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A highly diastereoselective series of Nicholas cyclisation reactions of *N*-Boc-protected propargylamines

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ABSTRACT

The reaction of *N*-Boc-protected propargylamine with salicylaldehyde derivatives and their subsequent Nicholas cyclisation reaction to provide a range of novel benzopyrans is reported. The cyclisation reactions proceeded with excellent levels of diastereoselectivity to afford compounds with cis-relative stereochemistry. As far as we are able to ascertain these are the first reported examples of Nicholas cyclisation reactions of propargyl alcohols that bear a terminal alkynyl *N*-protected amino motif.

1. Introduction

In a previous paper we described the antihypertensive activity of a range of novel benzopyrans[1] that were synthesized using a variation of an intramolecular Nicholas reaction[2] that was developed in our laboratories.[3] The key ring closure occurs by the reaction of a tri-substituted alkenyl moiety, the nucleophile, with a dicobalt hexacarbonyl-stabilised 'Nicholas' cation.[4] We also demonstrated that the reaction sequence that consists of cobalt complexation of the alkynyl moiety, intramolecular cyclisation and finally the oxidative decomplexation of dicobalt hexacarbonyl could be conveniently achieved in a one-pot process.[5] The compounds from this series of reactions are interesting from the point of view that they contain several of the key pharmacophores present in the benchmark antihypertensive agent cromakalim (**1**). Results obtained from a series of in vitro studies[6] suggested that despite the simplicity of our analogues they nevertheless exhibited antihypertensive activity albeit by a cellular mechanism other than potassium channel activation. From an array of novel benzopyrans screened the aryl monofluorinated compounds (**2a**) and (**2b**) proved to be the most potent (Fig. 1).

Encouraged by these results we directed our attention towards the synthesis of a more diverse range of benzopyrans containing both monofluorinated and difluorinated aryl substituents for further screening purposes. In order to introduce additional structural diversity into this range of benzopyrans we focused upon changes to the terminal alkynyl substituent. Our rationale for this

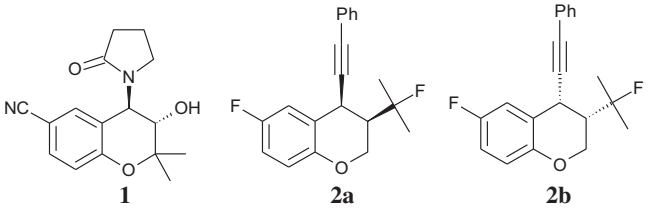

Fig. 1. Cromakalim **1** and novel benzopyrans **2a** and **2b**.

modification was twofold. The resulting benzopyrans would contain a propargylic amide moiety, which may confer interesting in vitro binding properties. Secondly most examples[7] of the Nicholas reaction involve a propargyl alcohol/ether that bears a terminal R group (R=H, CH_3, aryl), such as the substrate (**3**) employed on our previous studies. In this study we were keen to break with tradition in the use of an *N*-protected propargylamine moiety (**4**) and hence provide diversity in this chemistry (Fig. 2).

The chemistry of related ynamines has been the subject of a review[8] and the corresponding cobalt complexes have mainly been utilized in the Pauson–Khand reaction.[9] As far as we have been able to ascertain, however, the use of propargylamines in Nicholas chemistry is minimal[10] and we have been unable to retrieve an example. This modification would thus represent an important novel variation to existing Nicholas-style chemistry as well as provide benzopyrans with a propargylic amide bond. This is an important development as it facilitates the incorporation of handles, such as small peptides, for potential drug delivery purposes. Furthermore if the ynamino moiety is derived from an optically pure source, such as an amino acid, we have the potential means of controlling the stereochemistry of the subsequent ring closure. In

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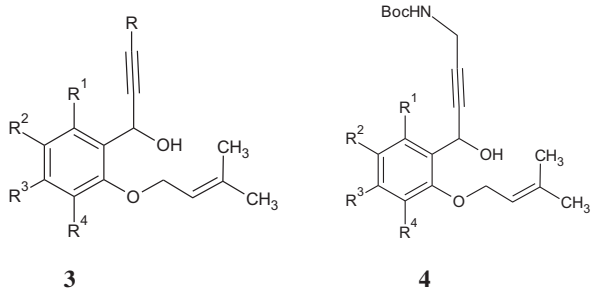
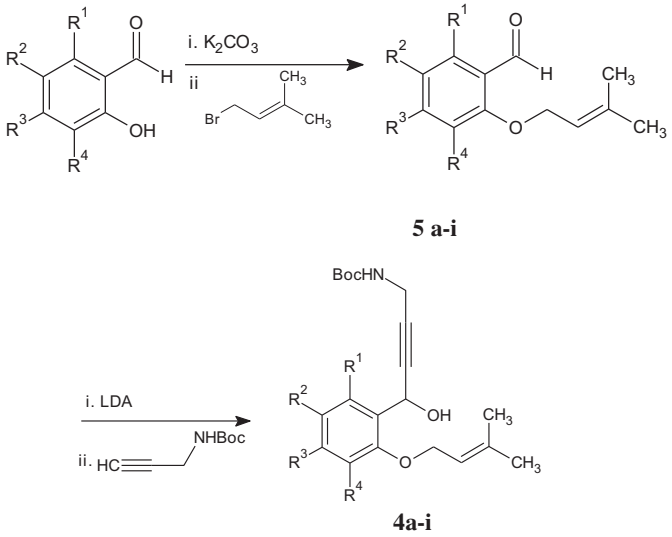


Fig. 2. Cyclisation precursors.

this paper we wish to disclose the results from the synthesis and cyclisation of novel compounds based upon compound (**4**). In particular we were keen to determine whether the presence of a terminal *N*-Boc-amino substituent might exert an influence upon either the efficiency and/or the selectivity of the subsequent cyclisation reactions.

2. Results and discussion

Our method of accessing propargyl alcohols **6a**–**i** is shown (Scheme 1) and the results tabulated (Table 1).



Scheme 1.

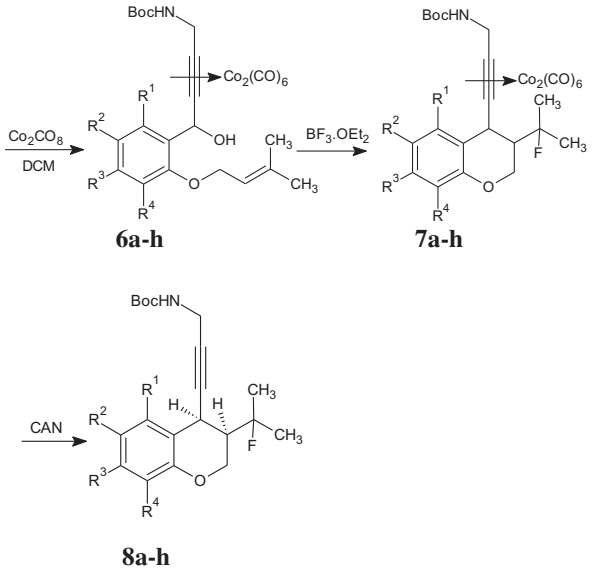
Table 1
The isolated yields for the syntheses of novel benzopyrans **8a**–**h**

Entry	Substituent	**5**a (%)	**4** (%)	**6** (%)	**7** (%)	**8** (%)
1	**a**. R^{1-4}=H	86	56	79	94	79
2	**b**. R^2=F	99	45	71	62	97
3	**c**. R^4=F	91	55	84	58	76
4	**d**. R^1, R^2=F	95	35	76	95	96
5	**e**. R^1, R^4=F	91	37	55	76	73
6	**f**. R^2, R^3=F	92	34	67	39	91
7	**g**. R^3=F	23	28	53	92	98
8	**h**. R^2, R^4=F	79	54	67	71	52
9	**i**. R^1=F	95	<5	—	—	—

[a] Isolated yields.

