Journal of Fluorine Chemistry 132 (2011) 850–857

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

ClickEnam. 1. Synthesis of novel 1,4-disubsituted-[1,2,3]-triazole-derived β-aminovinyl trifluoromethylated ketones and their copper(II) complexes

Nicolas Chopin [a], Sophie Decamps [a], Aude Gouger [a], Maurice Médebielle [a,*], Stéphane Picot [b], Anne-Lise Bienvenu [b], Guillaume Pilet [c]

[a] Université de Lyon, Université Claude Bernard Lyon 1 (UCBL), Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS), Synthèse de Molécules d'Intérêt Thérapeutique (SMITH), UMR 5246 CNRS-UCBL-INSA Lyon, Bâtiment Curien, 43 bd du 11 Novembre 1918, 69622 Villeurbanne Cedex, France
[b] Université Claude Bernard Lyon 1 (UCBL), Malaria Research Unit (MRU), Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS), Synthèse de Molécules d'Intérêt Thérapeutique (SMITH), UMR 5246 CNRS-UCBL-INSA Lyon, Faculté de Médecine, 8 avenue Rockefeller, 69373 Lyon, France
[c] Université de Lyon, Université Claude Bernard Lyon 1 (UCBL), Laboratoire des multiMatériaux et Interfaces (LMI), UMR CNRS 5615, Groupe de Cristallographie et Ingénierie Moléculaire, Bâtiment Chevreul, 43 bd du 11 Novembre 1918, 69622 Villeurbanne cedex, France

ARTICLE INFO

Article history:
Received 1 April 2011
Received in revised form 10 May 2011
Accepted 13 May 2011
Available online 23 May 2011

Keywords:
Cycloaddition
Propargylamine
Azide
Triazole
Enaminone
Copper
Antimalarial
Antifungal

Dedicated to Doctor Alain Tressaud with recognition on the occasion of his receipt of the 2011 ACS Award for Creative Work in Fluorine Chemistry.

ABSTRACT

The copper(I) catalyzed cycloaddition reaction of *N*-Boc propargyl amine (dipolarophile) **1** with benzyl azide (1,3-dipole) **2** was found to proceed smoothly in *t*-BuOH/H_2O at room temperature, to furnish the corresponding 1,4-disubstituted-[1,2,3]-triazole-derived *N*-Boc amine **3** in good yield. Deprotection of **3** with trifluoroacetic acid and addition of the trifluoroacetate salt **4** in the presence of triethylamine, with a series of methoxyvinyl(trifluoromethyl)ketones **10**–**14**, gave the corresponding β-aminovinyl trifluoromethylated ketones **15**–**19** in moderate to good yields. Two copper(II) complexes, one monomer and one dimer with chlorine double bridge, **20** and **21**, respectively, were also prepared and their crystal structure determined. β-Aminovinyl trifluoromethylated ketones **15**–**17** and complexes **20** and **21** have been screened as potential antifungal agents and the antimalarial activity of **15** and **16** were tested against two *Plasmodium falciparum* strains (3D7 and W2).

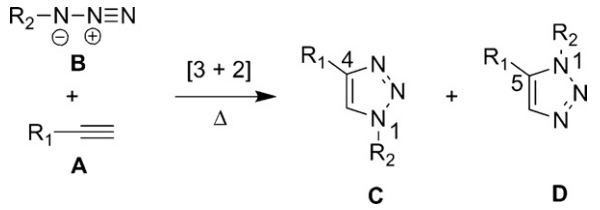
1. Introduction

[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 **A** and azides **B** (Scheme 1) [2].

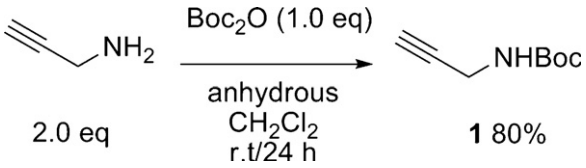
However, this strategy exhibits some disadvantages such as sometimes high temperature conditions with the potential for the decomposition of labile compounds and poor regioselectivity affording a mixture of 1,4 and 1,5-disubstituted triazoles (**C** and **D**), often difficult to separate. On the other 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, 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 and reactivity of β-aminovinyl chlorodifluoromethylated [7] and β-aminovinyl trifluoromethylated ketones [8] and their potential use to prepare novel acyclic and cyclic structures of potential biological importance, as well as novel ligands for the design of original metal

* Corresponding author.
E-mail address: maurice.medebielle@univ-lyon1.fr (M. Médebielle).

0022-1139/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2011.05.011



Scheme 1.



Scheme 3.

complexes [9]. As part of a research program directed to the synthesis of novel trifluoromethylated aromatics and heterocycles with therapeutic applications, we recently presented the copper(I)-catalyzed 1,3-dipolar cycloaddition of *N*-(2-trifluoroacetylaryl)propargylamines with a series of benzylic azides, carbohydrate and nucleoside-derived azides [10] that gave access to biologically relevant [1,2,3]-triazoles [11]. In the continuation of this study, we envisaged to use propargylamine in a copper(I)-catalyzed 1,3-dipolar cycloaddition reaction with benzyl azide, to prepare the corresponding [1,2,3]-triazole benzyl amine [12] that could be efficiently used in coupling reactions with β-trifluoromethylated enones, giving access to 1,4-disubsituted-[1,2,3]-triazole-derived β-aminovinyl trifluoromethylated ketones (Scheme 2). Although the [1,2,3]-triazole skeleton is often claimed and used as a potent amide replacement, [1,2,3]-triazole derivatives have been also designed as new ligands in catalysis, receptors for the recognition of metals and other applications [13]; our hybrid triazole-derived β-aminovinyl trifluoromethylated ketones offer also great potential to form stable metal complexes [9] and to coordinate a number of biologically relevant metals. For such reason, we were especially interested to screen our new triazole-derived β-aminovinyl trifluoromethylated ketones as potent antimalarials and antifungals, since there is a growing interest in designing metal complexes as potent anti-protozoal agents [14] and potent antifungals [15]. We present herein our preliminary results.

2. Results and discussion

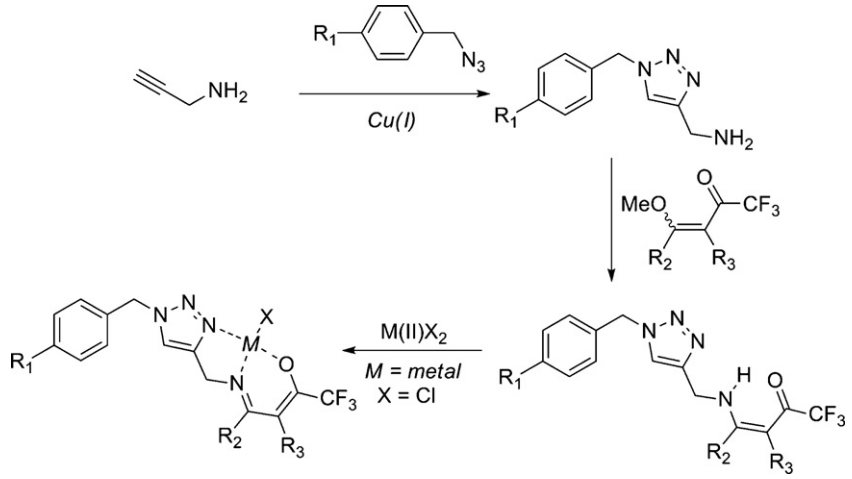
2.1. Syntheses of the dipolarophile and 1,3-dipole

The *N*-Boc propargyl amine **1** [16,17] was prepared in a 80% yield from a known literature procedure [16] with some slight modifications, using propargyl amine (2.0 equiv.) which acts as a base (to neutralize the formed acid) and a reactant and di-*tert*-butyl dicarbonate (Boc_2O) in anhydrous dichloromethane (Scheme 3). The product was isolated in a very good yield and used without further purification in the 1,3-dipolar cycloaddition. The 1,3-dipole (benzyl azide **2**) is a known compound [18] and is also commercially available.

