HRMS (ESI): m/z calcd for $C_{25}H_{15}F_9N_4O_2$ 574.1051; found: 574.1064.

4.5.3. 2,2,2-Trifluoro-1-[4-{[1-(4-methoxy-benzyl)-1H-[1,2,3]triazol-4-ylmethyl]-amino}-3-(2,2,2-trifluoro-acetyl)-naphtalen-1-yl]-ethanone, **28**



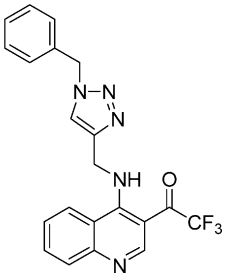
Yield: 65%, silica gel chromatography (PE/EA = 8/2), yellow solid, m.p.: 135 °C. ^{1}H NMR ($CDCl_3$): δ 11.00 (1H, s, NH), 9.09 (1H, d, J = 8.5 Hz, H_{arom}), 8.60 (1H, d, J = 8.60 Hz, H_{arom}), 8.32 (1H, d, J = 8.5 Hz, H_{arom}), 8.32 (1H, d, J = 8.5 Hz, H_{arom}), 7.78 (2H, m, H_{arom}), 7.50 (1H, m, H_{arom}), 7.47 (1H, s, $H_{triazole}$), 7.22 (1H, d, J = 8.8 Hz, H_{arom}), 6.89 (1H, d, J = 8.6 Hz, H_{arom}), 5.47 (2H, s, –CH_2Ph), 5.16 (2H, d, J = 5.5 Hz, –CH_2NH), 3.79 (3H, s, CH_3). ^{19}F NMR ($CDCl_3$): δ −69.04, −69.10. HRMS (ESI): m/z calcd for $C_{25}H_{18}F_6N_4O_3$ 536.1283; found: 536.1278.

4.5.4. 1-{1-[(1-Benzyl-1H-[1,2,3]triazol-4-ylmethyl)-amino]-naphtalen-2-yl}-2,2,2-trifluoro-etha-none, **30**



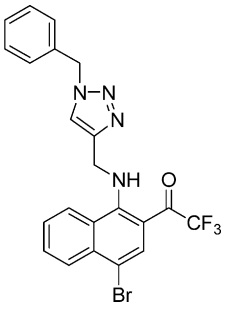
Yield: 64%, silica gel chromatography (PE/EA = 9/1), yellow solid, m.p.: 103–105 °C. ^{1}H NMR ($CDCl_3$): δ 10.08 (1H, s, NH), 8.31 (1H, d, J = 8.6 Hz, H_{arom}), 7.72 (2H, d, J = 9.0 Hz, H_{arom}), 7.62 (1H, m, H_{arom}), 7.49 (1H, s, $H_{triazole}$), 7.40 (2H, m, H_{arom}), 7.25 (3H, m, H_{arom}), 7.11 (2H, d, J = 9.0 Hz, H_{arom}), 5.54 (2H, s, –CH_2Ph), 5.08 (2H, d, J = 5.5 Hz, –CH_2NH). ^{19}F NMR ($CDCl_3$): δ –69.10 (3F, d, J_{HF} = 2.3 Hz). HRMS (ESI): m/z calcd for $C_{22}H_{17}F_3N_4O$ 410.1354; found: 410.1362.

4.5.5. 1-{4-[(1-Benzyl-1H-[1,2,3]triazol-4-ylmethyl)-amino]-quinolin-3-yl}-2,2,2-trifluoro-ethanone, **31**



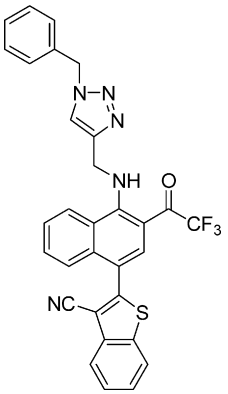
Yield: 62%, silica gel chromatography (PE/EA = 8/2), greenish solid, m.p.: 75–80 °C. ^{1}H NMR ($CDCl_3$): δ 10.89 (1H, d, J = 4.1 Hz, NH), 8.95 (1H, s, H_{arom}), 8.32 (1H, d, J = 8.6 Hz, H_{arom}), 7.97 (1H, d, J = 8.2 Hz, H_{arom}), 7.78 (1H, t, J = 6.9 Hz, H_{arom}), 7.54 (1H, s, $H_{triazole}$), 7.40 (6H, m, H_{arom}), 5.54 (2H, s, –CH_2Ph), 5.02 (2H, d, J = 5.8 Hz, –CH_2NH). ^{19}F NMR ($CDCl_3$): δ −68.84 (3F, d, J_{HF} = 2.28 Hz). HRMS (ESI): m/z calcd for $C_{21}H_{16}F_3N_5O$ 411.1307; found: 411.1312.

