2-Trifluoroacetyl-1-methoxycycloalkenes: A Convenient Precursor for the Synthesis of Geminated Polymethylene Trifluoromethyl Substituted Heterocycles

Helio Gauze Bonacorso,* Michelle Budke Costa, Cleber André Cechinel, Ronan Carlo Sehnem, Marcos Antonio Pinto Martins, and Nilo Zanatta

Núcleo de Química de Heterociclos (NUQUIMHE), Departamento de Química, Universidade Federal de Santa Maria, Santa Maria, RS, 97105-900, Brazil
*E-mail: heliogb@base.ufsm.br

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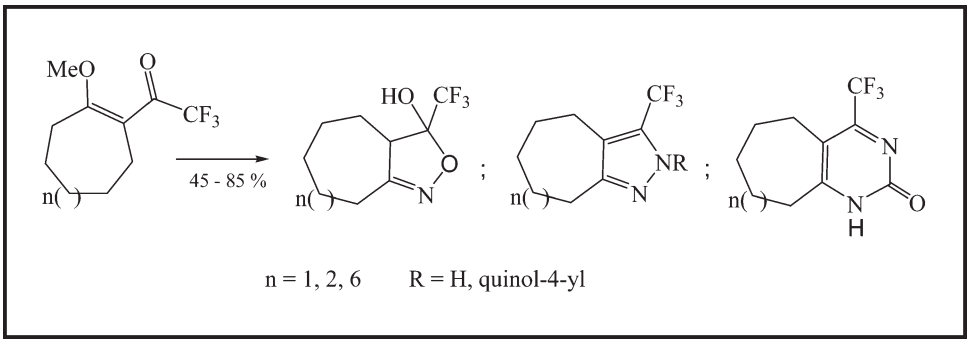

This article describes the methodology that allows the simultaneous introduction of a trifluoromethyl group and a 7-, 8-, and 10-membered cycloalkane ring fused to heterocyclic derivatives. A series of 10 geminated polymethylene trifluoromethyl substituted isoxazolines, pyrazoles, pyrimidinones, and a pyrazolyl-quinoline were obtained in moderate to good yields from the reaction of three 2-trifluoroacetyl-1-methoxycycloalkenes derived from cycloheptanone, cyclooctanone, and cyclododecanone with hydroxylamine hydrochloride, hydrazine hydrochloride, urea, and 7-chloro-4-hydrazinoquinoline.

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INTRODUCTION

Among some classes of compounds that show biological activity, heterocycles [1] such as isoxazolines, pyrazoles, and pyrimidinones have been shown to be of great importance. These compounds present a wide range of biological applications [2–9] both in the pharmaceutical area and the agrochemical industry, including as CNS depressants and analgesics, as well as for their antitumor, antibacterial, and anti-HIV activity, and antifungal, antiviral, antiparasitic, antitubercular, and insecticidal properties.

A review of the literature has shown that the synthesis of heterocyclic compounds derived from cycloalkane has been relatively unexplored. In many cases, it has been observed that enlargement of the cycloalkane ring-size influences the biological effect, where cyclododecane derivatives present an advantageous position (Fig. 1) [10–12]. Moreover, some cycloalkanespiro-5-hydantoins have a modest anticonvulsive effect.

However, a study of structure-activity relationships of various 3-aminocycloalkanespiro-hydantoins showed that (**I**) [10] and similar compounds, in contrast to hydantoins, exerted well pronounced atropinsensitive and contractile effects on guinea-pig ileum longitudinal muscle preparations.

In 2001, Kim *et al*. [11] prepared tetraoxacycloalkanes and the subsequent evaluation of antimalarial activity of the cyclic peroxides *in vitro* and *in vivo* revealed cyclododecane (**II**) derivatives to be a promising potent antimalarial drug.

Taylor *et al*. [12] synthesized cycloalka[*g*]pteridines (**III**) and studied their biological activity as dihydrofolate reductase inhibitors against *Lactobacillus casei* and *Trypanosoma cruzi*. Activity was found to depend upon ring size, with the greatest activity exhibited by the cyclododecane derivative, which was ~1000 times more active than the cyclohexane derivative.