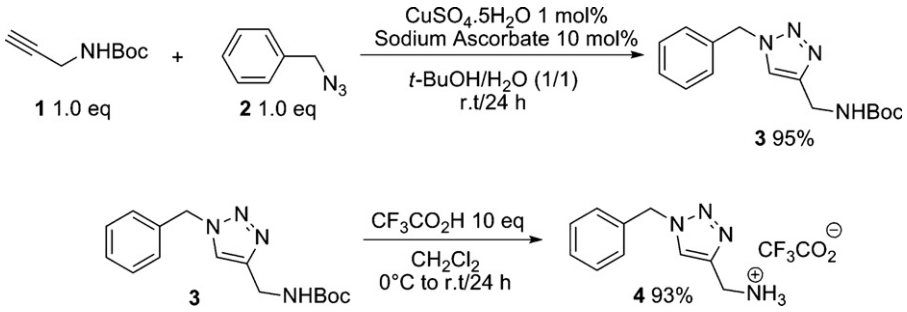
2.2. 1,3-Dipolar cycloaddition

The copper(I) catalyzed 1,3-dipolar cycloaddition between propargyl amine *hydrochloride salt* and benzyl azide **2**, giving the corresponding 1,4-disubstituted [1,2,3]-triazole as its hydrochloride salt, has been described [12]. Cu(0) nanosize activated powder in H_2O/*t*-BuOH solution has been used (no yield given) in the presence of $Et_3N{\cdot}HCl$ salt (1.0 equiv.) [12a] as well as the reaction of propargyl amine and **2** in the presence of a triazole catalyst or a *N*-heterocyclic carbene (NHC) copper(I) complex [(SIMes)CuBr], followed by subsequent protonation of the free $-NH_2$ with concentrated HCl [12b]. Since we were unable to repeat in a reasonable yield the procedure presented in [12b], we preferred to use *N*-Boc propargyl amine **1** in a more conventional procedure, using sodium ascorbate/$CuSO_4{\cdot}5H_2O$ [19] system in H_2O/*t*-BuOH solution (1/1). The 1,4-disubstituted-[1,2,3]-triazole-derived *N*-Boc amine **3** [12a] was obtained as a solid in an excellent 95% isolated yield (Scheme 4).

As expected, the triazole **3** was formed in a completely regioselective manner, with no contamination by the 1,5-regioisomer as highlighted from NOE experiments (Fig. 1): 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 addition according to the method presented by Dondoni and Marra [20], the difference of the ^{13}C chemical shift for the carbon atoms of the triazole is always between 21.5 and 22.4 ppm which is a good indication of the observed regioselectivity. The Boc protecting group in **3** was removed using excess (10 equiv.) of trifluoroacetic acid in dichloromethane to produce in



Scheme 2.



Scheme 4.

a 93% isolated yield the corresponding trifluoroacetate salt **4** as an oil. This salt can be stored for several months at room temperature with no evidence of decomposition.

2.3. Synthesis of the methoxyvinyl(trifluoromethyl)ketones

Methoxyvinyl(trifluoromethyl)ketones **10** [21], **11**–**14** [22–24] were prepared from ethyl vinyl ether **9** (for **10**) [21] or from corresponding dimethyl acetals **5**–**8** (acetal **8** is commercially available) using trifluoroacetic anhydride in the presence of pyridine in anhydrous dichloromethane (Scheme 5). Although the methoxyvinyl(trifluoromethyl)ketones **11**–**13** (and their dimethyl acetal precursors **5**–**7**) are mentioned in several papers, we were unable to find their full spectroscopic data.

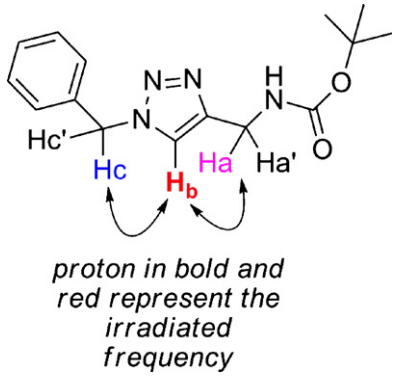


Fig. 1.

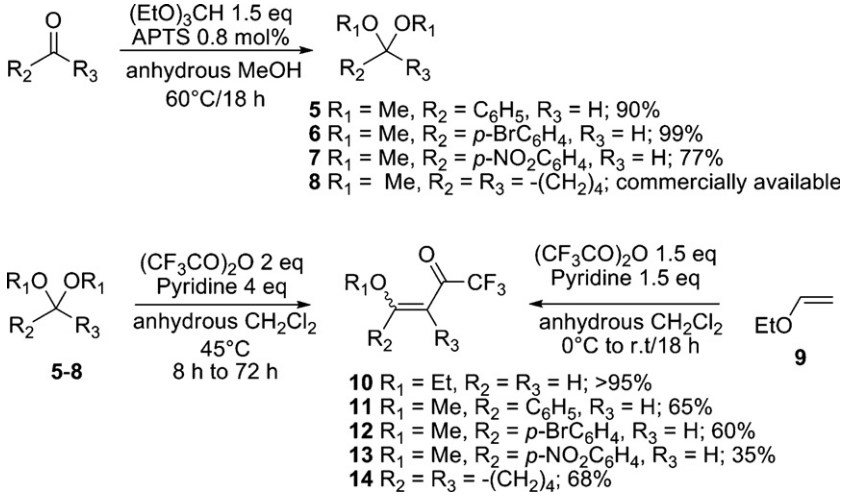
2.4. Synthesis of the β-aminovinyl trifluoromethylated ketones

All the β-aminovinyl trifluoromethylated ketones **15**–**19** were prepared by reacting trifluoroacetate salt **4** in the presence of Et_3N (1.2 equiv.) in anhydrous acetonitrile for 1 h, followed by the addition of the methoxyvinyl(trifluoromethyl)ketones **10**–**14**. The progress of the reaction was monitored by TLC and was stopped after complete conversion of the methoxyvinyl(trifluoromethyl)ketone (usually overnight). All the β-aminovinyl trifluoromethylated ketones **15**–**19** 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. Compounds **15**, **16**, **18**, **19** (solids) and **17** (oil) were obtained in moderate to good yields (44–87%) after evaporation of the solvent and silica gel chromatography purification (Scheme 6).