The data in Table 1 reveal some interesting trends; although the initial O-alkenylation was an efficient and high yielding reaction the subsequent alkynylation step proved to be a more capricious transformation. Initially we examined a number of bases for the deprotonation of *N*-Boc-propargylamine[11] including *n*-BuLi, sodamide and LiHMDS before settling on LDA (2 equiv in THF). The reaction of the subsequent alkynide anion proved, however, to be more of a challenge providing the propargyl alcohols **4a**–**i** in modest to good yields. The alkynylation reaction appears to be sensitive to both the presence of an *N*-Boc-amino substituent as well as the substitution pattern of the aryl ring. With regard to the influence of the amino moiety on the efficiency of the alkynylation step consider the three highest yielding alkynylations in Table 1: entry 1 **4a** (56%), entry 2 **4b** (45%) and entry 3 **4c** (55%). A comparison of these data, with those for the corresponding phenylethynyl alkynylations, give the following (84%), (82%) and (70%), respectively. With regard to the aryl substituents it seems that the aryl substitution pattern influences the electrophilic nature of the carbonyl to a greater degree than the actual number of aryl electron-withdrawing substituents present. Thus the presence of two fluorine substituents, entry **8** (54%), does not significantly reduce the reactivity of the carbonyl compared to an absence of fluorine, entry **1** (56%). On the other hand the relative position, of the aryl substituents, does have an impact. For example compare entry **8** (54%) with entry **4** (35%), entry **5** (37%) or entry **6** (34%). With regard to monofluorination the effects are even more marked compare entry **2** (45%) or entry **3** (55%) with entry **7** (28%) and entry **9** (>5%).

Conversion of the propargyl alcohols **4a**–**h** into their corresponding hexacarbonyl dicobalt complexes, **6a**–**h** (Scheme 2) occurred in good to excellent yields. The intramolecular Nicholas cyclisation reaction was carried out by exposure of a dichloromethane solution of the complexed propargyl alcohol, maintained at 0 °C, to a Lewis acid. This reaction, to afford **7a**–**h**, was remarkably facile taking place within the time it takes to carry out a TLC analysis of the reaction mixture. This process is facilitated by the intense red colour of the complex, which makes the product distribution readily visible by TLC analysis. In addition the complexation of alkynes, akin to **7a**–**h**, helps in the discrimination of diastereoisomers by facilitating differentiation[12] in chromatography retention times for instance. Although a number of decomplexing agents have been used[13] we have found that for this particular system the oxidative decomplexation of dicobalt hexacarbonyl using ceric ammonium nitrate (CAN) was the reagent of choice. This provided benzopyrans **8a**–**h** in good to excellent yields (Scheme 2).



Scheme 2.

In the synthetic sequence the alkynylation step proved to be the limiting transformation however the three steps consisting of complexation, cyclisation and decomplexation proved to be highly efficient ranging from 24% overall yield (entry **6**) to 69% (entry **4**). As the hexacarbonyl dicobalt complexes are highly coloured (red) we have found it convenient, and more efficient, to carry out the complexation, cyclisation and decomplexation steps in one-pot by simply monitoring each step by TLC analysis.

Analysis of the resulting benzopyrans **8a**–**h** confirmed that the key Nicholas cyclisation reaction had taken place with excellent levels of diastereoselectivity. The ^{1}H NMR spectrum for compound **8h**, for instance, showed that the benzylic proton, which was resonant at δ 3.9 ppm, overlapped with the resonance attributed to the methylene CH_2 derived from the propargyl group (Fig. 3A). When the NMR sample was run in acetone-d_6, from $CDCl_3$, the overlapping signals separated into two resonances. The first appeared as a broad singlet at δ 3.85 ppm attributed to CH_2 and the second resonance at δ 3.89 ppm attributed to the benzylic proton. This appeared as a broadened doublet with a coupling constant J 4.0 Hz (Fig. 3B).

The corresponding ^{19}F NMR spectrum of compound **8h** is shown (Fig. 5) and serves to confirm the presence of only one diastereoisomer. The second fluorine resonance at −139.7 ppm results from an incorporation of a fluoride ion derived from the Lewis acid.

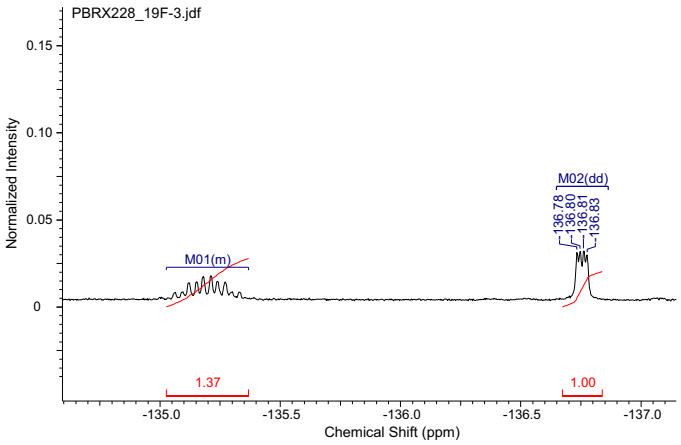


Fig. 5. Fluorine NMR spectrum of compound **8h**.

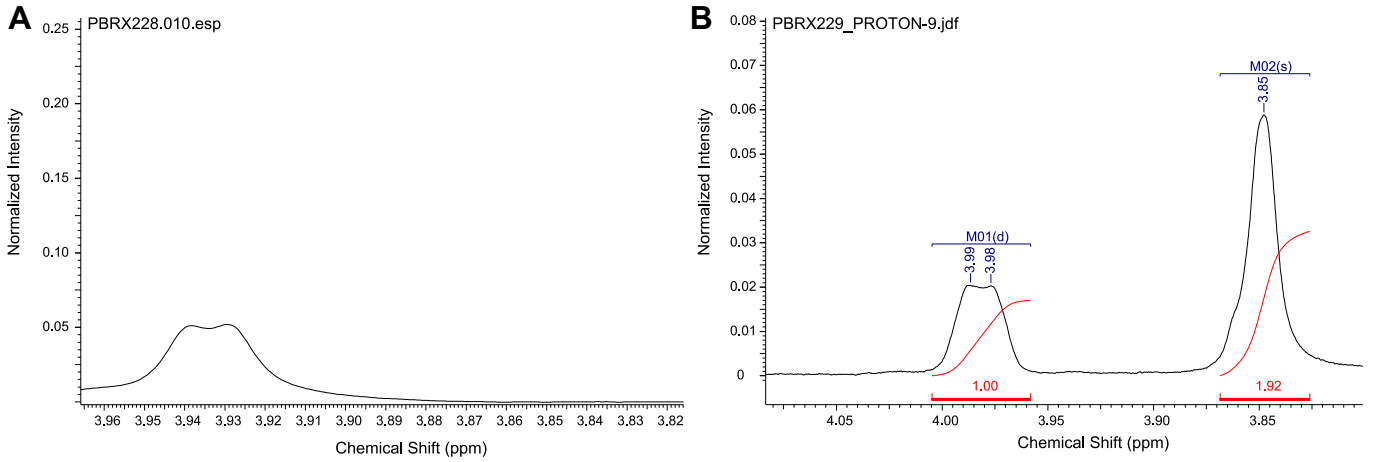


Fig. 3. Part of the ^{1}H NMR spectrum of **8h**.

With the information obtained in Fig. 3B, i.e., the precise chemical shift δ of the benzylic proton in acetone-d_6, we were then able to confirm the relative stereochemistry of the two adjacent protons by carrying out a NOESY experiment in acetone-d_6. The spectrum obtained is shown (Fig. 4). This clearly shows an interaction between the benzylic proton and the adjacent methine hydrogen atom, which resonates at δ 2.4 ppm. The information that we obtained from these experiments, based upon the magnitude of the coupling constant J, for the benzylic proton, as well as the results obtained from the NOESY NMR experiments, suggested that the two newly generated stereocentres, resulting from the Nicholas reaction, have a cis-stereochemical relationship.