In addition, fluorine-containing heterocyclic compounds are of significant interest because of their biological properties [13]. The introduction of a trifluoromethyl and its higher homologue groups into a heterocycle frequently results in more potent activity than that of the parent compound, a fact, which is probably related to the high lipophilicity of perfluoroalkyl substituents [14,15]. As a consequence, in recent years much attention has been devoted to the synthesis of

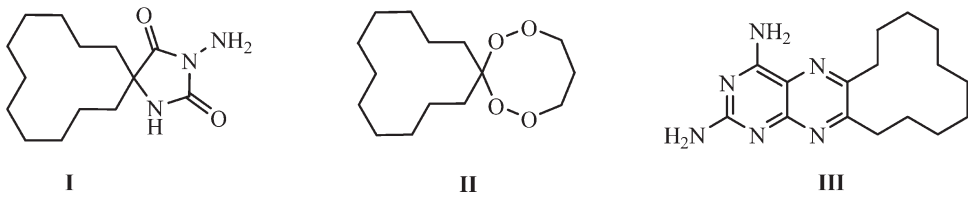


Figure 1. Cycloalkane derivatives of biological relevance.

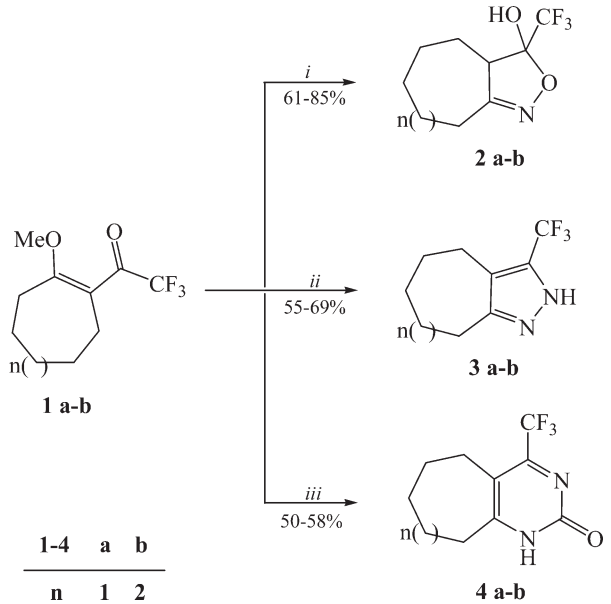
trifluorinated compounds and many have proven to be of important therapeutic value [16,17].

The preparation of trifluoromethylated heterocyclic compounds from cyclocondensation reactions of β-alkoxyvinyl trihalomethyl ketones with 1,2 and 1,3 dinucleophilic compounds has been developed by our research group [18–23]. Recently, the synthesis [24] and ^{17}O NMR spectroscopy of 2-trifluoroacetyl-1-methoxycycloalkenes [25] derived from cyclopentanone, cyclohexanone, cycloheptanone, cyclooctanone, and cyclododecanone [26] were reported. However, there is no publication in the literature with the objective of carrying out a regiospecific and simultaneous introduction of a trifluoromethyl group and a fused 7-, 8-, and 10-membered cycloalkane ring fused to heterocyclic derivatives starting from b-alkoxyvinyl trifluoromethyl ketones and hydroxylamine, hydrazines or urea.

Although many methods for the synthesis of isoxazolines, pyrazoles, and pyrimidinones and functionalized derivatives have been published, attempts at the synthesis of trifluoromethyl substituted and geminated cycloalka-heterocycles have not yet been successful. A search of the literature showed that by a conventional procedure, only 3-trifluoromethyl-1,4,5,6,7,8-hexahydrocyclohepta[*c*]pyrazole has been obtained from a direct reaction of trifluoroacetylcycloheptanone and hydrazine hydrochloride [27].

Considering the biological importance of trifluoromethyl substituted heterocyclic compounds derived from cycloalkanes, we reported our new results on the reaction of 2-trifluoroacetyl-1-methoxycycloalkenes derived from cycloheptanone and cyclooctanone in the synthesis and isolation of novel cycloalka -isoxazolines, -pyrazoles, and -pyrimidinones containing a fused 7-, 8-membered ring (Scheme 1). Because of the fact that heterocycles derived from cyclododecanone have shown greater activity in relation to derivatives of cyclohexanone, we also reported the synthesis and isolation of novel heterocyclic compounds fused to a cyclododecane ring (Scheme 2).