4.5.6. 1-{1-[(1-Benzyl-1H-[1,2,3]triazol-4-ylmethyl)-amino]-4-bromo-naphtalen-2-yl}-2,2,2-trifluoro-ethanone, **32**



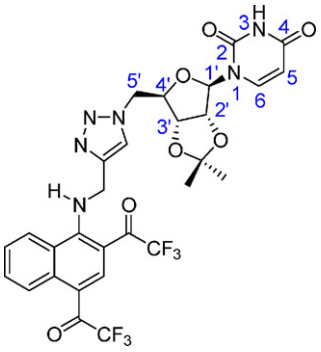
Yield: 71%, silica gel chromatography (PE/EA = 7/3), yellow solid, m.p.: 75–80 °C. ^{1}H NMR ($CDCl_3$): δ 9.98 (1H, d, J = 5.8 Hz, NH), 8.33 (1H, d, J = 8.4 Hz, H_{arom}), 8.20 (2H, d, J = 0.9 Hz, H_{arom}), 7.91 (1H, s, H_{arom}), 7.74 (1H, t, J = 7.2 Hz, H_{arom}), 7.52 (2H, t, J = 6.0 Hz, H_{arom}), 7.49 (1H, s, $H_{triazole}$), 7.36 (2H, d, J = 8.1 Hz, H_{arom}), 7.23 (1H, d, J = 1.9 Hz, H_{arom}), 5.54 (2H, s, –CH_2Ph), 5.02 (2H, d, J = 5.8 Hz, –CH_2NH). ^{19}F NMR ($CDCl_3$): δ −69.27. HRMS (ESI): m/z calcd for $C_{22}H_{16}BrF_3N_4O$ 488.046; found: 488.052.

4.5.7. 2-[4-[(1-Benzyl-1H-[1,2,3]triazol-4-ylmethyl)-amino]-3-(2,2,2-trifluoro-acetyl)-naphtalen-1-yl]-3-cyanobenzo[b]thiophene, **33**



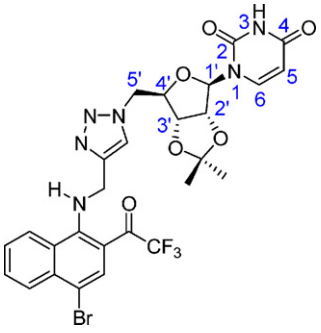
Yield: 90%, silica gel chromatography (PE/EA = 6/4 → 4/6), yellow solid, m.p.: 97 °C. ^{1}H NMR ($CDCl_3$): δ 10.47 (1H, t, J = 5.6 Hz, NH), 8.43 (1H, d, J = 8.2 Hz, H_{arom}), 8.03 (1H, d, J = 9.0 Hz, H_{arom}), 7.72 (3H, m, H_{arom}), 7.64 (4H, m, H_{arom}), 7.55 (m, 3H, H_{aro}), 7.36 (3H, m, H_{arom}), 5.58 (2H, s, –CH_2Ph), 5.17 (2H, d, J = 5.6 Hz, –CH_2NH). ^{19}F NMR ($CDCl_3$): δ −68.91 (3F, d, J_{HF} = 2.29 Hz). HRMS (ESI): m/z calcd for $C_{31}H_{20}F_3N_5OS$ 567.1341; found: 567.1351.

4.5.8. 5′-Deoxy-2′,3′-O-isopropylidene-5′-[4-{(2,4-bis-trifluoroacetyl)naphtalen-1-yl)aminomethyl}-1,2,3-triazol-1-yl]uridine, **34**