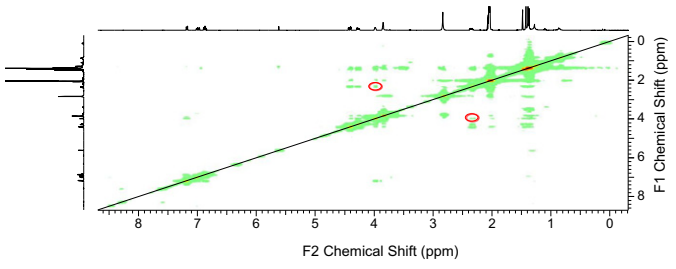


Fig. 4. NOESY ^{1}H NMR spectrum of **8h**. The relevant protons are circled.

3. Conclusion

Although we anticipated that the presence of the terminal *N*-Boc-protected propargylamine would not impede the subsequent Nicholas cyclisation it was nevertheless gratifying to establish that both the efficiency of the cyclisation reactions and the corresponding diastereoselectivity of the Nicholas cyclisations remained consistent. The benzopyrans that resulted from this novel modification to the Nicholas reaction will now be screened for their antihypertensive activity and the results will be disseminated in due course. In addition it is our intention to extend this study to include the use of chiral *N*-Boc-protected propargylamines. As cobalt complexes such as **6a**–**h** are known to exhibit more sp^2 character a chiral complex should adopt a non-linear geometry and thus facilitate stereocontrol over the subsequent cyclisation reaction.

4. Experimental[14]

4.1. Physical measurements and materials

Melting point determinations were recorded using a Stuart Scientific SMP3 digital melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1600 series

FTIR spectrophotometer and were calibrated using a standard polystyrene film. The spectra were recorded either as thin films for liquids, between sodium chloride discs or for solids as a Nujol mull. All infrared data are quoted in wave numbers (cm^{-1}). Proton nuclear magnetic resonance spectra (^1H NMR) were recorded at 400 MHz using a JEOL Eclipse 400 MHz spectrometer. Peak positions are quoted using the δ scale relative to tetramethylsilane (δ=0) as an internal standard. Carbon-13 NMR spectra (^{13}C NMR) were recorded at 100 MHz on a JEOL Eclipse 400 MHz spectrometer using deuterochloroform as an internal standard. Low-resolution mass spectra were recorded on a VG TRIO-2 mass spectrometer under electron impact conditions at an ionising potential of 70 eV and/or with a Hewlett Packard GC–MS HP5890 (GC) with capillary column and HP 5971 (MS). Accurate mass analyses were performed and reported on a VG-ZAB-E under EI conditions by the EPSRC National Mass Spectrometry Service Centre (Swansea) using the EI Peak Match on M+ method. Reactions were carried out under an atmosphere of dry nitrogen unless otherwise stated.

4.2. Preparation of 2-(3-methylbut-2-enyloxy)-benzaldehyde 5a

To a flame-dried two-necked flask containing dry DMF (100 mL), were added salicylaldehyde (5.21 g, 42.7 mmol), 4-bromo-2-methylbut-2-ene (7.00 g, 47.0 mmol), finely ground anhydrous potassium carbonate (23.6 g, 171 mmol) and potassium iodide (0.714 g, 4.30 mmol). The solution was left to stir at an ambient temperature under an atmosphere of nitrogen for 2.5 h. Analysis of the reaction mixture by TLC (1:3 diethyl ether/light petroleum spirit) showed the presence of a new compound with an R_f of 0.480. The reaction mixture was poured into water and partitioned between diethyl ether. The aqueous phase was isolated and then extracted with diethyl ether (6×20 mL). The combined organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to afford a yellow oil. Purification of the crude material was carried out by chromatography on silica,[15] eluted with diethyl ether/light petroleum spirit (1:3). This provided the title compound, **5a**, (7.02 g, 86%) as a colourless oil: R_f 0.48 (1:3 diethyl ether/light petroleum spirit): ν_{max} (NaCl)/cm^{-1} (thin film) 3034, 1686, 1598, 1286; ^1H NMR (400 MHz, $CDCl_3$): δ=10.46 (1H, s, CO–H), 7.78 (1H, dd J=1.8, 7.9 Hz, Ar–H); 7.50–7.45 (1H, m, H–Ar); 6.97–6.93 (2H, m, H–Ar); 5.48–5.43 (1H, m, H–C=C); 4.59 (2H, d, J=6.8 Hz, CH_2); 1.76 (3H, s, CH_3); 1.71 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=189.6, 161.1, 138.4, 135.6, 127.9, 124.8, 120.3, 118.8, 112.7, 65.2, 25.5, 18.0; LRMS (EI): m/z 191, 122, 104.93, 69, 51. HRMS (ES): calcd for $C_{12}H_{15}O_2$ [M^+] 191.1067; found 191.1066.

4.2.1. 5-Fluoro-2-[(3-methylbut-2-en-1-yl)oxy benzaldehyde ***5b***. Following the general procedure[16] the title compound was isolated (8.71 g, 82%) as a crystalline solid: R_f 0.80 (1:3 diethyl ether/light petroleum spirit), mp 45–46 °C (from hexane); ν_{max} (NaCl)/cm^{-1} (thin film) 2866, 1686, 1612, 1490, 1428, 1384, 1266, 1200, 1148; ^1H NMR (400 MHz, $CDCl_3$): δ=10.41 (1H, d, J=1.3 Hz, CO–H), 7.48 (1H, dd, J=3.3, 8.3 Hz, Ar–H); 7.22 (1H, ddd, J=1.3, 3.3, 8.3 Hz, H–Ar); 6.95 (1H, dd, J=3.3, 8.3 Hz, H–Ar); 5.49–5.44 (1H, m, H–C=C); 4.60 (2H, d, J=6.6 Hz, CH_2); 1.79 (3H, d, J=1.1 Hz, CH_3); 1.74 (3H, br s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=189.0 (d, $^4J_{C-F}$=1.54 Hz), 158.1 (d, $^4J_{C-F}$=1.54 Hz), 155.7, (d, $^2J_{C-F}$=241.38 Hz), 139.2, 125.5 (d, $^3J_{C-F}$=5.38 Hz), 122.5 (d, $^3J_{C-F}$=23.06 Hz), 118.8, 114.8, (d, $^3J_{C-F}$=6.92 Hz), 113.9 (d, $^3J_{C-F}$=23.06 Hz), 66.3, 25.9, 18.4. LRMS (EI): m/z 226 [M^++NH_4], 209, 140, 103, 86, 69. HRMS (ES): calcd for $C_{12}H_{17}FNO_2$ [M+NH_4]$^+$ 226.1238; found 226.1237.

4.2.2. 3-Fluoro-2-[(3-methylbut-2-en-1-yl)-oxybenzaldehyde ***5c***. Following the general procedure the title compound was isolated (7.97 g, 75%) as a colourless oil: R_f 0.76 (1:3 diethyl ether/light petroleum ether): ν_{max} (NaCl)/cm^{-1} (thin film) 2866, 1690, 1606, 1478, 1380, 1262, 1216, 1068; ^1H NMR (400 MHz, $CDCl_3$): δ=10.36 (1H, d, J=0.9 Hz, CO–H), 7.61–7.56 (1H, m, Ar–H), 7.31 (1H, ddd, J=1.6, 8.1, 11.4 Hz, H–Ar), 7.09 (1H, ddd, J=0.6, 4.5, 8.1 Hz, H–Ar), 5.51–5.46 (1H, m, H–C=C); 4.73 (2H, d, J=7.5 Hz, CH_2); 1.74 (3H, s, CH_3); 1.63 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=189.4 (d, $^3J_{C-F}$=3.1 Hz), 156.9 (d, J_{C-F}=248.29 Hz), 154.5, 149.4 (d, $^3J_{C-F}$=10.7 Hz), 141.1, 123.7 (J_{C-F}=7.7 Hz) 123.1 (d, $^4J_{C-F}$=3.0 Hz), 121.6 ($^3J_{C-F}$=19.2 Hz), 118.8, 71.2 (d, $^4J_{C-F}$=6.2 Hz), 25.9, 18.1; LRMS (EI): m/z 227 [M^+] 209, 140, 103, 86, 69; HRMS (ES): calcd for $C_{12}H_{17}FNO_2$ [M+NH_4]$^+$ 226.1238; found 226.1237.