Scheme 1. Reagents and conditions: (i) $NH_2OH.HCl$, Pyridine, H_2O, 45°C, 24 h; (ii) $NH_2NH_2.HCl$, Pyridine, EtOH, reflux, 8 h; (iii) $NH_2CONH_2/BF_3.OEt_2$, *i*-PrOH, reflux, 20 h.

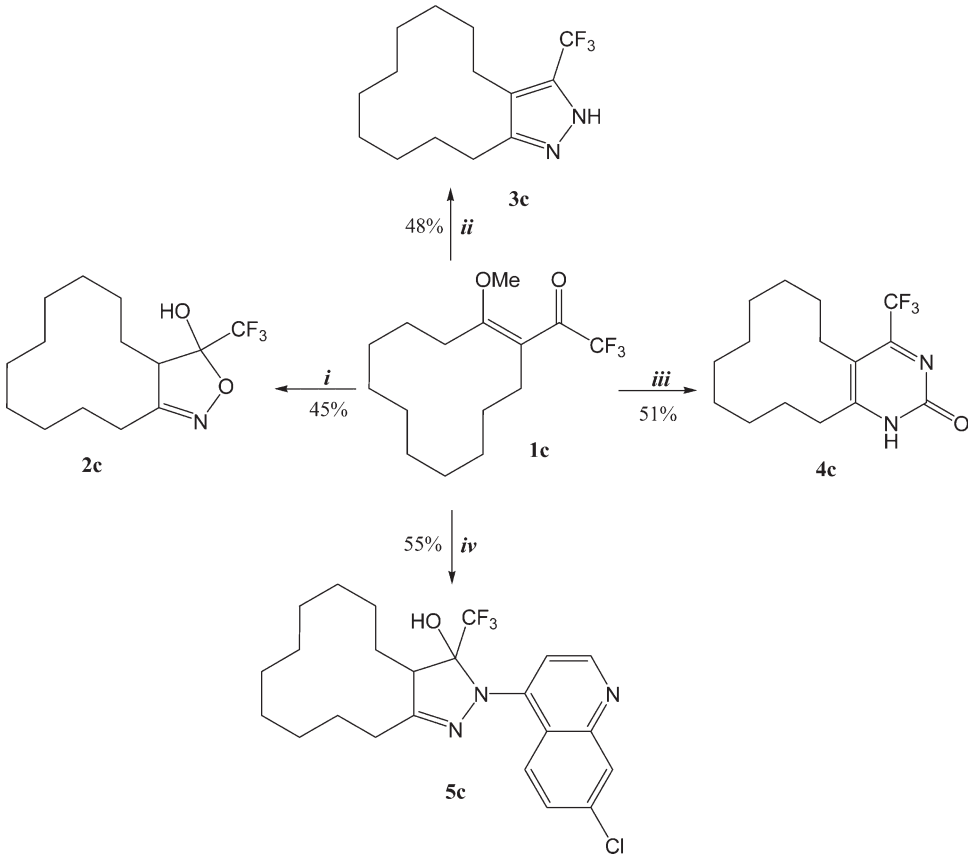


RESULTS AND DISCUSSION

2-Trifluoroacetyl-1-methoxycycloalkenes **1a–c** were obtained by a direct acylation reaction of the 1,1-dimethoxycycloalkanes derived from the respective cycloalkanones with trifluoracetic anhydride in the presence of pyridine, as described in the literature [20,28–30]. Subsequently, we reacted pure 2-trifluoroacetyl-1-methoxycycloalkenes **1a–c** with hydroxylamine, hydrazines, and urea, regiospecifically obtaining, in an one-step reaction, 3-hydroxy-3-trifluoromethyl-3,4-dihydro-cycloalka[*c*]isoxazoles **2a–c** (45–85%), 3-trifluoromethyl-3,4-dihydrocycloalka[*c*]pyrazoles **3a–c** (48–69%), 4-trifluoromethylcycloalka[*d*]-2(1*H*)pyrimidinones **4a–c** (50–58%) and 4-(3-hydroxy-3-trifluoromethyl-cyclododeca[*c*]pyrazol-2-yl)-7-chloroquinoline (**5c**) (55%).