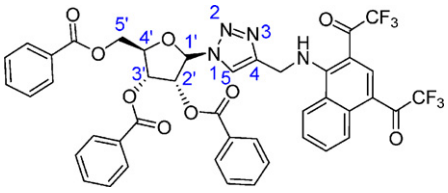
Yield: 61%, silica gel chromatography (DCM/MET = 99/1), yellowish viscous oil. ^{1}H NMR ($CDCl_3$): δ 10.97 (1H, d, J = 5.1 Hz, NH), 10.28 (1H, s, NH, N-3), 8.57 (1H, s, H_{arom}), 8.34 (1H, d, J = 8.3 Hz, H_{arom}), 7.77 (1H, t, J = 7.0 Hz, H_{arom}), 7.68 (1H, s, $H_{triazole}$), 7.54 (1H, t, J = 7.1 Hz, H_{arom}), 7.14 (1H, d, J = 8.1 Hz, H-5), 5.65 (1H, dd, J = 8.1, 0.7 Hz, H-6), 5.43 (1H, d, J = 0.7 Hz, $H_{1'}$), 5.19 (2H, d, J = 5.3 Hz, –CH_2NH), 5.16 (1H, dd, J = 6.4, 1.1 Hz, $H_{2',3'}$), 4.94 (1H, dd, J = 6.4, 4.5 Hz, $H_{2',3'}$), 4.76 (2H, dd, J = 14.1, 4.3 Hz, $H_{5'}$), 4.49 (1H, m, $H_{4'}$), 1.50 (3H, s, CH_3), 1.30 (3H, s, CH_3). ^{19}F NMR ($CDCl_3$): δ –69.02, –69.04. HRMS (ESI): m/z calcd for $C_{29}H_{24}F_6N_6O_7$ 682.1611; found: 682.1622.

4.5.9. 5′-Deoxy-2′,3′-O-isopropylidene-5′-[4-{(4-bromo-2-trifluoroacetyl)naphtalen-1-yl)aminomethyl}-1,2,3-triazol-1-yl]uridine, **35**



Yield: 53%, silica gel chromatography (DCM/MET = 98/2), yellow solid, m.p.: 114 °C. ^{1}H NMR ($CDCl_3$): δ 9.98 (1H, t, J = 5.6 Hz, NH), 9.57 (1H, s, NH, N-3), 8.34 (1H, d, J = 8.5 Hz, H_{arom}), 8.16 (1H, d, J = 8.1 Hz, H_{arom}),7.89 (1H, d, J = 1.9 Hz, H_{arom}), 7.73 (1H, t, J = 7.3 Hz, H_{arom}), 7.63 (1H, s, $H_{triazole}$), 7.50 (1H, t, J = 7.3 Hz, H_{arom}), 7.14 (1H, d, J = 8.1 Hz, H-5), 5.72 (1H, dd, J = 7.9, 1.7 Hz, H-6), 5.45 (1H, s, $H_{1'}$), 5.10 (1H, dd, J = 6.4, 1.3 Hz, $H_{2',3'}$), 5.02 (2H, d, J = 6.1 Hz, –CH_2NH), 4.92 (1H, dd, J = 6.4, 4.5 Hz, $H_{2',3'}$), 4.72 (2H, m, $H_{5'}$), 4.47 (1H, m, $H_{4'}$), 1.53 (3H, s, CH_3), 1.33 (3H, s, CH_3). ^{19}F NMR ($CDCl_3$): δ –69.14. HRMS (ESI): m/z calcd for $C_{27}H_{24}BrF_3N_6O_6$ 664.0893; found: 664.0891.

4.5.10. 1-(2′,3′,5′-Tris-O-benzoyl-β-D-ribos-1′-yl)-4-{(2,4-bis-trifluoroacetyl-naphthalen-1-yl) aminomethyl}-1,2,3-triazole, **36**



Yield: 63%, silica gel chromatography (EP/EA = 8/2), yellow solid, m.p.: 65 °C. ^{1}H NMR ($CDCl_3$): δ 11.05 (1H, s, NH), 9.13 (1H, d, J = 7.7 Hz, H_{arom}), 8.62 (1H, s, H_{arom}), 8.31 (1H, d, J = 8.1 Hz, H_{arom}), 7.95 (7H, m, H_{arom}), 7.81 (1H, m, H_{arom}), 7.57 (3H, m, H_{arom}), 7.37 (7H, m, H_{arom}), 6.47 (1H, d, J = 3.2 Hz, $H_{1'}$), 6.32 (1H, dd, J = 5.1, 3.2 Hz, $H_{2'}$), 6.14 (1H, t, J = 5.6 Hz, $H_{3'}$), 5.10 (2H, d, J = 5.3 Hz, –CH_2NH), 4.88 (2H, m, H5′), 4.58 (1H, dd, J = 12.4, 4.5 Hz, $H_{5'}$). ^{19}F NMR ($CDCl_3$): δ –69.04 (2× $COCF_3$). HRMS (ESI): m/z calcd for $C_{43}H_{30}F_6N_4O_9$ 860.1917; found: 860.1923.

Acknowledgments

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