4.2.3. 5,6-Difluoro-2-[(3-methylbut-2-en-1-yl)oxy]-benzaldehyde ***5d***. Following the general procedure the title compound was isolated as a colourless oil (1.37 g, 95%): R_f 0.53 (1:3 diethyl ether); ν_{max} (NaCl)/cm^{-1} (thin film) 2869, 1695, 1602, 1481, 1378, 1262, 1074; ^1H NMR (400 MHz, $CDCl_3$): δ=10.41 (1H, s, CO–H), 7.31 (1H, q, J=9.0 Hz, Ar–H); 6.67–6.73 (1H, m, H–Ar); 5.50–5.43 (1H, m, H–C=C); 4.62 (2H, d, J=6.5 Hz, CH_2); 1.81 (3H, s, CH_3); 1.75 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=189.4, 157.1 (dd, $^4J_{C-F}$=3.67, 2.20 Hz), 149.9 (dd, $^2J_{C-F}$=266.30, $^3J_{C-F}$=13.21 Hz), 144.8, (dd, $^2J_{C-F}$=242.82, $^3J_{C-F}$=12.47 Hz), 139.4, 122.32 (dd, $^3J_{C-F}$=19.07, $^4J_{C-F}$=2.93 Hz), 118.8, 115.5 (d, $^4J_{C-F}$=5.87 Hz), 108.0 (t, $^4J_{C-F}$=4.77 Hz), 66.5, 25.7, 18.3; LRMS (EI): m/z 226 [M^+] HRMS (EI): calcd for $C_{12}H_{16}F_2NO_2$ [M+NH_4]$^+$ 244.1144; found 244.1146.

4.2.4. 3,6-Difluoro-2-[(3-methylbut-2-en-1-yl)oxy]- benzaldehyde ***5e***. Following the general procedure the title compound was isolated as a colourless oil (1.29 g, 91%): R_f 0.64 (1:3 diethyl ether/light petroleum spirit): ν_{max} (NaCl)/cm^{-1} (thin film) 3060, 1690, 1606, 1582, 1444, 1284; ^1H NMR (400 MHz $CDCl_3$): δ=10.35 (1H, s, CO–H), 7.24–7.31 (1H, m, Ar–H); 6.81 (1H, td, J=9.3, 3.4 Hz, H–Ar); 5.45–5.53 (1H, m, H–C=C); 4.76 (2H, d, J=7.3 Hz, CH_2); 1.77 (3H, s, CH_3); 1.68 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=186.7, 157.7 (dd, $^2J_{C-F}$=260.43, $^4J_{C-F}$=2.93 Hz), 151.6 (dd, $^2J_{C-F}$=245.02, $^4J_{C-F}$=3.67 Hz), 148.8, (dd, $^3J_{C-F}$=13.20, $^4J_{C-F}$=5.13 Hz), 141.1, 122.2 (dd, $^3J_{C-F}$=22.74, $^3J_{C-F}$=11 Hz), 119.5 (dd, $^3J_{C-F}$=9.54, $^4J_{C-F}$=1.47 Hz), 118.5, 110.8 (dd, $^3J_{C-F}$=23.47 and ^4J=7.34 Hz), 71.2 (d, J_{C-F}=6.60 Hz), 25.6, 17.8; LRMS (EI): m/z 226 [M^+] HRMS (EI): calcd for $C_{12}H_{16}F_2NO_2$ [M+NH_4]$^+$ 244.1144; found 244.1148.

4.2.5. 4,5-Difluoro-2-[(3-methylbut-2-en-1-yl)oxy]-benzaldehyde ***5f***. Following the general procedure the title compound was isolated as a colourless oil (1.34 g, 92%): R_f 0.66 (1:3 diethyl ether/light petroleum spirit); ν_{max} (NaCl)/cm^{-1} (thin film) 3080, 1696, 1600, 1588, 1480, 1284; ^1H NMR (400 MHz $CDCl_3$): δ=10.38 (1H, d J=3.0 Hz, CO–H), 7.68 (1H, dt, J=3.0, 10 Hz, Ar–H); 6.84 (1H, dd, J=6.0, 10 Hz, Ar–H); 5.44–5.54 (1H, m, H–C=C); 4.63 (2H, d, J=6.8 Hz, CH_2); 1.85 (3H, s, CH_3); 1.79 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=186.7, 158.2 (dd, $^3J_{C-F}$=8.44, $^4J_{C-F}$=1.83 Hz), 154.7 (dd, $^2J_{C-F}$=258.96, $^3J_{C-F}$=14.67 Hz), 144.8 (dd, $^2J_{C-F}$=244.29, $^3J_{C-F}$=13.21 Hz), 139.6, 121.3 (t, $^4J_{C-F}$=3.30 Hz), 118.0, 115.9 (dd, $^3J_{C-F}$=18.3, $^4J_{C-F}$=2.93 Hz), 102.9 (d, $^3J_{C-F}$=21.27), 66.32, 25.56, 18.09; LRMS (EI): m/z 226 [M^+] HRMS (EI): calcd for $C_{12}H_{16}F_2NO_2$ [M+NH_4]$^+$ 244.1144; found 244.1146.

4.2.6. 4-Fluoro-2-[(3-methylbut-2-en-1-yl)oxy] benzaldehyde ***5g***. Following the general procedure the title compound was isolated as a yellow oil (0.34 g, 23%): R_f 0.78 (1:3 diethyl ether/light petroleum spirit); ν_{max} (NaCl)/cm^{-1} (thin film) 2875, 1695, 1612, 1486, 1394, 1258, 1228, 1069; ^1H NMR (400 MHz, $CDCl_3$): δ=10.38 (1H, d, J=0.8 Hz CO–H), 7.86 (1H, dd J=7.0, 8.5 Hz, Ar–H); 6.63–6.76 (2H, m, H–Ar); 5.44–5.54 (1H, m, H–C=C); 4.62 (2H, d, J=6.8 Hz, CH_2); 1.82 (3H, s, CH_3); 1.78 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.6, 167.1 (d, $^2J_{C-F}$=254.45 Hz), 163.7 (d, J_{C-F}=13.84 Hz), 140.3, 132.1 (d, J_{C-F}=11.53 Hz), 117.8, 109.4 (d, $^4J_{C-F}$=2.31 Hz), 107.1 (d,

$^{3}J_{C-F}$=22.29 Hz), 104.3 (d, $^{3}J_{C-F}$=23.83 Hz), 62.3, 25.8, 18.1; LRMS (EI): *m/z* 227 [M^{+}] 209, 140, 103, 86, 69. HRMS (ES): calcd for $C_{12}H_{17}FNO_2$ [M+NH_4]$^{+}$ 226.1238; found 226.1239.

4.2.7. 3,5-Difluoro-2-[(3-methylbut-2-en-1-yl)oxy]-benzaldehyde ***5h***. Following the general procedure the title compound was isolated as a colourless oil (1.03 g, 79%): R_f 0.64 (1:3 diethyl ether/light petroleum spirit); ν_{max} (NaCl)/cm^{-1} (thin film) 3090, 1695, 1610, 1586, 1484, 1279; ^{1}H NMR (400 MHz $CDCl_3$): δ=10.29 (1H, d, *J*=1.8 Hz, CO–H), 7.29 (1H, ddd *J*=1.8, 3.1 and 7.9 Hz, Ar–H); 7.09 (1H, ddd, *J*=3.1, 7.9 and 10.9 Hz, H–Ar); 5.49–5.43 (1H, m, H–C=C); 4.68 (2H, d, *J*=7.5 Hz, CH_2); 1.74 (3H, s, CH_3); 1.20 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=188.1, shoulder, 157.6 (dd, $^{2}J_{C-F}$=247.52 and $^{3}J_{C-F}$=10.76 Hz), 155.8 (dd, $^{2}J_{C-F}$=252.90, $^{3}J_{C-F}$=9.99 Hz), 145.9 (dd, $^{3}J_{C-F}$=15.37 and $^{4}J_{C-F}$=3.80 Hz), 141.7, 131.2 (dd, $^{3}J_{C-F}$=7.69, 2.31 Hz), 118.3, 110.8 (dd, $^{3}J_{C-F}$=26.91 and 23.06 Hz), 108.8 (dd, J_{C-F}=23.06 and 3.84 Hz), 71.4 (d, $^{3}J_{C-F}$=5.4 Hz), 25.8, 17.9; LRMS (EI): *m/z* 244 [M^{+}+NH_4]$^{+}$, 226, 175, 137, 86, 69. HRMS (ES): calcd for $C_{12}H_{16}F_2NO_2$ [M+NH_4]$^{+}$ 244.1144; found 244.1146.