Presumably, the reactions start with the Michael addition of the amino groups of the dinucleophiles at the β-carbon atom of the enones **1a–c** furnishing addition products. The aminoether function is unstable in pyridine/water or in alcohol (reaction solvents) and the methoxy group is eliminated as methanol. Subsequently,

Scheme 2. Reagents and conditions: (i) $NH_2OH.HCl$, Pyridine, H_2O, 45°C, 24 h; (ii) $NH_2NH_2.HCl$, Pyridine, EtOH, reflux, 8 h; (iii) NH_2CONH_2/$BF_3.OEt_2$, *i*-PrOH, reflux, 20 h; (iv) 7-chloro-4-hydrazino-quinoline, MeOH, reflux, 6 h.



the intramolecular cyclization reaction occurs and involves the carbonyl function of the not isolated β-enaminone and the second heteroatom of the dinucleophile reagent. In addition, the elimination of a water molecule is not likely to occur in the isoxazole structures (**2a–c**) because of the electron-withdrawing effect of the oxygen and the basic reaction condition employed (pyridine/water) or because of the electronic effect of cloro-quinoline substituent (**5c**).

The reactions of 2-trifluoroacetyl-1-methoxycycloalkenes **1a–c** with hydroxylamine hydrochloride using pyridine/H_2O as solvent were carried out under mild conditions at 45°C for 24 h. After 24 h, the isoxazolines **2a–c** were isolated by a simple extraction with diethyl ether.

Cycloalka[*c*]pyrazoles **3a–c**, were obtained from the reaction of 2-trifluoroacetyl-1-methoxycycloalkenes **1a–c**, with hydrazine hydrochloride in the presence of pyridine. The reactions to obtain **3a–b, 7** were carried out at a molar ratio of 1:1 in methanol as solvent at 80°C for 8 h.

Cycloalka[*d*]-2(1*H*)pyrimidinones **4a–c**, were prepared from the cyclocondensation reaction of 2-trifluoroacetyl-1-methoxycycloalkenes **1a–c**, with urea, carried out at a 1:1.5 molar ratio in anhydrous propan-2-ol as solvent. The most satisfactory results were obtained when the reactions were performed under mild conditions by stirring the reagents for 20 h at 80–85°C, using a Lewis acid as catalyst ($BF_3.OEt_2$). After 20 h, the reactions were refrigerated and the solids were isolated by filtration.

Subsequently, 2-trifluoroacetyl-1-methoxycyclododecene (**1c**) was used to prepare cyclododeca[*c*]pyrazoles (**5c**) derived from 7-chloro-4-hydrazinoquinoline. The objective of synthesizing compound **5c** was to build a molecule that would serve as the foundation for a family of new antimalarials. The reaction was carried out in methanol for 6 h at 65°C, similar to the methodology systematized by Bonacorso *et al*. [31] to obtain pyrazolylquinolines. Compound **5c** was obtained in satisfactory yield (55%), after recrystallization from methanol.

The unambiguous ^1H and ^{13}C NMR chemical shift assignments of cycloalka -isoxazolines (**2a–c**), -pyrazoles (**3a–c**), -pyrimidinones (**4a–c**), and -pyrazoline (**5c**), were made with the help of homo- and hetero- nuclear COSY, HMQC, and HMBC 2D NMR experiments

and by comparison with NMR data of the literature [27] and from other 2-pyrazolines previously synthesized in our laboratory [26,31(a)].

In conclusion, we consider the one-step and regiospecific reaction reported here to be a useful, simple, new, and convenient method, which employs commercially available reagents and mild conventional conditions to obtain novel interesting trifluoromethylated heterocycles fused to a cycloalkane ring.

