Four-component reaction between cyclohexyl isocyanide, aromatic aldehydes, aromatic amines and trifluoroacetic anhydride

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Reaction of cyclohexyl isocyanide with aromatic aldehydes, aniline derivatives and trifluoroacetic anhydride in dichloromethane at room temperature afforded *N*-[cyclohexylcarbamoyl(aryl)methyl]-2,2,2-trifluoro-N-arylacetamide derivatives in nearly quantitative yields after 10 min. The work-up procedure is very easy and the products are precipitated in ether as pure solids. The structure of one of the products was established by X-ray single crystal analysis.

Keywords: isocyanide, four-component reaction, trifluoroacetic anhydride, aromatic aldehydes, aromatic amines, Ugi reaction

An important issue that has gained much attention from organic and bioorganic chemists during the last few decades has been the development of new strategies for the synthesis of complex molecular structures from easily available substrates by short and effective routes. The most important of these strategies has been the development of multi-component reactions (MCRs), reactions in which three or more compounds connect together by covalent bonds to produce a complex molecule which contains the main structure of all the starting materials. As MCRs are one-pot reactions, they are easier to carry out than multistep syntheses. Coupled with high-throughput library screening, this strategy was an important development in the drug discovery in the context of rapid identification and optimisation of biologically active lead compounds.[1–9]

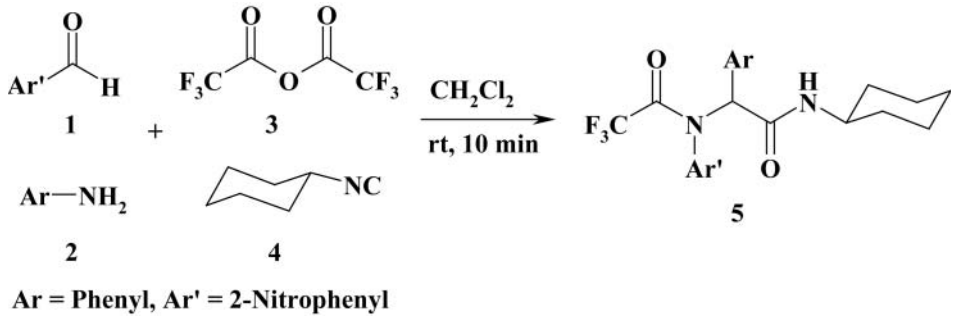
Among MCRs, isocyanide-based multi-component reactions (IMCRs) have gained the most attention by organic chemists. Ugi four component reactions (U-4CR)[6–8] and Passerini three-component reactions (P-3CR)[10] are among the most important IMCRs. U-4CR describes the reaction of isocyanides with an acidic compound in the presence of imines formed initially by the reaction between an aldehyde and an amine. Different functional groups, such as carboxylic acids, thiosulfates, hydrogen selenide, hydrazoic acids, hydrogen cyanate and thiocyanate, aminoacids, thioacids and alkoxycarboxylic acids have been used as the acid component in U-4CR.

N-Trifluoroacetylated amines have become common and useful protected forms of a wide variety of amines.[11] Ease of removal is one important factor that has contributed to the many applications of the *N*-trifluoroacetyl protecting group in organic chemistry.[12] Because of this widespread use, several methods for the trifluoroacetylation of amines using, for example, trifluoroacetic anhydride,[15] *S*-ethyl trifluorothioacetate,[13] *N*-(trifluoroacetyl)imidazole,[14] 2-[(trifluoroacetyl)oxy] pyridine,[15] trifluoroacetyl triflate,[16] *N*-(trifluoroacetoxy)succinimide,[17] (trifluoroacetyl)benzotriazole[18] and *N*-(trifluoroacetyl) succinimide[19] as trifluoroacetylating reagents have been developed.

Continuing our studies on IMCRs,[20–23] we report here the results of our study on the reaction between cyclohexyl isocyanide, aromatic aldehydes, aromatic amines and trifluoroacetic anhydride (TFAA).