4.2.8. 6-Fluoro-2-[(3-methylbut-2-en-1-yl)oxy]-benzaldehyde ***5i***. Following the general procedure the title compound was isolated as a colourless oil (1.01 g, 95%): R_f 0.74 (1:3 diethyl ether/light petroleum ether); ν_{max} (NaCl)/cm^{-1} (thin film) 2869, 1695, 1602, 1469, 1380, 1262, 1216, 1068; ^{1}H NMR (400 MHz $CDCl_3$): δ=10.45 (1H, s, CO–H), 7.45 (1H, td *J*=6.3 and 7.9 Hz, Ar–H); 6.77 (1H, d, *J*=8.8 Hz, H–Ar); 6.71 (1H, dd, *J*=8.8 and 10.0 Hz, H–Ar); 5.42–5.53 (1H, m, H–C=C); 4.64 (2H, d, *J*=6.5 Hz, CH_2); 1.81 (3H, s, CH_3); 1.76 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=187.6 (d, $^{4}J_{C-F}$=1.47 Hz), 162.6 (d, $^{2}J_{C-F}$=246.49 Hz), 161.6 (d, ^{3}J=22.01 Hz), 139.1, 135.8 (d, J_{C-F}=711.74 Hz), 118.6, 114.4 (d, *J*=8.80 Hz), 108.5 (d, *J*=8.80 Hz), 108.4 (d, *J*=8.80 Hz), 66.2, 25.8, 18.3. LRMS (EI): *m/z* 227 [M^{+}] 209, 140, 103, 86, 69. HRMS (ES): calcd for $C_{12}H_{17}FNO_2$ [M+NH_4]$^{+}$ 226.1238; found 226.1234.

4.3. Preparation of 1-{2-[(3-methylbut-2-en-1-yl)oxy] phenyl}-3-*N*-Boc-methylaminoprop-2-yn-o1 4a

N-Boc-propargylamine (0.30 g, 1.94 mmol) was dissolved in THF (20 mL) at −78 °C in a flame-dried round-bottom flask. To this solution was added dropwise LDA (1.80 M in heptane 2.11 mL, 3.80 mmol) to effect alkynide formation. The solution was left to stir at −78 °C for 60 min whereupon **5a** (0.43 g, 2.25 mmol) was added in one portion. The reaction mixture was left to stir for a further 30 min and then allowed to reach ambient temperature. TLC analysis of the reaction mixture (3:7 ethyl acetate/light petroleum spirit) showed the presence of a slower moving compound R_f 0.41. The reaction mixture was quenched by the addition of a saturated aqueous solution of ammonium chloride (20 mL). The solvent was removed in vacuo and the mixture partitioned between water and dichloromethane. The organic phase was isolated and washed with water (3×20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give the crude product. Purification by column chromatography on silica (3:7 ethyl acetate/light petroleum spirit) provided the title compound **4a** as a yellow oil (0.46 g, 56% yield): ν_{max} (NaCl)/cm^{-1} (thin film) 3455, 2980, 2932, 2252, 1709, 1601; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (dd, 1H, *J*=7.5, 1.7 Hz, Ar–H), 7.30 (dt, 1H, *J*=8.2, 1.7 Hz, Ar–H), 7.0 (dt, 1H, *J*=7.5, 0.9 Hz, Ar–H), 6.92 (d, 1H, *J*=8.2 Hz, Ar–H), 5.69 (dt, 1H, *J*=6.0 and 1.8 Hz, C*H*–OH), 5.50–5.46 (m, 1H, CH=C), 4.68 (s, 1H, NH), 4.60 (d, 2H, *J*=6.5 Hz, CH_2O), 4.02 (d, 2H, *J*=4.3, CH_2–NH), 3.16 (d, 1H, *J*=6.1 Hz, OH), 1.79 (br s, 3H, CH_3–C=C), 1.74 (s, 3H, CH_3–C=C), 1.44 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.2, 155.3, 138.6, 129.6, 128.9, 122.9, 120.8, 119.4, 112.1, 82.4, 82.3, 80.0, 65.2, 61.2, 30.7, 28.4, 25.8, 18.2; LRMS (EI): *m/z* 363 (M+NH_4)$^{+}$; HRMS (ES): calcd for $C_{20}H_{31}N_2O_4$ [M+NH_4]$^{+}$ 363.2278; found [363.2279].

4.3.1. 1-{5-Fluoro-2-[(3-methylbut-2-en-1-yl)oxy]phenyl}-3-N-Boc-methylaminoprop-2-yn-o1 ***4b***. Following the general procedure the title compound was isolated as a yellow oil (0.80 g, 45%): R_f 0.55 (3:7 ethyl acetate/light petroleum spirit); ν_{max} (NaCl)/cm^{-1} (thin film) 3412, 2924, 2228, 1674, 1598, 1492, 1246, 1190; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.28 (m, 1H, Ar–H), 6.96 (dd, 1H, *J*=8.0, 3.0 Hz, Ar–H), 6.84 (dd, 1H, *J*=8.9, 4.4 Hz, Ar–H), 5.68 (d, 1H, *J*=5.3 Hz, C*H*–OH), 5.47 (bd s, 1H, CH=C), 4.77–4.66 (m, 1H, NH), 4.57 (d, 2H, *J*=4.0 Hz, CH_2O), 4.03 (d, 2H, *J*=3.8 Hz, CH_2–NH), 3.12 (d, 1H, *J*=5.3 Hz, OH), 1.80 (s, 3H, CH_3–C=C), 1.74 (s, 3H, CH_3–C=C), 1.46 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.9 (d, $^{2}J_{C-F}$=239.89 Hz), 153.1, 152.1 (d, $^{4}J_{C-F}$=2.2 Hz), 138.7, 130.5 (d, $^{4}J_{C-F}$=6.6 Hz), 119.2, 115.3 (d, $^{3}J_{C-F}$=22.74 Hz), 114.9 (d, $^{3}J_{C-F}$=24.21 Hz), 113.2 (d, $^{4}J_{C-F}$=8.07 Hz), 82.8, 81.6, 80.1, 66.0, 61.0 (d, $^{4}J_{C-F}$=1.5 Hz), 30.75, 28.32, 25.75, 18.25; LRMS (EI): *m/z* 381 (M+NH_4)$^{+}$; HRMS (ES): calcd for $C_{20}H_{30}FN_2O_4$ [M+NH_4]$^{+}$ 381.2184; found [381.2188].