EXPERIMENTAL

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split–splitless injector, auto sampler, cross-linked HP-5 capillary column (30 m, 0.32 mm internal diameter), and helium was used as the carrier gas. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 200 or Bruker DPX 400 spectrometer (^{1}H at 20.13 MHz or 40.13 MHz and ^{13}C at 50.32 MHz or 100.62 MHz, respectively), 5 mm sample tubes, 298 K digital resolution ± 0.01 ppm, in methyl sulfoxide-d_6 using tetramethylsilane as internal reference. The CHN elemental analyses were performed on a Perkin–Elemer 2400 CHN elemental analyzer (São Paulo University, USP/Brazil).

Synthetic procedures. ***General procedure for the preparation of 3-hydroxy-3-trifluoromethyl-3,4-dihydro-cycloalka[c]isoxazoles (2a–c).*** To a stirred solution of 2-trifluoroacetyl-1-methoxycycloalkenes (**1a–c**) (5 mmol) in pyridine (0.4 g; 5 mmol), was added a solution of hydroxylamine hydrochloride (0.35 g; 5 mmol) in H_2O (2 mL). The mixture was stirred at 45°C for 24 h. After 24 h, water (50 mL) was added and extracted with diethyl ether (3 × 15 mL), dried with Na_2CO_3 and evaporated. The solids were recrystallized from methanol or diethyl ether.

3-Hydroxy-3-trifluoromethyl-3H-3a,4,5,6,7,8-hexahydro-cyclohepta[c]isoxazole (2a). This compound was obtained as white crystals (85% yield), Mp. 128–130°C.^{1}H NMR (DMSO-d_6): δ 8.02 (s, 1H, OH), 3.52 (m, 1H, CH), 2.63–2.42 (m, 2H, CH_2), 1.74–1.48 (m, 8H, CH_2).^{13}C NMR (DMSO)-d_6): δ 163.7 (C-8a), 122.8 (q, CF_3, ^1J = 285.4), 102.7 (q, C-3, ^2J = 31.8) 54.3 (C-3a), 30.4 (CH_2), 27.5 (CH_2), 26.6 (CH_2), 25.2 (CH_2), 23.8 (CH_2). Anal. Calc. for $C_9H_{12}F_3NO_2$ (223.08): C, 48.43%; H, 5.42%; N, 6.28% Found: C, 48.24%; H, 5.18%; N, 6.09%. MS [m/z(%)] for $C_9H_{12}F_3NO_2$ (223.08): 223 (M^+, 10), 154 (32), 136 (38), 108 (100), 69 (70).

3-Hydroxy-3-trifluoromethyl-3,3a,4,5,6,7,8,9-octahydro-cycloocta[c]isoxazole (2b). This compound was obtained as white crystals (61% yield), Mp. 105–107°C. ^{1}H NMR (DMSO-d_6): δ 8.1 (s, 1H, OH), 3.43–3.36 (m, 1H, CH), 2.6–2.5 (m, 2H, CH_2), 1.82–1.49 (m, 10H, CH_2). ^{13}C NMR (DMSO)-d_6): δ 162.8 (C-9a), 122.8 (q, CF_3, ^1J = 284.7), 103.3 (q, C-3, ^2J = 31.1) 52.3 (C-3a), 26.0 (CH_2), 25.2 (CH_2), 24.9 (CH_2), 24.8 (CH_2), 24.2 (CH_2), 22.3 (CH_2). Anal. Calc. for $C_{10}H_{14}F_3NO_2$ (237.10): C, 50.63%; H, 5.95%; N, 5.90% Found: C, 50.56%; H, 5.73%; N, 5.79%. MS [m/z(%)] for $C_{10}H_{14}F_3NO_2$ (237.10): 237 (M^+, 34), 168 (26), 150 (15), 122 (82), 112 (86), 99(70), 69 (34), 55(100).