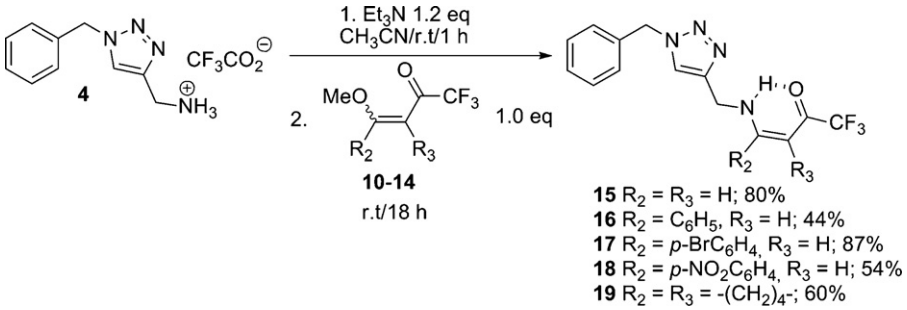
2.5. Synthesis of the copper(II) complexes

Two copper(II) complexes **20** and **21** were prepared in very good yields (>80%) from the corresponding β-aminovinyl trifluoromethylated ketones **15** (**L15**, L for ligand) and **17** (**L17**, L for ligand) by mixing a methanolic solution of $CuCl_2{\cdot}2H_2O$ to a dichloromethane solution of the corresponding ligands **15** and **17** and stirring the resulting solution at room temperature for 2 h. Filtration, short filtration over silica gel and evaporation gave the desired complexes as green powders. Slow evaporation of a MeOH/CH_2Cl_2 solution of these complexes gave single crystals suitable for X-ray determination.

Both **20** and **21** are copper(II)-based complexes: the first one is mononuclear with the following refined formula [Cu^{II}(**L15**)Cl] (see



Scheme 5.



Scheme 6.

Fig. 2, **20**) while the second one is a dimer with $[Cu^{II}_2(\mathbf{L17})_2Cl_2]\cdot 2(CH_2Cl_2)$ as refined formula and exhibits a double chlorine bridge between the metallic centres (see Fig. 2, **21**). Both are neutral and no counter-ion crystallizes within the unit-cell. In case of **21**, dichloromethane co-crystallized solvent molecules have been also found in the unit-cell.

Copper cation in **20** is located in a $N_2O_1Cl_1$ square plane environment and is then surrounded by one **L15H** ligand and one coordinated chlorine atom coming from the starting metal salt. One nitrogen and one oxygen atoms belong to the β-aminovinyl trifluoromethylated ketone entity while the second nitrogen atom is coming from the triazole moiety of the **L15** ligand. All Cu–N (average: 1.966 Å), Cu–O (1.907(2) Å) and Cu–Cl (2.2228(9) Å) bond lengths are in good agreement with those previously reported in the literature [25].

Complex **21** can be viewed as two mononuclear complexes [Cu**L17**Cl], isostructural of **20**, connected together in a face-to-face arrangement. Then, a double chlorine bridge is created between the two complexes to form a dimmer. The copper(II) ion is thus located in a $N_2O_1Cl_2$ square base pyramidal environment. Within this dissymmetric Cl bridge, the top of the pyramid of one metal centre (long Cu–Cl bond) is occupied by the chlorine atom of the environment of the second metal cation (chlorine atom located in the square base, short Cu–Cl bond) of the dimer. In structure of **21**, all Cu–N (average ~2.00 Å), Cu–O (~1.93 Å) and Cu–Cl (~2.27 Å and ~2.90 Å for the short and long bonds, respectively) bond lengths are in good agreement with those previously reported in the literature [9a,b]. The global packing of complexes **20** and **21** is characterized by a number of F···F, F···H and Br···H weak bonds forming then a dense 3D network.

2.6. Biological evaluation

β-Aminovinyl trifluoromethylated ketones **15**–**17**, and complexes **20** and **21** were screened as potential antifungal agents. They demonstrated to have MICs of >32 μg/ml and were considered to have no antifungal activity on *C. albicans* susceptible reference strain. β-Aminovinyl trifluoromethylated ketones **15** and **16** were also tested against *P. falciparum* 3D7 and W2 strains, and results revealed weak in vitro activities ($IC_{50} > 16$ μM).

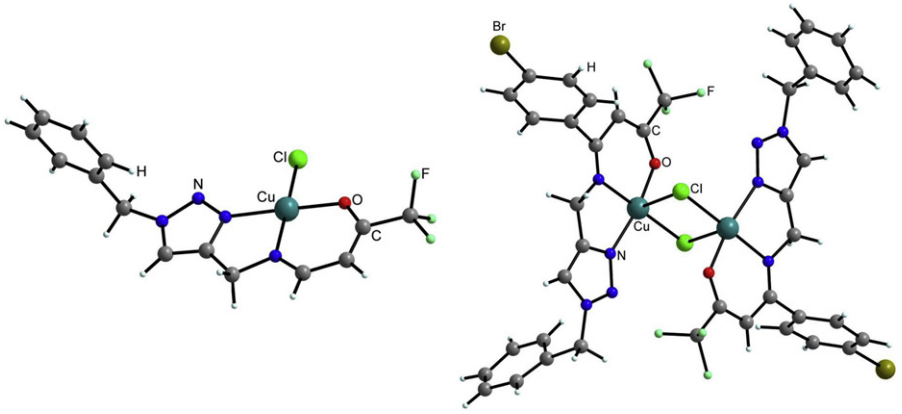
3. Conclusions

In this study we have presented the mild and efficient preparation of some 1,4-disubstituted-[1,2,3]-triazole derived β-aminovinyl trifluoromethylated ketones and the synthesis of two copper(II) complexes. The copper(I)-catalyzed 1,3-dipolar cycloaddition methodology to prepare these new scaffolds is of particular interest to prepare libraries of compounds for biological screening, since variation of R_1, R_2, R_3 (Scheme 2) as well as substitutions on the triazole can be readily attained. Work under these lines is under progress. Preliminary biological evaluation of some compounds as antifungals and antimalarials was performed, and preliminary data indicate that the structures are weakly active. New derivatives will be prepared and will be screened again.

4. Experimental

4.1. General comments

Solvents were distilled before use. Reagents were obtained commercially and used without further purification. Compound **2**



20 **21**

Fig. 2.

was prepared as described in Ref. [18]. Compound **10** was prepared as described in Ref. [21]. Compound **14** was prepared as described in Ref. [24]. ^{1}H, ^{19}F and ^{13}C NMR were recorded with a Bruker Avance 300 spectrometer (in $CDCl_3$) at 300 MHz, 282 MHz 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 Macherey-Nagel Silica gel 60 M (0.04–0.063 mm). Solvents for chromatography and work-up are: dichloromethane (DCM), ethyl acetate (AcOEt), methanol (MeOH) and petroleum ether (EP). Mass spectra were recorded using a FINIGAN MAT 95 [EI and ESI]. Melting points (uncorrected) were determined in capillary tubes on a Büchi apparatus. High resolution mass spectra of the dimethyl acetals were not recorded due their relative instability.