4.3.2. 1-{3-Fluoro-2-[(3-methylbut-2-en-1-yl)oxy]phenyl}-3-N-Boc-methylaminoprop-2-yn-o1 ***4c***. Following the general procedure the title compound was isolated as a yellow oil (2.0 g, 55%): R_f 0.50 (3:7 ethyl acetate/light petroleum spirit); ν_{max} (NaCl)/cm^{-1} (thin film) 3356, 2978, 2931, 2404, 1694, 1476; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (bd d, *J*=7.3 Hz, 1H, Ar–H), 7.11–6.99 (m, 2H, Ar–H), 5.71–5.64 (m, 1H, C*H*–OH), 5.59–5.51 (m, 1H, CH=C), 4.70–4.64 (m, 3H, NH and CH_2O), 4.02 (d, 2H, *J*=4.0 Hz, CH_2–NH), 3.00 (d, 1H, *J*=6.2 Hz, OH), 1.79 (s, 3H, CH_3–C=C), 1.79 (s, 3H, CH_3–C=C), 1.45 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (100 MHz, $CDCl_3$): 155.3 (d, $^{2}J_{C-F}$=247.53 Hz), 144.5, 143.9 (d, $^{3}J_{C-F}$=12.30 Hz), 139.9, 135.2, 123.7 (d, $^{4}J_{C-F}$=7.69 Hz), 122.9 (d, $^{4}J_{C-F}$=3.07 Hz), 119.6, 117.0 (d, $^{3}J_{C-F}$=19.22 Hz), 82.6, 82.3, 79.9, 70.5 (d, $^{4}J_{C-F}$=6.15 Hz), 60.9, 30.7, 38.3, 25.8, 18.0; LRMS (EI): *m/z* 381 (M+NH_4)$^{+}$; HRMS (ES): calcd for $C_{20}H_{30}FN_2O_4$ [M+NH_4^{+}] 381.2184; found [381.2184].

4.3.3. 1-{5,6-Difluoro-2-[(3-methylbut-2-en-1-yl)oxy] phenyl}-3-N-Boc-methylaminoprop-2-yn-o1 ***4d***. Following the general procedure the title compound was isolated as a yellow oil (0.62 g, 35%): R_f 0.50 (3:7 ethyl acetate/light petroleum spirit); ν_{max} (NaCl)/cm^{-1} (thin film) 3422, 2914, 2228, 1672, 1598, 1476; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, *J*=9.5 Hz, 1H, Ar–H), 6.67–6.57 (m, 1H, Ar–H), 5.74 (d, *J*=10.8 Hz, 1H, C*H*–OH), 5.52–5.42 (m, 1H, CH=C), 4.66–4.51 (m, 3H, NH and CH_2O), 3.96 (d, 2H, *J*=2.8 Hz, CH_2–NH), 3.69 (d, 1H, *J*=10.8 Hz, OH), 1.81 (s, 3H, CH_3–C=C), 1.76 (s, 3H, CH_3–C=C), 1.44 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (100 MHz, $CDCl_3$); 158.5 (dd, $^{3}J_{C-F}$=16.87, $^{4}J_{C-F}$=4.40 Hz), 153.6 (dd, $^{2}J_{C-F}$=272.16 Hz, $^{3}J_{C-F}$=13.20 Hz), 152.7, 144.9 (dd, $^{2}J_{C-F}$=241.35 Hz, $^{3}J_{C-F}$=12.47 Hz), 139.4, 122.2 (dd, $^{3}J_{C-F}$=17.61 Hz, $^{4}J_{C-F}$=1.47 Hz), 118.6, 116.0 (dd, $^{3}J_{C-F}$=18.34 Hz, $^{4}J_{C-F}$=2.20 Hz), 107.7 (dd, $^{4}J_{C-F}$=6.60, 3.30 Hz), 82.2, 81.4, 79.9, 66.4, 60.3, 30.7, 28.3, 25.8, 18.3; LRMS (EI): *m/z* 399 (M+NH_4)$^{+}$; HRMS (ES): calcd for $C_{20}H_{29}F_2N_2O_4$ [M+NH_4]$^{+}$ 399.2090; found [399.2095].

4.3.4. 1-{3,6-Difluoro-2-[(3-methylbut-2-en-1-yl)oxy] phenyl}-3-N-Boc-methylaminoprop-2-yn-o1 ***4e***. Following the general procedure the title compound was isolated as a yellow oil (0.67 g, 37%): R_f 0.38 (3:7 ethyl acetate/light petroleum spirit); ν_{max} (NaCl)/cm^{-1} (thin film) 3422, 2914, 2230, 1677, 1596, 1476; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (ddd, *J*=10.9, 9.2, 5.0 Hz, 1H, Ar–H), 6.76 (ddd, *J*=9.2, 9.0, 3.7 Hz, 1H, Ar–H) 5.71 (d, *J*=10.5 Hz, 1H, CH–OH), 5.57 (d, *J*=7.2 Hz, 1H, CH=C), 4.74–4.60 (m, 3H, NH and CH_2O), 3.97 (bd s, 2H, CH_2–NH), 3.53 (d, 1H, *J*=10.5 Hz, OH), 1.81 (s, 3H, CH_3–C=C), 1.75 (s, 3H, CH_3–C=C), 1.44 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (100 MHz, $CDCl_3$): 155.7 (dd, $^{2}J_{C-F}$=273.63, $^{4}J_{C-F}$=2.93 Hz), 152.8, 152.1 (dd,

$^{2}J_{C-F}$=254.56 Hz, $^{4}J_{C-F}$=2.20 Hz), 146.4 (dd, $^{3}J_{C-F}$=13.94 Hz, $^{4}J_{C-F}$=3.70 Hz), 140.4, 119.1, 118.4 (dd, $^{3}J_{C-F}$=16.14 Hz, $^{4}J_{C-F}$=2.20 Hz), 116.6 (dd, $^{3}J_{C-F}$=22.01 Hz, $^{4}J_{C-F}$=10.30 Hz), 110.4 (dd, $^{3}J_{C-F}$=24.21, $^{4}J_{C-F}$=8.10 Hz), 82.5, 81.1, 80.5, 71.0 (d, $^{4}J_{C-F}$=7.34 Hz), 66.4, 30.6, 28.3, 25.9, 18.1; LRMS (EI): *m/z* 399 $(M+NH_4)^+$; HRMS (ES): calcd for $C_{20}H_{29}F_2N_2O_4$ $[M+NH_4]^+$ 399.2090; found [399.2091].

4.3.5. 1-{4,5-Difluoro-2-[(3-methylbut-2-en-1-yl)oxy] phenyl}-3-N-Boc-methylaminoprop-2-yn-o1 ***4f***. Following the general procedure the title compound was isolated as a yellow oil (0.60 g, 34%): R_f 0.38 (3:7 ethyl acetate/light petroleum spirit); ν_{max} (NaCl)/cm^{-1} (thin film) 3425, 2924, 2228, 1675, 1602, 1477; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (dd, *J*=10.5, 9.5 Hz, 1H, Ar−H), 6.73 (dd, *J*=11.8, 6.5 Hz, 1H, Ar−H), 5.67 (d, *J*=5.3 Hz, 1H, C*H*−OH), 5.49−5.40 (m, 1H, CH=C), 4.81−4.62 (m, 1H, NH), 4.54 (d, *J*=4.3 Hz, 2H, CH_2−O), 4.02 (d, *J*=4.3 Hz, 2H, CH_2−NH), 3.53 (d, 1H, *J*=5.3 Hz, OH), 1.81 (s, 3H, CH_3−C=C), 1.75 (s, 3H, CH_3−C=C), 1.46 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=158.5 (dd, $^{4}J_{C-F}$=16.9 Hz, $^{5}J_{C-F}$=4.4 Hz), 153.6 (dd, $^{2}J_{C-F}$=272.2 Hz, $^{3}J_{C-F}$=13.2 Hz), 152.7, 144.9 (dd, $^{2}J_{C-F}$=241.4 Hz, $^{3}J_{C-F}$=12.5 Hz), 139.4, 122.2 (dd, $^{3}J_{C-F}$=17.6 Hz, $^{4}J_{C-F}$=1.5 Hz), 118.6, 116.0 (dd, $^{3}J_{C-F}$=18.3 Hz, $^{4}J_{C-F}$=2.0 Hz), 107.7 (d, $^{4}J_{C-F}$=6.6 Hz, $^{5}J_{C-F}$=3.3 Hz), 82.2, 81.4, 79.9, 66.4, 60.3, 30.7, 28.3, 25.8, 18.3; LRMS (EI): *m/z* 399 $(M+NH_4)^+$; HRMS (ES): calcd for $C_{20}H_{29}F_2N_2O_4$ $[M+NH_4]^+$ 399.2090; found [399.2091].