3-Hydroxy-3-trifluoromethyl-3,3a,4,5,6,7,8,9,10,11,12,13-dodecahydro-cyclododeca[c]isoxazole (2c). This compound was obtained as white crystals (45% yield), Mp. 129–132°C. ^{1}H NMR (DMSO-d_6): δ 8.3 (s, 1H, OH), 3.3–3.2 (m, 1H, CH), 2.47–2.41 (m, 2H, CH_2), 1.66–1.60 (m, 2H, CH_2), 1.36–1.27 (m, 16H, CH_2). ^{13}C NMR (DMSO)-d_6): δ 162.5 (C-13a), 122.8 (q, CF_3, ^1J = 285.4), 103 (q, C-3, ^2J = 31.8) 50.4 (C-3a), 25.3 (CH_2), 24.2 (CH_2), 23.9 (CH_2), 23.8 (CH_2), 23.6 (CH_2), 23.2 (CH_2), 22.7 (CH_2), 22.5 (CH_2), 21.9 (CH_2). Anal. Calc. for $C_{14}H_{22}F_3NO_2$ (293.16): C, 57.33%; H, 7.56%; N, 4.78% Found: C, 57.38%; H, 7.82%; N, 5.03%. MS [m/z(%)] for $C_{14}H_{22}F_3NO_2$ (293.16): 293 (M^+, 5), 224 (100), 100 (25), 69 (20), 55(43).

General procedure for the preparation of 3-trifluoromethyl-cycloalka[c]1H-pyrazole (3a–c). To a solution of hydrazine hydrochloride (0.35 g; 5 mmol) in the presence of pyridine (0.4 g; 5 mmol), was added 2-trifluoroacetyl-1-methoxycycloalkenes (5 mmol) (1**a–c**) in ethanol (10 mL) and the mixture was stirred in ice bath. The mixture was then stirred at room temperature for 30 min and under reflux for another 8 h. After 8 h, the solution was concentrated and cooled (<10°C). The crystalline solids were isolated by filtration and washed with cold ethanol.

3-Trifluoromethyl-1,4,5,6,7,8-hexahydrocyclohepta[c]pyrazole (3a). This compound was obtained as white crystals [27] (69% yield), Mp. 132–134°C. (Lit. [27], Mp. 154.1°C). ^{1}H NMR (DMSO-d_6): δ 13.09 (s, 1H, NH), 2.76–2.74 (m, 2H, CH_2), 2.61–2.58 (m, 2H, CH_2), 1.80–1.61 (m, 6H, CH_2). ^{13}C NMR (DMSO)-d_6): δ 144.63 (C-8a), 138.46 (q, C-3, ^2J = 34.6), 122.51 (q, CF_3, ^1J = 269.15), 117.17 (C-3a), 30.96 (CH_2), 27.93 (CH_2), 26.43 (CH_2), 25.75 (CH_2), 23.19 (CH_2). Anal. Calc. for $C_9H_{11}F_3N_2$ (204.19): C, 52.94%; H, 5.43%; N, 13.72% Found: C, 52.38%; H, 5.71%; N, 13.63%. MS [m/z(%)] for $C_9H_{11}F_3N_2$ (204.19): 204 (M^+, 98), 203 (100), 175 (63), 162 (85), 135(55), 69(9).

3-Trifluoromethyl-4,5,6,7,8,9-hexahydrocycloocta[c]1H-pyrazole (3b). This compound was obtained as white crystals (55% yield), Mp. 119–122°C. ^{1}H NMR (DMSO-d_6): δ 13.09 (s, 1H, NH), 2.77–2.71 (m, 2H, CH_2), 2.642.57 (m, 2H, CH_2), 1.59–1.33 (m, 8H, CH_2). ^{13}C NMR (DMSO)-d_6): δ 142.85 (C-8a), 138.31 (q, C-3, ^2J = 33.91), 122.51 (q, CF_3, ^1J = 269.15), 114.73 (C-3a), 28.84 (CH_2), 4.78 (CH_2), 22.71 (CH_2), 19.9 (CH_2). Anal. Calc. for $C_{10}H_{13}F_3N_2$ (218.22): C, 55.04%; H, 6.00%; N, 12.84% Found: C, 55.38%; H, 5.82%; N, 13.03%. MS [m/z(%)] for $C_{10}H_{13}F_3N_2$ (218.22): 218 (M^+, 83), 189 (72), 162 (100), 149 (53), 69(10).