4.2. X-ray characterization

It was possible to determine by single-crystal X-ray diffraction the structure of two original copper(II) complexes (**20** and **21**) and to completely refine the structure of one (**20**). CCDC 819565 and 819566 contain the supplementary crystallographic data of complex **20** and **21**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Diffraction data sets were collected on an Oxford Gemini diffractometer equipped with a CCD camera using the related softwares [25]. An absorption correction (analytical) based on the crystal shape has been applied to all the data sets [26]. Structures of **20** and **21** were solved by direct methods using the SIR97 program [27] combined to Fourier difference syntheses and refined against F and using the CRYSTALS program [28]. In case of **20**, all atomic displacements for non-hydrogen atoms were refined using an anisotropic model. Hydrogen atoms belonging to carbon atoms have been placed theoretically and the others (belonging to oxygen atoms) by Fourier Difference. All hydrogen atoms have been refined using a *riding* method.

In case of complex **21**, crystal and data quality did not allow a complete structural refinement. Blue plate crystals of **21** were very thin (0.03 mm) and always twinned (at least two individuals) giving bad refinement results when considering atoms with an anisotropic model. It has never been possible to isolate a single crystal. Results presented here in case of **21** are then a model where atoms are refined using isotropic terms. Hydrogen atoms belonging to carbon atoms have been placed theoretically and the others (belonging to oxygen atoms) by Fourier Difference. All hydrogen atoms have been refined using a *riding* method.

X-ray crystallographic data and refinement details for complexes **20** and **21** are reported in Refs. [29] and [30], respectively.

4.3. Antifungal susceptibility testing

Molecules were tested in vitro for their antifungal activities using the Clinical and Laboratory Standards Institute (CLSI) reference method for antifungal susceptibility testing. Drugs were diluted in DMSO as stock solutions and in RPMI 1640 medium as test solutions in order to obtain a non-toxic concentration of DMSO (final concentration of DMSO = 0.005%, demonstrated to be non-toxic on yeasts). Fluconazole solution was provided by the hospital pharmacy and diluted in RPMI 1640 medium. *Candida albicans* reference susceptible strain (ATCC 90028) was used to perform susceptibility testing. Personnel performing the tests were blinded to the molecules tested. CLSI broth microdilution method was performed as outlined in document M27-A3 [31], in microplate, by using RPMI 1640 medium with 0.2% glucose, inocula of 0.5×10^3 to 2.5×10^3 cells/ml, and incubation at 35 °C. Minimal Inhibitory Concentration (MIC) values were determined visually after 24 h of incubation as the lowest concentration of drug that caused a significant diminution (≥50% inhibition) of growth relative to that of the growth control.

4.3.1. In vitro drug sensitivity assay with cultured parasites

After they were taken out of liquid nitrogen, the cultured parasites were grown for 10–12 days until a predominance of ring-stage parasites of no less than 70% was reached. These parasites were used for the drug sensitivity assays. Once the parasitemia levels of the in vitro cultures reached an optimum density of 5–8%, the infected red blood cells were centrifuged at 350 *g* for 5 min; the supernatant was aspirated and the cells were suspended in RPMI with and without phenol red (Invitrogen) supplemented with 0.5% Albumax I (0.005 g/ml), HEPES (5.94 g/liter), and $NaHCO_3$ (2.4 g/l). An aliquot of the culture was diluted to reduce the parasitemia to 0.5%, and the hematocrit was adjusted to 2% with fresh RBCs. A total of 180 μL/well of 0.5% parasitized RBCs at 2% hematocrit was added, and the plates were incubated in a humidified modular incubator chamber (Flow Laboratories) at 37 °C under a gas mixture of 5% O_2, 5% CO_2, and 90% N_2 for 72 h.

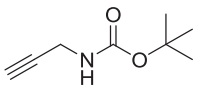
4.3.2. IC_{50} determination by the SYBR green I assay

Following incubation, the plates were frozen and stored at −80 °C until the SYBR green I assay was performed. The plates were thawed for 2 h at room temperature and each sample was mixed by pipetting. Briefly, a total of 100 μL of the culture was transferred to a new 96-well plate, followed by the addition of 100 μL of SYBR green I (Molecular Probes, Invitrogen, Carlsbad, CA) in lysis buffer (0.2 μL of SYBR green I/ml of lysis buffer, which consisted of Tris 20 mM [pH 7.5], EDTA [5 mM], saponin [0.008%; wt/vol], and Triton X-100 [0.08%; wt/vol]). The plates were covered and incubated at room temperature for 1 h. The fluorescence intensity was measured from below with a Berthold plate reader.

4.4. Synthesis of 1

To an anhydrous dichloromethane solution (6.45 mL) containing propargylamine (12.9 mmol, 0.83 mL) was added 1.4 g (6.45 mmol) of Boc_2O. The solution was stirred under argon at room temperature for 24 h and quenched with water (15 mL). The resulting solution was extracted with dichloromethane (2 × 25 mL), the organic phases were combined and washed with water (2 × 30 mL), dried over Na_2SO_4 and filtered. Evaporation to dryness under reduced pressure left the product which was pure enough for the next step.

4.4.1. tert-Butyl prop-2-ynyl carbamate [16,17]



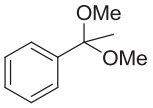
Yield: 80%, yellowish oil. ^{1}H NMR ($CDCl_3$): δ 5.92 (1H, s, NH), 3.90 (2H, d, *J* = 3 Hz), 2.37 (1H, t, *J* = 2.1 Hz), 1.45 (9H, s). ^{13}C NMR ($CDCl_3$): δ 155.2 (C=O), 80.12 (C), 80.06 (C), 71.20 (CH), 30.40 (CH_2), 28.30 (3 × CH_3).

4.5. General procedure for the acetalization

To a solution of ketone (1 mmol), in anhydrous methanol (10 mL), was added *p*-TsOH (1.4 mg, 0.008 mmol) and triethylorthoformate (0.25 mL, 1.5 mmol). The mixture was stirred at 60 °C overnight under argon. After cooling down to room temperature, solid Na_2CO_3 was added and the solution was

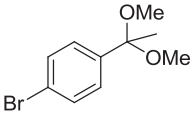
filtered before removing solvents under reduced pressure. The dimethyl acetal is pure enough to be used for the next step.

4.5.1. (1,1-Dimethoxyethyl)benzene **5**



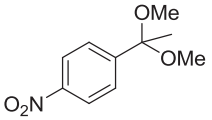
Yield: 90%, orange oil. ^{1}H NMR ($CDCl_3$): δ 7.19 (5H, m, H_{arom}), 2.97 (6H, s, $-OCH_3$), 1.34 (3H, s, $-CH_3$). ^{13}C NMR ($CDCl_3$): δ 142.9 (C), 128.1 (2CH), 127.5 (CH), 126.2 (2CH), 101.7 (C), 48.9 ($2CH_3$), 26.1 (CH_3).

4.5.2. 1-Bromo-4-(1,1-dimethoxyethyl)benzene **6**



Yield: 99%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.31 (2H, d, J = 8.7, H_{arom}), 7.22 (2H, d, J = 8.7, H_{arom}), 3.00 (6H, s, $-OCH_3$), 1.35 (3H, s, $-CH_3$). ^{13}C NMR ($CDCl_3$): δ 141.8 (C), 131.0 (2CH), 128.0 (2CH), 121.4 (C), 101.0 (C), 48.6 ($2CH_3$), 25.7 (CH_3).