Treatment of cyclohexyl isocyanide (**4**) with 2-nitrobenzaldehyde (**1a**), aniline (**2a**) and TFAA (**3**) in dichloromethane at room temperature after 10 min afforded *N*-[cyclohexylcarbamoyl(2-nitrophenyl)methyl]-2,2,2-trifluoro-*N*-phenylacetamide (**5a**) in nearly quantitative yield (Scheme 1). The work-up procedure was very easy and the product was precipitated in ether as a pure solid.

The IR spectrum of compound **5a** showed absorption bands at 3300, 1691 and 1655 cm^{-1}, for NH and two amide carbonyl groups respectively. Asymmetric and symmetric stretching vibrations due to a nitro group were observed at 1528 and 1350 cm^{-1}, respectively. In the ^1H NMR spectrum of **5a**, multiplets between 1.15 and 1.97 ppm and between 3.78 and 3.82 ppm were observed for the cyclohexyl protons, along with a doublet at 5.65 (D_2O–exchangable) and a singlet at 6.43 ppm for NH and CH protons, respectively. Protons of the unsubstituted nitrophenyl ring resonated as multiplets at 7.18–7.92 ppm. Protons of the phenyl ring were observed as broad



Scheme 1

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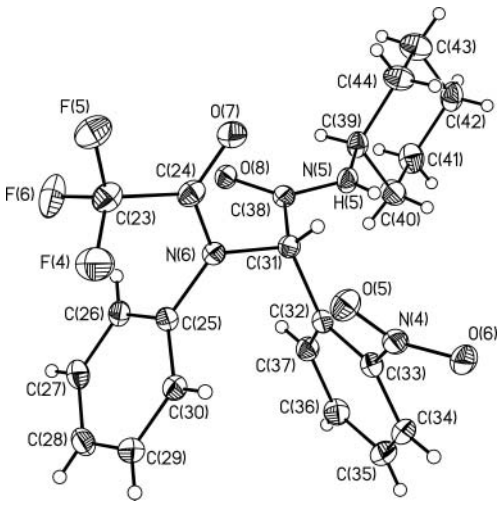


Fig. 1 ORTEP representation of the molecular structure of **5a**.

signals at 6.71, 7.15 and 7.82 ppm. It seems that rotation around the N–C bond between the nitrogen atom and phenyl ring is slow in the time scale of NMR and this causes the broadening of the signals related to the phenyl ring in the ^{1}H NMR spectrum. This broadening of the signals related to the phenyl ring was also observed in the ^{13}C NMR spectrum of compound **5a**. The ^{13}C NMR spectrum of compound **5a** showed 20 distinct signals in consistent with the proposed structure. Carbons related to trifluoroacetyl group were observed as two quartets at 117.5 (J = 285 Hz) and 157.3 (J = 37 Hz). Finally, the structure of compound **5a** was unambiguously established by single crystal X-ray analysis (Fig. 1).

As presented in Scheme 2, it is reasonable to assume that compound **5a** is produced by the addition of cyclohexyl isocyanide to the imine **6,** initially produced by condensation of the aldehyde with aniline, in the presence of TFAA affording intermediate **7,** which is then hydrolysed to the product.

Table 1 Reaction of cyclohexyl isocyanide with aromatic aldehydes, anilines and TFAA

5	Ar	Ar′	Yield*/%
a	C_6H_5	2-$NO_2C_6H_4$	98
b	C_6H_5	3-$NO_2C_6H_4$	98
c	C_6H_5	4-$NO_2C_6H_4$	95
d	C_6H_5	4-ClC_6H_4	95
e	C_6H_5	4-BrC_6H_4	95
f	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	98
g	4-$MeOC_6H_4$	4-ClC_6H_4	95
h	4-$MeOC_6H_4$	4-BrC_6H_4	95
i	4-MeC_6H_4	4-ClC_6H_4	95
j	4-MeC_6H_4	4-BrC_6H_4	95