4.3.6. 1-{4-Fluoro-2-[(3-methylbut-2-en-1-yl)oxy]phenyl}-3-N-Boc-methylaminoprop-2-yn-o1 ***4g***. Following the general procedure the title compound was isolated as a yellow oil (0.48 g, 28%): R_f 0.39 (3:7 ethyl acetate/light petroleum spirit); ν_{max} (NaCl)/cm^{-1} (thin film) 3346, 2968, 2398, 1690, 1602, 1476; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24−7.08 (m, 1H, Ar−H), 6.69−6.60 (m, 2H, Ar−H), 5.67 (br s, 1H, C*H*−OH), 5.50−5.42 (m, 1H, CH=C), 4.84−4.67 (m, 1H, NH), 4.57 (d, 2H, *J*=5.8 Hz, CH_2O), 4.02 (br s, 2H, CH_2−NH), 3.38 (br s, 1H, OH), 1.81 (s, 3H, CH_3−C=C), 1.76 (s, 3H, CH_3−C=C), 1.46 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=164.4 (d, $^{3}J_{C-F}$=16.91 Hz), 147.9 (d, $^{4}J_{C-F}$=5.38 Hz), 137.6, 129.6 (d, $^{3}J_{C-F}$=9.9 Hz), 119.0 (d, $^{3}J_{C-F}$=23.06 Hz), 118.7, 106.7 (d, $^{3}J_{C-F}$=22.74 Hz), 114.9 (d, $^{3}J_{C-F}$=24.21 Hz), 113.2 (d, $^{3}J_{C-F}$=13.84 Hz), 100.3 (d, $^{3}J_{C-F}$=26.14 Hz), 89.6, 80.9, 77.2, 65.2 (d, $^{4}J_{C-F}$=2.31 Hz), 31.4, 28.3, 25.8, 18.3; LRMS (EI): *m/z* 381 $(M+NH_4)^+$; HRMS (ES): calcd for $C_{20}H_{30}FN_2O_4$ $[M+NH_4]^+$ 381.2184; found [381.2187].

4.3.7. 1-{3,5-Difluoro-2-[(3-methylbut-2-en-1-yl)oxy] phenyl}-3-N-Boc-methylaminoprop-2-yn-o1 ***4h***. Following the general procedure the title compound was isolated as a yellow oil (0.93 g, 54%): R_f 0.40 (3:7 ethyl acetate/light petroleum spirit); ν_{max} (NaCl)/cm^{-1} (thin film) 3425, 2924, 2228, 1675, 1602, 1477; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, *J*=8.4 Hz, 1H, Ar−H), 6.89−6.84 (m, 1H, Ar−H), 5.68 (br s, 1H, C*H*−OH), 5.56−5.48 (m, 1H, CH=C), 4.73 (bd s, 1H, NH), 4.63 (d, *J*=7.0 Hz, 2H, CH_2−O), 4.01 (bd s, 2H, CH_2−N), 2.99 (d, 1H, *J*=5.5 Hz, OH), 1.79 (s, 3H, CH_3−C=C), 1.71 (s, 3H, CH_3−C=C), 1.45 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.5 (d, $^{2}J_{C-F}$=259.82 Hz), 155.6 (d, $^{2}J_{C-F}$=262.9 Hz), 152.1 (dd, $^{3}J_{C-F}$=11.5, $^{4}J_{C-F}$=2.3 Hz), 149.4, 140.3, 137.0 (d, $^{3}J_{C-F}$=21.5, $^{4}J_{C-F}$=2.31 Hz), 119.3, 109.7 (dd, $^{3}J_{C-F}$=24.6, $^{4}J_{C-F}$=2.31 Hz), 105.0 (dd, $^{3}J_{C-F}$=26.14, 23.06 Hz), 83.1, 81.7, 80.1, 70.7 (d, $^{4}J_{C-F}$=5.4 Hz), 60.2, 30.6, 28.3, 25.8, 18.0; LRMS (EI): *m/z* 399 $(M+NH_4)^+$; HRMS (ES): calcd for $C_{20}H_{29}F_2N_2O_4$ $[M+NH_4]^+$ 399.2090; found [399.2091].

4.4. Preparation of hexacarbonyl[1-{2-[(3-methylbut-2-en-1-yl)oxy]phenyl}-3-*N*-Boc-methylaminoprop-2-yn-o1] dicobalt 6a[14]

1-{2-[(3-Methylbut-2-en-1-yl)oxy]phenyl}-3-*N*-Boc-methyl aminoprop-2-yn-o1 **4a** (1.27 g, 3.7 mmol) was dissolved in a flame-dried round-bottom flask containing dichloromethane (20 mL) and charged with a magnetic stirrer. To the stirred solution was added octacarbonyl dicobalt (1.36 g, 4.0 mmol), which was then left to stir for 10 min. TLC analysis of the reaction mixture showed the presence of a faster moving compound R_f 0.6 (DCM). To the reaction mixture was added hexane (30 mL) and silica (1 g). The solvent was then removed, in vacuo, leaving the cobalt complex adsorbed onto the silica medium. Extraction of the silica with dichloromethane (30 mL) and solvent removal in vacuo, provided the title compound **6a** as a red oil (1.84 g, 79%), which required no further purification. ν_{max} (NaCl)/cm^{-1} (thin film) 2090, 2050, 2024, 1600, 1484, 1454, 1382, 1286, 1230; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, 1H, *J*=7.4 Hz, Ar−H), 7.23 (dd, 1H, *J*=8.0, 7.4 Hz, Ar−H), 7.01 (d, 1H, *J*=7.4 Hz, Ar−H), 6.89 (d, 1H, *J*=8.0 Hz, Ar−H), 6.21 (d, 1H, *J*=4.5 Hz, CH−O*H*), 5.50 (bd s, 1H, CH=C), 5.16 (bd s, 1H, NH), 4.66−4.27 (m, 4H, CH_2O, CH_2N), 4.24 (d, 1H, *J*=4.5, OH), 1.78 (br s, 3H, CH_3−C=C), 1.75 (s, 3H, CH_3−C=C), 1.46 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.2, 154.8, 138.3, 131.6, 128.7, 127.8, 120.4, 127, 120.9. 119.3, 111.4, 102.0, 95.1, 80.2, 69.1, 64.8, 28.3, 25.7, 18.1; LRMS (EI): *m/z* 632 $(M-H^+)$ HRMS (ES): calcd for $C_{26}H_{26}Co_2NO_{10}$ $[M-H^+]$ 632.0183; found [632.0196].

4.4.1. Hexacarbonyl[1-{5-fluoro-2-[(3-methylbut-2-en-1yl) oxy]phenyl}-3-N-Boc-methylaminoprop-2-yn-o1]dicobalt ***6b***. Following the general procedure the title compound was isolated as a red oil (0.69 g, 71%): R_f 0.36 (DCM); ν_{max} (NaCl)/cm^{-1} (thin film) 2098, 2050, 2028, 1610, 1458: ^{1}H NMR (400 MHz, $CDCl_3$): 6.96−6.89 (m, 1H, Ar−H), 6.81 (bd s, 2H, Ar−H), 6.21 (d, 1H, *J*=4.5 Hz, CH−O*H*), 5.59−5.51 (m, 1H, CH=C), 5.25−5.19 (m, 1H, NH), 4.56 (bd s, 2H, CH_2O), 4.36 (br s, 1H, CH_2N), 3.75 (bd s, 1H, OH), 1.96−1.64 (m, 6H, CH_3−C=C), 1.47 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (100 MHz, $CDCl_3$): 134.6, 119.1, 114.3, 112.3, 80.6, 68.5, 43.2, 28.3, 27.8, 22.2, 18.1; LRMS (EI): *m/z* 672 $[M-Na^+]$ HRMS (ES): calcd for $C_{26}H_{25}Co_2FNNaO_{10}$ $[M+Na^+]$ 672.0097; found [672.0087].