4.5.3. 1-(1,1-Dimethoxyethyl)-4-nitrobenzene **7**

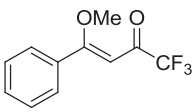


Yield: 77%, yellow solid, m.p. 54 °C. ^{1}H NMR ($CDCl_3$): δ 7.99 (2H, d, J = 8.7, H_{arom}), 7.50 (2H, d, J = 8.7, H_{arom}), 3.00 (6H, s, $-OCH_3$), 1.35 (3H, s, $-CH_3$). ^{13}C NMR ($CDCl_3$): δ 149.8 (C), 147.0 (C), 127.0 (2CH), 122.8 (2CH), 100.7 (C), 48.5 ($2CH_3$), 25.2 (CH_3).

4.6. General procedure for the synthesis of methoxyvinyl(trifluoromethyl)ketones **11–13**

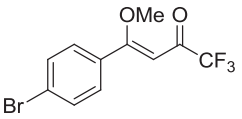
To an ice-cold stirred mixture of dimethyl acetal (1 mmol), pyridine (0.33 mL, 4 mmol), and anhydrous dichloromethane (2 mL) was added dropwise trifluoroacetic anhydride (0.28 mL, 2 mmol). After the addition was complete, the solution was warmed up to 45 °C and stirred overnight for **11** and **12** and 3 days for **13**. Then, ice-water was added (1.5 mL) and the mixture was extracted with dichloromethane. Organic phase was washed with 2 N hydrochloric acid solution (1.5 mL), aqueous 10% sodium carbonate (2 mL), and water (2 × 2 mL), and was dried over Na_2SO_4. After filtration the solvent was evaporated to dryness and the crude product was purified by silica gel chromatography using (EP/DCM = 1/1).

4.6.1. (Z)-1,1,1-Trifluoro-4-methoxy-4-phenylbut-3-en-2-one **11**



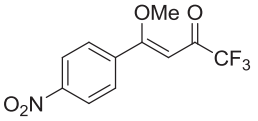
Yield: 65%, orange oil. ^{1}H NMR ($CDCl_3$): δ 7.50 (5H, m, H_{arom}), 7.26 (1H, s, =CH-CO), 3.97 (3H, s, $-OCH_3$). ^{13}C NMR ($CDCl_3$): δ 178.0 (C), 177.5 (C, q, J = 33.3), 133.6 (C), 131.1 (CH), 128.7 (2CH), 127.9 (2CH), 116.7 (C, q, J = 290.0), 91.7 (CH), 57.2 (CH_3). ^{19}F NMR ($CDCl_3$): δ −78.81. HRMS (ESI): m/z calcd for $C_{11}H_{10}F_3O_2$ $[M+H]^+$ 231.06274; found: 231.06272.

4.6.2. (Z)-4-(4-Bromophenyl)-1,1,1-trifluoro-4-methoxybut-3-en-2-one **121**



Yield: 60%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.31 (2H, d, J = 8.4, H_{arom}), 7.15 (2H, d, J = 8.4, H_{arom}), 5.63 (1H, s, =CH–CO), 3.69 (3H, s, $-OCH_3$). ^{13}C NMR ($CDCl_3$): δ 177.0 (C, q, J = 33.6), 176.7 (C), 132.4 (C), 131.0 (2CH), 130.4 (2CH), 125.5 (C), 91.9 (CH), 57.23 (CH_3). ^{19}F NMR ($CDCl_3$): δ −78.96. HRMS (ESI): m/z calcd for $C_{11}H_9BrF_3O_2$ $[M+H]^+$ 308.97325; found: 308.97324.

4.6.3. (Z)-1,1,1-Trifluoro-4-methoxy-4-(4-nitrophenyl)but-3-en-2-one **13**



Yield: 35%, yellow solid, m.p. 64 °C. ^{1}H NMR ($CDCl_3$): δ 8.15 (2H, d, J = 9.0, H_{arom}), 7.65 (2H, d, J = 9.0, H_{arom}), 5.92 (1H, s, =CH–CO), 3.96 (1H, s, $-OCH_3$). HRMS (ESI): m/z calcd for $C_{11}H_9F_3NO_4$ $[M+H]^+$ 276.04782; found: 276.04784.

4.7. Synthesis of **4**

To a stirred solution of **3** (0.287 g, 1.0 mmol) in dichloromethane (20 mL), was added dropwise trifluoroacetic acid (0.73 mL, 10 mmol) with cooling (0 °C). The solution was slowly 'warmed up and stirred at room temperature for 24 h. Solvents were carefully removed under reduced pressure and the resulting oil was triturated with diethyl ether and evaporation to dryness left a brownish oil (0.283 g, 93 mmol, 93%).

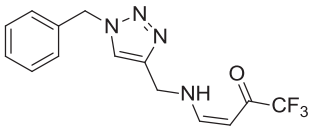
4.7.1. (1-Benzyl-1H-1,2,3-triazol-4-yl)methanaminium 2,2,2-trifluoroacetate **4**

^{1}H NMR (D_2O): δ 8.07 (1H, s, $H_{triazole}$), 7.24 (5H, m, H_{arom}), 5.45 (2H, s, $-CH_2Ph$), 4.30 (2H, s, $-CH_2NH$). ^{13}C NMR (D_2O): δ 161.8 (C), 134.4 (2C), 128.9 (2CH), 128.6 (CH), 128.0 (2CH), 125.4 (C), 125.3 (CH), 54.0 (CH_2), 34.1 (CH_2). ^{19}F NMR (D_2O): δ −75.85. HRMS (ESI): m/z calcd for $C_{10}H_{13}N_4$ $[M+H]^+$ 189.1135; found: 189.1134.

4.8. General procedure for the synthesis of **15–19**

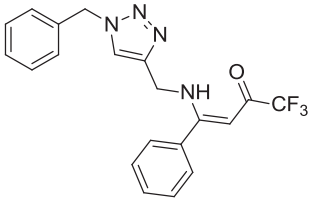
To a solution of 4 (302 mg, 1 mmol) in acetonitrile (2 mL) was added triethylamine (0.14 mL, 1.2 mmol) and the mixture was stirred at room temperature during 1 h. A solution of enone (1 mmol) in acetonitrile (0.6 mL) was added dropwise and the mixture was stirred overnight. Solvent was removed under reduced pressure and the crude material was purified by silica gel chromatography using EP/AcOEt (1/1) for **15**, **18** and **19**, (3/1) for **16** and **17**.