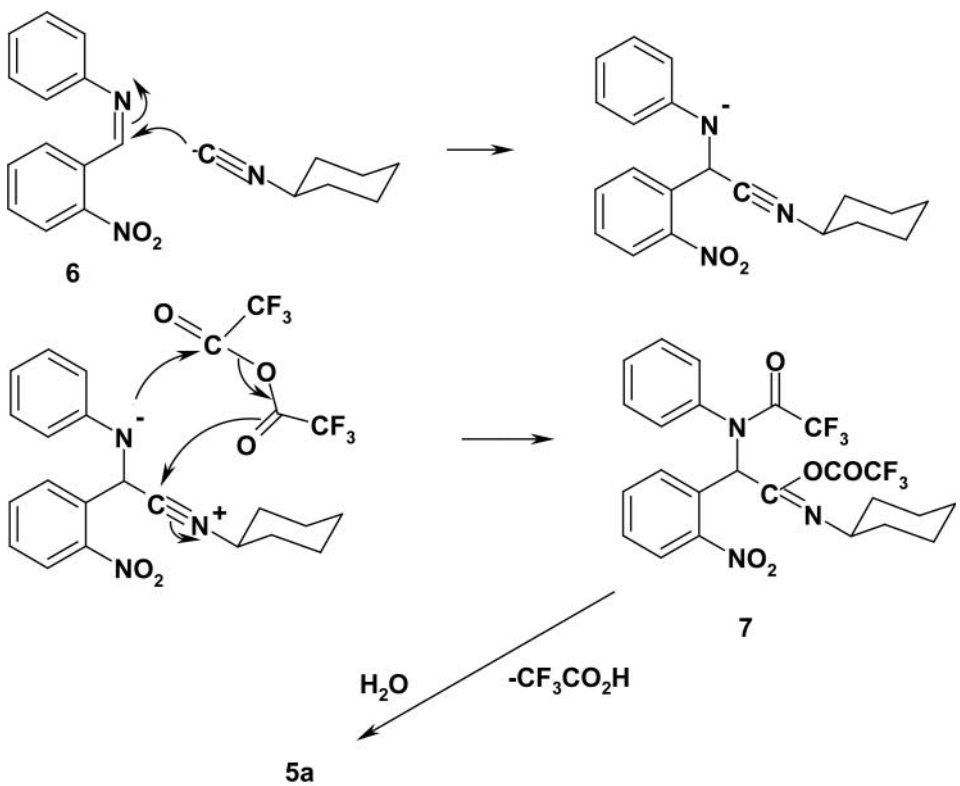
*Isolated yields.

To explore the scope and limitations of this reaction further, we extended our studies to the reaction of cyclohexyl isocyanide with various aromatic aldehydes and anilines in the presence of TFAA. As indicated in Table 1, the reactions proceeded very efficiently with excellent yields.

In conclusion, we report here a four-component reaction between cyclohexyl isocyanide, aromatic aldehydes, aniline derivatives and trifluoroacetic anhydride as a simple and quick method for the synthesis of trifluoroacetylated Ugi-type tetra adducts *N*-[cyclohexylcarbamoyl(aryl)methyl]-2,2,2-trifluoro-*N*-arylacetamide derivatives. The advantages of the method are the use of simple starting materials, short reaction time, easy work-up procedure and high yield of products.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyser at the analytical laboratory of Islamic Azad university, Yazd branch. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}CNMR spectra were recorded on Bruker DRX-500 Avance spectrometer at 500.13 and 125.77 MHz, respectively. ^{1}H and ^{13}CNMR



Scheme 2

spectra were obtained on solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure

To a magnetically stirred solution of the aromatic aldehyde (1 mmol) and the aniline derivative (1 mmol) in CH_2Cl_2 (10 mL) after 5 min were added cyclohexyl isocyanide (1 mmol) and TFAA (1 mmol). After 10 min stirring at room temperature, solvent was removed and diethyl ether (5 mL) was added. The solid was filtered off and washed with cold diethyl ether (2 × 5 mL) to give the desired product.