3-Trifluoromethyl-4,5,6,7,8,9,10,11,12,13-decahydrocyclododeca[c]-1H-pyrazole (3c). This compound was obtained as white crystals (48% yield), Mp. 147–148°C. ^{1}H NMR (DMSO-d_6): δ 2.55–2.59 (m, 2H, CH_2), 2.44–2.48 (m, 2H, CH_2), 1.73 (s, 2H, CH_2), 1.59–1.58 (d, 2H, CH_2), 1.41 (s, 4H, CH_2), 1.22–1.35 (m, 8H, CH_2). ^{13}C NMR (DMSO)-d_6): δ 142.63 (C-13a), 138.1 (q, C-3, ^2J = 35.0), 122.6 (q, CF_3, ^1J = 268.7), 115.3 (C-3a), 28.0 (CH_2), 26.8 (CH_2), 24.5 (CH_2), 24.4 (CH_2), 23.9 (CH_2), 23.7 (CH_2), 22.2 (CH_2), 21.7 (CH_2), 20.0 (CH_2), 19.1 (CH_2). Anal. Calc. for $C_{14}H_{21}F_3N_2$ (274.33): C, 61.30%; H, 7.72%; N, 10.21% Found: C, 61.38%; H, 7.62%; N, 10.19%. MS [m/z(%)] $C_{14}H_{21}F_3N_2$ (274.33): 274 (M^+, 66), 205 (62), 162 (100), 69 (22), 55(47).

General procedure for the preparation of 4-trifluoromethyl-cycloalka[d]-2(1H)pyrimidinone (4a–c). To a stirred solution of urea (0.42 g; 7 mmol) in propan-2-ol (10 mL) kept

at room temperature (20–25°C), were added 2-trifluoroacetyl-1-methoxycycloalkenes (1**a–c**) (5 mmol) and boron trifluoride diethyl etherate (sol. 45% in MeOH) (10 drops). The mixture was stirred at 85°C for 20 h. After cooling (<10°C), the crystalline solids were isolated by filtration, washed with cold propan-2-ol, and recrystallized from ethanol.

4-Trifluoromethyl-5H-6,7,8,9-tetrahydrocyclohepta[d]-2(1H)pyrimidinone (4a). This compound was obtained as white crystals (58% yield), Mp. 229–230°C. ^{1}H NMR (DMSO-d_6): δ 12.5 (s, 1H, NH), 2.8 (m, 2H, CH_2), 2.7 (m, 2H, CH_2), 1.7 (m, 2H, CH_2), 1.6 (m, 2H, CH_2), 1.5 (m, 2H, CH_2). ^{13}C NMR (DMSO)-d_6): δ 170.7 (C=O), 156.8 (C-4), 156.3 (C-9a), 120.7 (q, CF_3, ^1J = 278.3), 116.4 (C-4a), 33.7 (CH_2), 30.8 (CH_2), 26.4 (CH_2), 25.2 (CH_2), 24.7 (CH_2). Anal. Calc. for $C_{10}H_{11}F_3N_2O$ (232.20): C, 51.73%; H, 4.77%; N, 12.06%. Found: C, 51.46%; H, 4.74%; N, 11.97%. MS [*m*/*z*(%)] for $C_{10}H_{11}F_3N_2O$ (232.20): 232 (M^+, 100), 163 (21), 69 (7).

4-Trifluoromethyl-5,6,7,8,9,10-hexahydrocycloocta[d]-2(1H) pyrimidinone (4b). This compound was obtained as white crystals (50% yield), Mp. 145–147°C. ^{1}H NMR (DMSO-d_6): δ 2.8 (m, 1H, CH_2), 2.7 (m, 1H, CH_2), 2.65–2.61 (m, 2H, CH_2), 2.4 (m, 1H, CH_2), 1.63–1.61 (m, 3H, CH_2), 1.27 (m, 4H, CH_2). ^{13}C NMR (DMSO)-d_6): δ 164.3 (C=O), 158.1 (q, C-4, ^2J = 28.3), 156.5 (C-10a), 120.6 (CF_3, ^1J = 279), 113.0 (C-4a), 31.2 (CH_2), 30.4 (CH_2), 29.8 (CH_2), 25.2 (CH_2), 25.3 (CH_2), 23.2 (CH_2). Anal. Calc. for $C_{11}H_{13}F_3N_2O$ (246.10): C, 53.66%; H, 5.32%; N, 11.38% Found: C, 54.01%; H, 5.42%; N, 11.74%. MS [*m*/*z*(%)] for $C_{11}H_{13}F_3N_2O$ (246.10): 246 (M^+, 40), 217 (100), 177 (18), 69 (30).