4.8.1. (Z)-4-(((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)-1,1,1-trifluorobut-3-en-2-one **15**



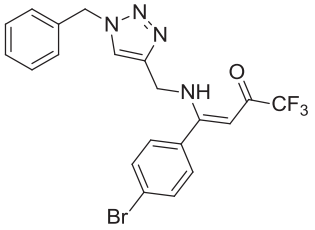
Yield: 80%, yellow solid, m.p. 108 °C. ^{1}H NMR ($CDCl_3$): δ 10.35 (1H, s br, –NH), 7.47 (1H, s, $H_{triazole}$), 7.30 (6H, m, H_{arom}, –N–CH=), 5.46 (2H, s, $-CH_2Ph$), 5.32 (1H, d, J = 6.9, =CH–CO), 4.54 (2H, d, J = 6.0, $-CH_2NH$). ^{13}C NMR ($CDCl_3$): δ 177.9 (C, q, J = 33.1), 157.8 (CH), 143.4 (C), 134.2 (C), 128.9 (2CH), 128.6 (CH), 127.9 (2CH), 121.9 (CH), 116.9 (C, q, J = 287.0), 87.5 (CH), 54.02 (CH_2), 44.06 (CH_2). ^{19}F NMR ($CDCl_3$): δ −77.88. HRMS (ESI): m/z calcd for $C_{14}H_{14}F_3N_4O$ $[M+H]^+$ 311.1114; found: 311.1110.

4.8.2. (Z)-4-(((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)-1,1,1-trifluoro-4-phenylbut-3-en-2-one **16**



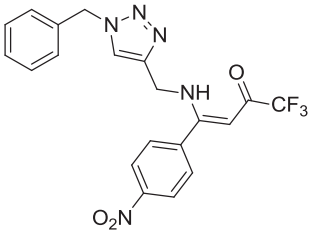
Yield: 44%, brown solid, m.p. 109 °C. ^{1}H NMR ($CDCl_3$): δ 11.33 (1H, s, –NH), 7.44 (11H, m, H_{arom}, $H_{triazole}$), 5.53 (2H, s, =CH–CO), 5.49 (2H, s, $-CH_2Ph$), 4.60 (2H, d, J = 6.3, $-CH_2NH$). ^{13}C NMR ($CDCl_3$): δ 175.8 (C, q, J = 32.6), 170.12 (C), 143.4 (C), 134.2 (C), 132.9 (C), 130.3 (CH), 128.7 (2CH), 128.5 (2CH), 128.3 (CH), 127.6 (2CH), 127.2 (2CH), 121.8 (CH), 117.2 (C, q, J = 286.0), 90.2 (CH), 53.7 (CH_2), 40.4 (CH_2). ^{19}F NMR ($CDCl_3$): δ −77.11. HRMS (ESI): m/z calcd for $C_{20}H_{18}F_3N_4O$ $[M+H]^+$ 387.1427; found: 387.1428.

4.8.3. (Z)-4-(((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)-4-(4-bromophenyl)-1,1,1-trifluorobut-3-en-2-one **17**



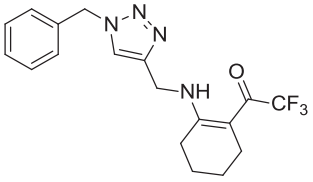
Yield: viscous colorless oil. ^{1}H NMR ($CDCl_3$): δ 11.24 (1H, s br, –NH), 7.55 (2H, d, J = 8.4, H_{arom}), 7.42 (1H, s, $H_{triazole}$), 7.34–7.32(5H, m, H_{arom}), 7.25–7.22 (2H, m, H_{arom}), 5.47 (2H, s, $-CH_2Ph$), 5.40 (1H, s, =CH–CO), 4.51 (2H, d, J = 6.3, $-CH_2NH$). ^{13}C NMR ($CDCl_3$): δ 176.5 (C, q, J = 33.1), 168.96 (C), 143.5 (C), 134.2 (2C), 132.0 (2CH), 129.1 (2CH), 128.9 (2CH), 128.6 (CH), 127.9 (2CH), 125.0 (C), 121.7 (CH), 117.2 (C, q, J = 286.9), 90.4 (CH), 54.0 (CH_2), 40.5 (CH_2). ^{19}F NMR ($CDCl_3$): δ −77.04. HRMS (ESI): m/z calcd for $C_{20}H_{16}BrF_3N_4NaO$ $[M+Na]^+$ 487.0352; found: 487.0342.

4.8.4. (Z)-4-(((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)-1,1,1-trifluoro-4-(4-nitrophenyl)but-3-en-2-one **18**



Yield: 54%, pale yellow solid, m.p. 120 °C. ^{1}H NMR ($CDCl_3$): δ 11.20 (1H, s br, –NH), 8.31 (2H, d, J = 8.1, H_{arom}), 7.71 (2H, d, J = 8.4, H_{arom}), 7.43 (1H, s, $H_{triazole}$), 7.38 (3H, s, H_{arom}), 7.28 (2H, s, H_{arom}), 5.52 (2H, s, $-CH_2Ph$), 5.44 (1H, s, =CH–CO), 4.51 (2H, d, J = 6.3, $-CH_2NH$). ^{13}C NMR ($CDCl_3$): δ 177.2 (C, q, J = 33.5 Hz), 167.5 (C), 148.9 (C), 143.3 (C), 139.2 (C), 134.1 (C), 129.1 (2CH), 129.0 (2CH), 128.9 (CH), 128.1 (2CH), 124.0 (2CH), 121.7 (CH), 116.5 (C, q, J = 286.0 Hz), 90.7 (CH), 54.3 (CH_2), 40.6 (CH_2). ^{19}F NMR ($CDCl_3$): δ −77.21. HRMS (ESI): m/z calcd for $C_{20}H_{16}F_3N_5NaO_3$ $[M+Na]^+$ 454.1103; found: 454.1090.

4.8.5. 1-(2-(((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)cyclohex-1-en-1-yl)-2,2,2-trifluoroethanone **19**



Yield: 60%, brown solid, m.p. 74 °C. ^{1}H NMR ($CDCl_3$): δ 12.09 (1H, s br, –NH), 7.41 (1H, s, $H_{triazole}$), 7.29–7.27 (3H, m, H_{arom}), 7.20–7.17 (2H, m, H_{arom}), 5.41 (2H, s, $-CH_2Ph$), 4.52 (2H, d, J = 6.0, $-CH_2NH$), 2.54–2.52 (2H, m, $-CH_2$), 2.39–2.37 (2H, m, $-CH_2$), 1.62–1.52 (4H, m, $2CH_2$). ^{13}C NMR ($CDCl_3$): δ 174.8 (C, q, J = 31.0), 179.1 (C), 144.1 (C), 134.2 (C), 129.0 (2CH), 128.7 (CH), 127.9 (2CH), 121.7 (CH), 98.0 (C), 54.1 (CH_2), 38.4 (CH_2), 27.0 (CH_2), 22.2 ($2CH_2$), 21.0 (CH_2), $-CF_3$ overlaped in the baseline. ^{19}F NMR ($CDCl_3$): δ −72.32. HRMS (ESI): m/z calcd for $C_{18}H_{19}F_3N_4NaO$ $[M+Na]^+$ 387.1409; found: 387.1403.

4.9. General procedure for the synthesis of the Cu(II) complexes **20** *and* **21**

A methanolic solution (10 mL) of $CuCl_2{\cdot}2H_2O$ (184 mg, 1.08 mmol), was added dropwise to a solution of enaminone in dichloromethane (20 mL). The mixture was stirred at room temperature for 2 h. After filtration, and short filtration over silica gel, the complexes were obtained as green powders (>80%). Single crystals suitable for X-ray characterization were obtained by slow evaporation of a methanol/dichloromethane solution.