N-[Cyclohexylcarbamoyl(2-nitro-phenyl)methyl]-2,2,2-trifluoro-N-phenylacetamide (**5a**): Yellow crystals, (0.44 g, 98%); m.p. 217–219 °C. IR (KBr) (ν_{max}, cm^{-1}): 3300 (N–H), 1691, 1655 (C=O). MS (*m/z*,%): 450 (M^+ +1, 9). Anal. Calcd for $C_{22}H_{22}F_3N_3O_4$ (449) C, 58.79; H, 4.93; N, 9.35. Found: C, 58.85; H, 4.73; N, 9.42%. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ = 1.15–1.97 (10 H, m, 5 CH_2 of Cy), 3.80 (1 H, m, CHN), 5.67 (1 H, d, $^3J_{HH}$ = 7.8 Hz, NH), 6.43 (1 H, s, CH), 7.18–7.92 (4 H, m, 2-$NO_2C_6H_4$), 6.71, 7.15 and 7.82 (5 H, broad, C_6H_5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.7, 24.8, 25.4, 32.5 and 32.6 (5 CH_2 of Cy), 49.4 (CHN), 61.3 (CH), 117.5 (q, $^1J_{FC}$ = 285 HZ, *C*F_3), 124.8, 127.2, 128.5, 129.3, 129.72, 130.2, 131.4, 132.5, 132.9 and 135.8 (c, aromatic), 157.3 (q,$^2J_{FC}$ = 37 Hz, *C*OCF_3), 166.8 (*C*=O) ppm.

N-[Cyclohexylcarbamoyl(3-nitro-phenyl)methyl]-2,2,2-trifluoro-N-phenylacetamide (**5b**): Yellow crystals, (0.44 g, 98%); m.p. 195–197 °C. IR (KBr) (ν_{max}, cm^{-1}): 3275 (N–H), 1690, 1654 (C=O). MS (*m/z*,%): 450 (M^+ +1, 6). Anal. Calcd for $C_{22}H_{22}F_3N_3O_4$ (449) C, 58.79; H, 4.93; N, 9.35. Found: C, 58.72; H, 4.88; N, 9.30%. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ = 1.08–1.88 (10 H, m, 5 CH_2 of Cy), 3.84 (1 H, m, CHN), 5.67 (1 H, d, $^3J_{HH}$ = 7.6 Hz, NH), 6.02 (1 H, s, CH), 7.27-8.13 (4 H, m, 3-$NO_2C_6H_4$), 6.55, 7.06, 7.75 and 8.03 (5H, broad, C_6H_5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.7, 24.8, 25.3, 32.7 and 32.8 (5 CH_2 of Cy), 49.3 (CHN), 65.6 (CH), 118.1(q, $^1J_{FC}$ = 285 HZ, *C*F_3), 124.0, 125.7, 128.5, 129.0, 129.5, 129.6, 130.7, 134.7, 135.5, 136.5 and 147.9 (c, aromatic), 157.7 (q,$^2J_{FC}$ = 36 Hz, *C*OCF_3), 166.2 (*C*=O) ppm.

N-[Cyclohexylcarbamoyl(4-nitro-phenyl)methyl]-2,2,2-trifluoro-N-phenylacetamide (**5c**): Yellow crystals, (0.42 g, 95%); m.p. 196–199 °C. IR (KBr) (ν_{max}, cm^{-1}): 3280 (N–H), 1689, 1650 (C=O). MS (*m/z*,%): 450 (M^+ +1, 5). Anal. Calcd for $C_{22}H_{22}F_3N_3O_4$(449) C, 58.79; H, 4.93; N, 9.35. Found: C, 58.72; H, 4.82; N, 9.42%. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ = 1.03–1.74 (10 H, m, 5 CH_2 of Cy), 3.57 (1 H, m, CHN), 5.35 (1 H, d, $^3J_{HH}$ = 7.6 Hz, NH), 6.06 (1 H, s, CH), 7.37 (2H, d, $^3J_{HH}$ = 8.5 Hz, 4-$NO_2C_6H_4$), 7.95 (2H, d, $^3J_{HH}$ = 8.5 Hz, 4-$NO_2C_6H_4$), 6.80, 7.01, 7.15 7.27 and 7.74 (5 H, broad, C_6H_5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.2, 25.3, 25.9, 32.8 and 32.9 (5 CH_2 of Cy), 49.0 (CHN), 65.6 (CH), 118.3 (q, $^1J_{FC}$ = 287 Hz, *C*F_3), 123.7, 129.1, 129.9, 131.8, 132.8, 136.4, 141.6 and 147.9 (c, aromatic), 157.5 (q,$^2J_{FC}$ = 36Hz, *C*OCF_3), 167.1 (*C*=O) ppm.