4-Trifluoromethyl-5,6,7,8,9,10,11,12,13,14-decahydro-cyclododeca[d]-2(1H)pyrimidinone (4c). This compound was obtained as white crystals (51% yield), Mp. 221–223°C. ^{1}H NMR (DMSO-d_6): δ 12.5 (s, 1H, NH), 2.69 (m, 2H, CH_2), 2.6 (m, 2H, CH_2), 1.79 (m, 2H, CH_2), 1.50–1.42 (m, 14H, CH_2). ^{13}C NMR (DMSO)-d_6): δ 167.4 (C=O), 158.8 (C-4), 156.5 (C-14a), 120.7 (CF_3, ^1J = 278.3), 114.1 (C-4a), 28.9 (CH_2), 26.9 (CH_2), 26.5 (CH_2), 25.9 (CH_2), 23.2 (CH_2), 22.3 (CH_2), 21.6 (CH_2). Anal. Calc. For $C_{15}H_{23}F_3N_2O$ (304.18): C, 59.59%; H, 7.00%; N, 9.27% Found: C, 59.61%; H, 6.79%; N, 9.17%. MS [*m*/*z*(%)] for $C_{15}H_{23}F_3N_2O$ (304.18): 302 (M^+, 9), 245 (20), 233 (100), 192 (41), 69 (5).

General procedure for the preparation of 4-(3-hydroxy-3-trifluoromethyl-3,3a,4,5,6,7,8,9,10,11,12,13-dodecahydrocyclododeca[c]pyrazol-2-yl)-7-chloroquinoline (5c). To a stirred solution of 2-trifluoroacetyl-1-methoxycyclododeceno (1c) (5 mmol) in methanol (30 mL), was added 7-chloro-4-hydrazinoquinoline (0.96 g; 5 mmol). The mixture was stirred at 65°C for 6 h. Subsequently, the solvent was evaporated and a solution of methanol/H_2O (3:1) was added. The solids were filtered and recrystallized from methanol. This compound was obtained as white crystals (55% yield), Mp. 108–110°C. ^{1}H NMR (DMSO-d_6) δ 8.28 (s,1H, OH), 3.20–3.21 (d, 1H, H-3a);(quinoline) = δ 8.79–8.80 (s,1H, H-2), 8.36–8.39 (d,1H, H-8), 8.01–8.02 (d,1H, H-6), 7.69–7.70 (d, 1H, H-5), 7.54–7.57 (m, 1H, H-8); (cyclododeca) = δ 3.20–3.21 (m, 2H, CH_2), 1.83–1.87 (d, 2H, CH_2), 1.57–1.66 (m, 3H, CH_2), 1.46 (s, 4H, CH_2), 1.38 (s, 9H, CH_2). ^{13}C NMR (DMSO-d_6): δ 156.8 (C-13a), 123.1 (q, CF_3, ^1J = 287.5), 94.7 (q, C-3, ^2J = 29.9), 51.4 (C-3a); (quinolyl): δ151.2 (C-2), 149.8 (C-8a), 147.0 (C-4), 133.6 (C-7), 128.0 (C-8), 127.4 (C-6), 125.5 (C-5), 122.6 (C-4a), 113.4 (C-3); (cyclododeca): δ 25.6 (CH_2), 25.3 (CH_2), 24.2 ($2CH_2$), 23.8 (CH_2), 23.7 (CH_2), 23.4 (CH_2), 22.8 (CH_2), 22.5 (CH_2), 21.1 (CH_2). Anal. Calc. for $C_{23}H_{27}ClF_3N_3O$ (453.93): C, 60.86%; H, 6.00%; N, 9.26%. Found: C, 61.01%; H, 5.78%; N, 9.54%. MS [*m*/*z*(%)] for $C_{23}H_{27}ClF_3N_3O$ (453.93): 435 (M^+-H_2O, 100), 336 (61), 325 (72), 162 (45), 69(8).

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