Acknowledgments

Part of this work was supported by the Région Rhône-Alpes "Cluster de Chimie" and the CNRS. N. Chopin is grateful to the Région Rhône-Alpes for a PhD fellowship. The Centre de Spectrométrie de Masse (CCSM) of Université Lyon 1 is sincerely thanked for recording the mass spectra. The Centre de Diffractométrie Henri Longchambon from the University of Lyon 1 is gratefully acknowledged for the X-Ray data collection. We would like to thank C. Perez for the synthesis of **14**.

References

[1] Selected references:
(a) F.G. de las Heras, R. Alonso, G. Alonso, J. Med. Chem. 22 (1979) 496;
(b) E.K. Moltzen, H. Pedersen, K.P. Bogeso, E. Meier, K. Frederiksen, C. Sanchez, H.L. Lembol, J. Med. Chem. 37 (1994) 4085;
(c) K. Dabak, Ö. Sezer, A. Akar, O. Anac, Eur. J. Med. Chem. 38 (2003) 215;
(d) F. Reck, F. Zhou, M. Girardot, G. Kern, C.J. Eyermann, N.J. Hales, R.R. Ramsay, M.B. Gravestock, J. Med. Chem. 48 (2005) 499.

[2] (a) R. Huisgen, in: A. Padwa (Ed.), 1,3-Dipolar Cycloaddition Chemistry, Wiley, New York, 1984, pp. 1–176;
(b) K.V. Gothelf, K.A. Jorgensen, Chem. Rev. 98 (1998) 863.

[3] V.V. Rostovtsev, L.G. Green, V.V. Fokin, K.B. Sharpless, Angew. Chem. Int. Ed. 41 (2002) 2596.

[4] (a) C.W. Tornøe, C. Christensen, M. Meldal, J. Org. Chem. 67 (2002) 3057;
(b) M. Meldal, C.W. Tornøe, Chem. Rev. 108 (2008) 2952.

[5] J.-P. Bégué, D. Bonnet-Delpon, Bioorganic and Medicinal Chemistry of Fluorine, Wiley, Hoboken, 2008.

[6] P. Kirsch, Modern Fluoroorganic Chemistry: Synthesis, Reactivity Applications, Wiley-VCH, Weinheim, Germany, 2004.

[7] (a) M. Médebielle, O. Onomura, R. Keirouz, E. Okada, H. Yano, T. Terauchi, Synthesis (2002) 2601;
(b) F. Fenain, M. Médebielle, M. Rocher, O. Onomura, E. Okada, D. Shibata, J. Fluorine Chem. 128 (2007) 1286.

[8] (a) M. Médebielle, S. Hohn, E. Okada, H. Myoken et, D. Shibata, Tetrahedron Lett. 46 (2005) 7817;
(b) N. Ota, T. Tomoda, N. Terai, Y. Kamitori, D. Shibata, M. Médebielle, E. Okada, Heterocycles 76 (2008) 1205.

[9] (a) G. Pilet, J.-B. Tommasino, F. Fenain, R. Matrak, M. Médebielle, Dalton Trans. (2008) 5621;
(b) G. Pilet, M. Médebielle, J-.B. Tommasino, G. Chastanet, B. Le Guennic, C. Train, Eur. J. Inorg. Chem. (2009) 4718;
(c) PhD thesis of Nicolas Chopin in progress.;
(d) Journées de Chimie Organique, JCO-2010, September 21–23, 2010: "Synthesis of azobenzene-derived trifluoromethylated enaminone ligands and their Cu complexes", abstract no. P078.

[10] J.-F. Lamarque, C. Lamarque, S. Lassara, M. Médebielle, J. Molette, E. David, S. Pellet-Rostaing, M. Lemaire, E. Okada, D. Shibata, G. Pilet, J. Fluorine Chem. 129 (2008) 788.

[11] Selected references:
(a) O.L. Acevedo, S.H. Krawczyk, L.B. Townsend, J. Med. Chem. 51 (1986) 1050;
(b) J.C. Bussalori, R.P. Panzica, Bioorg. Med. Chem. 7 (1999) 2373;
(c) G. O'Mahony, E. Ehrman, M. Grøtli, Tetrahedron Lett. 46 (2005) 6745;
(d) F. Seela, A.M. Jawalekar, I. Münster, Helv. Chim. Acta 88 (2005) 751;
(e) L. Cosyn, K.K. Palaniappan, S.-K. Kim, H.T. Duong, Z.-G. Gao, K.A. Jacobson, S. Van Calenbergh, J. Med. Chem. 49 (2006) 7373;
(f) J.H. Cho, D.L. Bernard, R.W. Sidwell, E.R. Kern, C.K. Chu, J. Med. Chem. 49 (2006) 1140;
(g) P. Kočalka, N.K. Andersen, F. Jensen, P. Nielsen, ChemBioChem 8 (2007) 2106;
(h) K. El Akri, K. Bougrin, J. Balzarini, A. Faraj, R. Benhida, Bioorg. Med. Chem. Lett. 17 (2007) 6656;
(i) A. Goeminne, M. McNaughton, G. Bal, G. Surpateanu, P. Van der Veken, S. De Prol, W. Versées, J. Steyaert, S. Apers, A. Heemers, K. Augustyns, Bioorg. Med. Chem. Lett. 17 (2007) 2523;
(j) M. Nakane, S. Ichikawa, A. Matsuda, J. Org. Chem. 73 (2008) 1842;
(k) E.N. Da Sliva Jr., R.F.S. Menna-Barreto, M. Do Carmo, F.R. Pinto, R.S.F. Silva, D.V. Teixeira, M.C.B.V. De Souza, C.A. De Simone, S.L. De Castro, V.F. Ferreira, A.V. Pinto, Eur. J. Med. Chem. 43 (2008) 1774;
(l) J.A. Stefely, R. Palchaudhuri, P.A. Miller, R.J. Peterson, G.C. Moraski, P.J. Hergenrother, M.J. Miller, J. Med. Chem. 53 (2010) 3389.

[12] The hydrochloride salt of this amine is known:
(a) A. Maisonial, P. Serafin, M. Traikia, E. Debiton, V. Théry, D.J. Aitken, P. Lemoine, B. Viossat, A. Gautier, Eur. J. Inorg. Chem. (2008) 298;
(b) H.A. Orgueira, D. Fokas, Y. Isome, P.C.-M. Chan, C. Baldino, Tetrahedron Lett. 46 (2005) 2911.

[13] Selected references:
(a) D. Liu, W. Gao, Q. dai, X. Zhang, Org. Lett. 7 (2005) 4907;
(b) S.-I. Fukuzawa, H. Oki, M. Hosaka, J. Sugasawa, S. Kikuchi, Org. Lett. 9 (2007) 5557;
(c) U. Monkowius, S. Ritter, B. König, M. Zabel, H. Yersin, Eur. J. Inorg. Chem. (2007) 4597;
(d) M. Obata, A. Kitamura, A. Mori, C. Kameyama, J.A. Czaplewska, R. Tanaka, I. Konishita, T. Kusumoto, H. Hashimoto, M. harada, Y. Mikata, T. Funabiki, S. Yano, Dalton Trans. (2008) 3292;
(e) H. Struthers, B. Spingler, T.L. Mindt, R. Schibli, Chem. Eur. J. 14 (2008) 6173;
(f) B. Schulze, C. Friebe, M.D. Hager, A. Winter, R. Hoogenboom, H. Görls, U.S. Schubert, Dalton. Trans. (2009) 787;
(g) D. Schweinfurth, R. Pattacini, S. Strobel, B. Sarkar, Dalton Trans. (2009) 9291.