N-[(4-Chloro-phenyl)cyclohexylcarbamoylmethyl]-2,2,2-trifluoro-N-phenylacetamide(**5d**)**:** Yellow crystals, (0.41 g, 95%); m.p. 196–199 °C. IR (KBr) (ν_{max}, cm^{-1}): 3280 (N–H), 1688, 1651 (C=O). MS (*m/z*,%): 439 (M^+ (^{35}Cl) +1, 9). Anal. Calcd for $C_{22}H_{22}ClF_3N_2O_2$(438) C, 60.21; H, 5.05; N, 6.38. Found: C, 60.24; H, 5.12; N, 6.42%. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ = 1.18–1.97 (10 H, m, 5 CH_2 of Cy), 3.81 (1 H, m, CHN), 5.45 (1 H, d, $^3J_{HH}$ = 7.8 Hz, NH), 5.86 (1 H, s, CH), 6.60–7.71 (9 H, m, aromatic) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.6, 24.7, 25.4, 32.7 and 32.8 (5 CH_2 of Cy), 49.0 (CHN), 65.6 (CH), 118.3 (q, $^1J_{FC}$ = 287 Hz, *C*F_3), 123.7, 129.1, 130.1, 131.5, 132.8, 135.4, 141.6 and 146.9 (c, aromatic), 157.5 (q,$^2J_{FC}$ = 36 Hz, *C*OCF_3), 166.5 (*C*=O) ppm.

N-[(4-Bromo-phenyl)cyclohexylcarbamoylmethyl]-2,2,2-trifluoro-N-phenylacetamide (**5e**): Yellow crystals, (0.45 g, 95%); m.p. 192–193 °C. IR (KBr) (ν_{max}, cm^{-1}): 3381 (N–H), 1696, 1655 (C=O). MS (*m/z*,%): 483 (M^+ (^{79}Br) +1, 5). Anal. Calcd for $C_{22}H_{22}BrF_3N_2O_2$ (482) C, 54.67; H, 4.59; N, 5.80. Found: C, 54.69; H, 4.62; N, 5.75%. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ = 1.10–1.95 (10 H, m, 5 CH_2 of Cy), 3.81 (1 H, m, CHN), 5.38 (1 H, d, $^3J_{HH}$ = 7.2 Hz, NH), 5.82 (1 H, s, CH), 6.97 (2H, d, $^3J_{HH}$ = 7 Hz, 4-BrC_6H_4), 7.42 (2H, d, $^3J_{HH}$ = 7.6 Hz, 4-BrC_6H_4), 6.61, 7.08, 7.26, 7.58 and 7.69 (5 H, broad, C_6H_5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.1, 25.2, 25.8, 33.1 and 33.2 (5 CH_2 of Cy), 49.5 (CHN), 66.8 (CH), 118.3 (q, $^1J_{FC}$ = 287 Hz, *C*F_3), 124.0, 129.6, 129.9, 132.2, 132.5, 136.5, 141.6 and 148.7 (c, aromatic), 157.5 (q,$^2J_{FC}$ = 36 *C*OCF_3), 166.9 (*C*=O) ppm.