[14] Selected references:
(a) M. Navarro, E.J. Cisneros-Fajardo, T. Lehmann, R.A. Sánchez-Delgado, R. Atencio, P. Silva, R. Lira, J.A. Urbina, Inorg. Chem. 40 (2001) 6879;
(b) B. Pradines, J.M. Rolain, F. Ramiandrasoa, T. Fusai, J. Mosnier, C. Rohgier, W. Daries, E. Baret, G. Kunesch, J. Le Bras, D. Parzy, J. Antimicrobial Chemother. 50 (2002) 177;
(c) N.H. Gokhale, S.B. Padhye, S.L. Croft, H.D. Kendrick, W. Davies, C.E. Anson, A.K. Powell, J. Inorg. Biochem. 95 (2003) 249;
(d) N.H. Gokhale, S.B. Padhye, D.C. Billington, D.L. Rathbone, S.L. Croft, H.D. Kendrick, C.E. Anson, A.K. Powell, Inorg. Chem. Acta 349 (2003) 23;
(e) R. Magán, C. Marín, M.J. Rosales, J.M. Salas, M. Sánchez-Moreno, Pharmacology 73 (2005) 41;
(f) N.H. Gokhale, S.B. Padhye, S.L. Croft, H.D. Kendrick, V. Mckee, Bioorg. Med. Chem. Lett. 16 (2006) 430;
(g) S. Boutaleb-Charki, C. Marín, C.R. Maldonado, M.J. Rosales, J. Urbano, R. Guitierrez-Sánchez, M. Quirós, J.M. Salas, M. Sánchez-Moreno, Drug Metab. Lett. 3 (2009) 35;
(h) C.R. Maldonado, C. Marín, F. Olmo, O. Huertas, M. Sánchez-Moreno, M.J. Rosales, J.M. Salas, J. Med. Chem. 53 (2010) 6964.

[15] 1,2,4-Triazoles are a known class of antifungal drugs such as Fluconazole, Voricanozole, Ravuconazole, Itraconazole, Posaconazole. Selected references for 1,2,3-triazoles:
(a) N.G. Aher, V.S. Pore, N.M. Mishra, A. Kumar, P.K. Shulka, A. Sharma, M.K. Bhat, Bioorg. Med. Chem. Lett. 19 (2009) 759;
(b) X.-L. Wang, K. Wan, C.-H. Zhou, Eur. J. Med. Chem. 45 (2010) 4631;
(c) S. Yu, X. Chai, H. Hu, Y. Yan, Z. Guan, Y. Zou, Q. Sun, Q. Wu, Eur. J. Med. Chem. 45 (2010) 4435.

[16] A. Paul, J. Einsiedel, R. Waibel, F.W. Heinemann, K. Meyer, P. Gmeiner, Tetrahedron 65 (2009) 6156.

[17] M.I. Antczak, J.-L. Montchamp, Synthesis (2006) 3080.

[18] P.Z. Demko, K.B. Sharpless, Angew. Chem. Int. Ed. 41 (2002) 2110.

[19] (a) J.E. Moses, A.D. Moorhouse, Chem. Soc. Rev. 36 (2007) 1249;
(b) V.D. Bock, H. Hiemstra, J.H. van Maarseveen, Eur. J. Org. Chem. (2006) 51.

[20] A. Dondoni, A. Marra, J. Org. Chem. 71 (2006) 7546.

[21] M. Hojo, R. Masuda, Y. Kokuryo, H. Shioda, S. Matsuo, Chem. Lett. (1976) 499.

[22] G.M. Siqueira, A.F.C. Flores, G. Clar, N. Zanatta, M.A.P. Martins, Quim. Nova 17 (1994) 24.

[23] A.F.C. Flores, G.M. Siqueira, R. Freitag, N. Zanatta, M.A.P. Martins, Quim. Nova 17 (1994) 298.

[24] H.G. Bonacorso, M.B. Costa, S. Moura, L. Pizzuti, M.A.P. Martins, N. Zanatta, A.F.C. Flores, J. Fluorine Chem. 126 (2005) 1396.

[25] CrysAlisPro, Oxford Diffraction Ltd., Version 1.171.33.46 (release 27-08-2009 CrysAlis171.NET).

[26] Analytical numeric absorption correction using a multifaceted crystal model based on expressions derived by R.C. Clark and J.S. Reid: R.C. Clark, J.S. Reid, Acta Cryst. A51 (1995) 887–897.

[27] G. Cascarano, A. Altomare, C. Giacovazzo, A. Guagliardi, A.G.G. Moliterni, D. Siliqi, M.C. Burla, G. Polidori, M. Camalli, Acta Crystallogr. A52 (1996), C-79.

[28] D.J. Watkin, C.K. Prout, J.R. Carruthers, P.W. Betteridge, CRISTAL Issue 11, Chemical Crystallography Laboratory, Oxford, UK, 1999.

[29] Structure refinement details and results for **20**: $C_{14}H_{12}Cl_1Cu_1F_3N_4O_1$, M = 408.3 g mol^{-1}, monoclinic, λ(Mo) = 0.71069 Å, a = 14.6915(4) Å, b = 9.4734(3) Å, c = 11.7399(4) Å, β = 95.211(3)°, V = 1627.18(8) Å^3, T = 293 K, space group $P2_1/c$ (no. 14), Z = 4, 8216 reflections measured, 2651 unique (R_{int} = 0.021), $R(F, I/\sigma(I) > 3)$ = 0.0307, $R_W(F, I/\sigma(I) > 3)$ = 0.0323, S = 1.11, $\Delta\rho_{max}$ = 0.26 e$^-$ Å^{-3}, $\Delta\rho_{min}$ = −0.27 e$^-$ Å^{-3}, 2800 reflections used to refine 217 parameters.

[30] Structure refinement details and results for **21**: $C_{40}H_{30}Br_2Cl_2Cu_2F_6N_8O_2$, $C_2H_4Cl_4$, M = 12.96.4 g mol^{-1}, triclinic, λ(Mo) = 0.71069 Å, a = 17.737(2) Å, b = 17.747(2) Å,c = 18.305(1) Å, α = 74.829(8)°, β = 89.967(7)°, γ = 61.88(1)°, V = 4853.2(3) Å^3, T = 110 K, space group $P-1$ (no. 2), Z = 4, 22,636 reflections measured, 22,636 unique (R_{int} = 0.084), $R(F, I/\sigma(I) > 3)$ = 0.1486, $R_W(F, I/\sigma(I) > 3)$ = 0.1720, S = 1.11, $\Delta\rho_{max}$ = 2.625 e$^-$ Å^{-3}, $\Delta\rho_{min}$ = −2.625 e$^-$ Å^{-3}, 8406 reflections used to refine 545 parameters.

[31] Reference method for broth dilution antifungal susceptibility testing of yeasts, 3rd ed. M27-A3, Clinical and Laboratory Standards Institute, Wayne, PA, 2008.