N-[Cyclohexylcarbamoyl(4-nitro-phenyl)methyl]-2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide (**5f**): Yellow crystals, (0.46 g, 98%); m.p. 232–234 °C. IR (KBr) (ν_{max}, cm^{-1}): 3275 (N–H), 1693, 1652 (C=O). MS (*m/z*,%): 480 (M^+ +1, 5). Anal. Calcd for $C_{23}H_{24}F_3N_3O_5$ (479) C, 57.62; H, 5.05; N, 8.76. Found: C, 57.71; H, 5.22; N, 8.64%. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ = 1.09-2.02 (10 H, m, 5 CH_2 of Cy), 3.73 (3 H, s, OCH_3), 3.80 (1 H, m, CHN), 5.52 (1 H, m, NH), 5.96 (1 H, s, CH), 6.45, 6.52, 6.84 and 7.65 (4 H, broad, 4-$MeOC_6H_4$), 7.35 (2H, d, $^3J_{HH}$ = 7.6 Hz, 4-$NO_2C_6H_4$), 8.06 (2H, d, $^3J_{HH}$ = 8 Hz, 4-$NO_2C_6H_4$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.6, 24.7, 25.3, 32.7 and 32.7 (5 CH_2 of Cy), 49. (CHN), 55.3 (OCH_3), 65.6 (CH), 118.3 (q, $^1J_{FC}$ = 285 Hz, *C*F_3), 123.5, 127.9, 131.6, 132.1, 139.7, 148.0, 158.2 and 160.0 (c, aromatic), 156.5 (q,$^2J_{FC}$ = 36.12 Hz, *C*OCF_3),166.1 (*C*=O) ppm.

N-[(4-Chloro-phenyl)cyclohexylcarbamoylmethyl]-2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide (**5g**): Yellow crystals, (0.44 g, 95%); m.p. 230–232 °C. IR (KBr) (ν_{max}, cm^{-1}): 3395 (N–H), 1692, 1648 (C=O). MS (*m/z*,%): 469 (M^+ (^{35}Cl) +1, 7). Anal. Calcd for $C_{23}H_{24}ClF_3N_2O_3$ (468) C, 58.91; H, 5.16; N, 5.97. Found: C, 58.85; H, 5.25; N, 5.85%. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ = 1.06–2.12 (10 H, m, 5 CH_2 of Cy), 3.76 (3 H, s, OCH_3), 3.82 (1 H, m, CHN), 5.38 (1 H, m, NH), 5.87 (1 H, s, CH), 6.45, 6.55, 6.81 and 7.72 (4 H, broad, 4-ClC_6H_4), 7.04–7.27(4H,m, 4-$MeOC_6H_4$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.6, 24.7, 25.3, 32.7 and 32.7 (5 CH_2 of Cy), 49.0 (CHN), 55.3 (OCH_3), 65.9 (CH), 118.3 (q, $^1J_{FC}$ = 287 Hz, *C*F_3), 113.4, 128.4, 128.8, 131.4, 131.8, 131.9, 135.2 and 159.7 (c, aromatic), 157.5 (q,$^2J_{FC}$ = 34.9 Hz, *C*OCF_3), 166.3 (*C*=O) ppm.

N-[(4-Bromo-phenyl)cyclohexylcarbamoylmethyl]-2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide (**5h**): Yellow crystals, (0.48 g, 95%); m.p. 217–219 °C. IR (KBr) (ν_{max}, cm^{-1}): 3295 (N–H), 1692, 1649 (C=O). MS (*m/z*,%), 513 (M^+ (^{79}Br) +1, 5). Anal. Calcd for $C_{23}H_{24}BrF_3N_2O_3$ (512) C, 53.81; H, 4.71; N, 5.46. Found: C, 53.89; H, 4.78; N, 5.39%. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ = 1.01–2.16 (10 H, m, 5 CH_2 of Cy), 3.77 (3 H, s, OCH_3), 3.82 (1 H, m, CHN), 5.35 (1 H, m, NH), 5.85 (1 H, s, CH), 6.31, 6.46, 6.56 and 7.58 (4 H, broad, 4-BrC_6H_4), 6.98–7.44 (4H, m, 4-$MeOC_6H_4$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.7, 24.8, 25.3, 32.7, and 32.8 (5 CH_2 of Cy), 49.1 (CHN), 55.3 (OCH_3), 66.1 (CH), 118.3 (q, $^1J_{FC}$ = 287 Hz, *C*F_3), 113.5, 123.5, 128.9, 131.8, 132.2, 135.2, 148.1 and, 159.8 (c, aromatic), 157.5 (q,$^2J_{FC}$ = 35.2 Hz, *C*OCF_3), 166.4 (*C*=O) ppm.

N-[(4-Chloro-phenyl)cyclohexylcarbamoylmethyl]-2,2,2-trifluoro-N-p-tolylacetamide (**5i**): Yellow crystals, (0.43 g, 95%); m.p. 206–209 °C. IR (KBr) (ν_{max}, cm^{-1}): 3270 (N–H), 1698, 1650 (C=O). MS (*m/z*,%): 453 (M^+ (^{35}Cl) +1, 11). Anal. Calcd for $C_{23}H_{24}ClF_3N_2O_2$ (452) C, 61.00; H, 5.34; N, 6.19. Found: C, 61.12; H, 5.32; N, 6.23%. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ = 1.03–2.12(10 H, m, 5 CH_2 of Cy), 2.31 (3H, s, CH_3), 3.82 (1 H, m, CHN), 5.40 (1 H, m, NH), 5.84 (1 H, s, CH), 6.48–7.54 (8 H, m, aromatic) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.1 (CH_3), 24.7, 24.7, 25.4, 32.7 and 32.8 (5 CH_2 of Cy), 49.0 (CHN), 66.3 (CH), 117.6 (q, $^1J_{FC}$ = 287 Hz, *C*F_3), 128.8, 129.8, 130.3, 131.4, 131.9, 133.4, 135.2 and 139.3 (c, aromatic), 157.6 (q,$^2J_{FC}$ = 36.2 Hz, *C*OCF_3),166.5 (*C*=O) ppm.

N-[(4-Bromo-phenyl)cyclohexylcarbamoylmethyl]-2,2,2-trifluoro-N-p-tolylacetamide (**5j**): Yellow crystals, (0.47 g, 95%). M.p. 198–200 °C. IR (KBr) (ν_{max}, cm^{-1}): 3265 (N–H), 1700, 1646 (C=O). MS (*m/z*,%): 497 (M^+ (^{79}Br) +1, 7). Anal. Calcd for $C_{23}H_{24}BrF_3N_2O_2$ (496) C, 55.54; H, 4.86; N, 5.63. Found: C, 55.65; H, 4.82; N, 5.76%. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ = 1.01–1.96 (10 H, m, 5 CH_2 of Cy), 2.30 (3H, s, CH_3), 3.82 (1 H, m, CHN), 5.40 (1 H, d, $^3J_{HH}$ = 6.5 Hz, NH), 5.81 (1 H, s, CH), 6.55, 6.91, 7.11 and 7.55 (4 H, broad, 4-BrC_6H_4), 6.99 (2H, d, $^3J_{HH}$ = 8.4 Hz, 4-MeC_6H_4), 7.35 (2H, d, $^3J_{HH}$ = 8.4 Hz, 4-MeC_6H_4) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.1 (CH_3), 24.4, 24.6, 25.3, 32.7 and 32.8 (5 CH_2 of Cy), 49.1 (CHN), 66.4 (CH), 116.1 (q, $^1J_{FC}$ = 287 Hz, *C*F_3), 120.6, 123.5, 129.1, 129.7, 131.8, 132.4, 133.4 and 136.0 (c, aromatic), 157.5 (q,$^2J_{FC}$ = 36 Hz, *C*OCF_3), 166.3 (*C*=O) ppm.

Selected X-ray crystallographic data for compound **5a**

Empirical formula ($C_{22}H_{22}F_3N_3O_4$), F. w = 449.43, monoclinic, space group P 2(1)/*n*, Crystal size 0.15 x 0.13 x 0.08 mm^3, *a* = 11.7501(15) Å, *b* = 18.334(2) Å, *c* = 20.200(3) Å, α = 90°, β = 93.182(3) °, γ = 90°, V = 4344.9 (9) $Å^3$, Z = 8, D_{calcd} =1.374 Mg m^{-3}, F (000) =1872, Index ranges –15<=*h*<=15, –23<=*k*<=23, –25<=*l*<=25, Final R indices [for 5708 refl. with I>2σ (I)] R^1 = 0.0536, wR^2 = 0.0948, R indices (all data) R^1 = 0.0856, wR^2 = 0.1029, largest peak (0.221 e $Å^{-3}$) and hole (–0.227 e $Å^{-3}$).

CCDC-734385 contains the supplementary crystallographic data for **5a.** The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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