4.4.2. Hexacarbonyl[1-{3-fluoro-2-[(3-methylbut-2-en-1yl) oxy] phenyl}-3-N-Boc-methylaminoprop-2-yn-o1]dicobalt ***6c***. Following the general procedure the title compound was isolated as a red oil (2.66 g, 84%): R_f 0.28 (DCM) ν_{max} (NaCl)/cm^{-1} (thin film) 3080, 2914, 2228, 1672, 1598, 1476; ^{1}H NMR (400 MHz, $CDCl_3$): 7.35 (d, 1H, *J*=7.5 Hz, Ar−H), 7.11−6.97 (m, 2H, Ar−H), 6.18 (d, 1H, *J*=3.8 Hz, CH−OH), 5.50 (t, 1H, *J*=6.9 Hz, CH=C), 5.40 (t, 1H, *J*=6.0 Hz NH), 4.85−4.77 (m, 1H, CH_2N), 4.58−4.44 (m, 2H, CH_2), 4.27 (dd, 1H, *J*=15.7, 6.0 Hz, CH_2N), 4.23 (d, 1H, *J*=3.8 Hz, OH), 1.75 (s, 3H, CH_3−C=C), 1.69 (s, 3H, CH_3−C=C), 1.47 (s, 9H, $(CH_3)_3C$): ^{13}C NMR (100 MHz, $CDCl_3$): 138.6, 121.8, 119.6, 80.4, 77.3, 70.2, 68.4, 43.2, 28.3, 25.7, 22.2, 17.9; LRMS (EI): *m/z* 672 $[M+Na^+]$ HRMS (ES): calcd for $C_{26}H_{25}Co_2FNNaO_{10}$ $[M+Na^+]$ 672.0097; found [672.0090].

4.4.3. Hexacarbonyl[1-{5,6-difluoro-2-[(3-methylbut-2-en-1-yl)oxy] phenyl}-3-N-Boc-methylaminoprop-2-yn-o1]dicobalt ***6d***. Following the general procedure the title compound was isolated as a red oil (0.31 g, 76%): R_f 0.25 (DCM); ν_{max} (NaCl)/cm^{-1} (thin film) 2914, 2052, 2028, 1609, 1598, 1476; ^{1}H NMR (400 MHz, $CDCl_3$): 7.06 (d, 1H, *J*=9.4 Hz, Ar−H), 6.56 (d, 1H, *J*=9.4 Hz, Ar−H), 6.26 (d, 1H, *J*=10.0 Hz, C*H*−OH), 5.50 (br s, 1H, CH=C), 5.13 (m, 1H, NH), 4.78 (d, 1H, *J*=10 Hz, OH), 4.66−4.51 (d, 2H, *J*=7.9 Hz, C*H*$_2$), 4.41 (dd, 2H, *J*=6.5, 10.5 Hz, C*H*$_2$N), 1.79 (s, 3H, CH_3−C=C), 1.76 (s, 3H, CH_3−C=C), 1.45 (s, 9H, $(CH_3)_3C$): ^{13}C NMR (100 MHz, $CDCl_3$); 139.8, 117.4, 115.7, 107.23, 79.84, 68.7, 65.8, 42.7, 28.3, 25.7, 22.2, 18.1: LRMS (EI): *m/z* 690 $[M+Na^+]$ HRMS (ES): calcd for $C_{26}H_{25}Co_2F_2NNaO_{10}$ $[M+Na^+]$ 690.0003; found [690.0000].

4.4.4. Hexacarbonyl[1-{3,6-difluoro-2-[(3-methylbut-2-en-1-yl)oxy] phenyl}-3-N-Boc-methylaminoprop-2-yn-o1]dicobalt ***6e***. Following the general procedure the title compound was isolated as a red oil (0.66 g, 55%): R_f 0.22; ν_{max} (NaCl)/cm^{-1} (thin film) 2099, 2055,

2028, 1612, 1598, 1476; ^{1}H NMR (400 MHz, $CDCl_3$): 7.01 (br s, 1H, Ar–H), 6.77 (br s, 1H, Ar–H), 6.18 (br s, 1H, CH–OH), 5.54 (br s, 1H, CH=C), 5.17 (br s, 1H, NH), 4.90–4.69 (m, 2H, CH_2), 4.35 (bd s, 3H, CH_2N and OH), 1.87–1.63 (m, 6H, CH_3–C=C), 1.44 (s, 9H, $(CH_3)_3$C); ^{13}C NMR (100 MHz, $CDCl_3$):118.5, 116.3, 110.3, 79.8, 70.8 (d, $^4J_{C-F}$=8.1 Hz), 69.0, 42.8, 28.3; 25.6, 22.0, 18.0; LRMS (EI): *m*/*z* 666 [M–H$^+$] HRMS (ES): calcd for $C_{26}H_{25}Co_2F_2NO_{10}$ [M–H$^+$] 666.0038; found [666.0026].

4.4.5. Hexacarbonyl[1-{4,5-difluoro-2-[(3-methylbut-2-en-1-yl)oxy] phenyl}-3-N-Boc-methylaminoprop-2-yn-o1]dicobalt ***6f***. Following the general procedure the title compound was isolated as a red oil (0.67 g, 67%): R_f 0.20 (DCM); ν_{max} (NaCl)/cm^{-1} (thin film) 2950, 2917, 2228, 2098, 2050, 1604, 1598, 1476; ^{1}H NMR (400 MHz, $CDCl_3$): 7.43 (t, 1H, *J*=10.0 Hz, Ar–H), 6.72 (dd, 1H, *J*=6.3 and 11.8 Hz, Ar–H), 6.21 (br s, 1H, CH–OH), 5.50–5.42 (m, 1H, CH=C), 5.31 (br s, 1H, NH), 4.84 (br s, 1H, OH), 4.63–4.51 (m, 2H, CH_2), 4.45 (d, 1H, *J*=6.0 Hz, CH_2N), 4.31 (dd, 1H, *J*=6.0 and 15.4 Hz, CH_2N), 1.79 (br s, 3H, CH_3–C=C), 1.75 (s, 3H, CH_3–C=C), 1.49 (s, 9H, $(CH_3)_3$C): ^{13}C NMR (100 MHz, $CDCl_3$): 138.8, 118.6, 115.8, 101.4, 81.0, 66.9, 65.6, 43.4, 28.3, 25.7, 18.1: LRMS (EI): *m*/*z* 690 [M+Na]$^+$ HRMS (ES): calcd for $C_{26}H_{25}Co_2F_2NNaO_{10}$ [M$^+$+Na]$^+$ 690.0003; found [689.9985].

4.4.6. Hexacarbonyl[1-{4-fluoro-2-[(3-methylbut-2-en-1-yl)oxy] phenyl}-3-N-Boc-methylaminoprop-2-yn-o1]dicobalt ***6g***. Following the general procedure the title compound was isolated as a red oil (0.92 g, 53%): R_f 0.25 (DCM); ν_{max} (NaCl)/cm^{-1} (thin film) 2230, 2226, 2051, 1610, 1597, 1476; ^{1}H NMR (400 MHz, $CDCl_3$): 7.51 (t, 1H, *J*=7.5 Hz Ar–H), 6.74–6.69 (m, 1H, Ar–H), 6.64–6.58 (m, 1H, Ar–H), 6.19 (d, 1H, *J*=4.1 Hz, CH–O*H*), 5.52–5.42 (m, 1H, CH=C), 5.23–5.15 (m, 1H, NH), 4.59 (bd s, 1H, CH_2N), 4.54–4.45 (m, 2H, CH_2), 4.38 (d, 1H, *J*=4.1 Hz, OH), 4.30 (dd, 1H, *J*=15.8 and 6.0 Hz, CH_2N), 1.78 (s, 3H, CH_3–C=C), 1.75 (s, 3H, CH_3–C=C), 1.47 (s, 9H, $(CH_3)_3$C): ^{13}C NMR (100 MHz, $CDCl_3$): 156.3, 138.7, 127.9, 118.8, 106.9, 99.5, 95.2, 80.4, 67.9, 65.2, 43.2, 28.3, 25.6, 18.1: LRMS (EI): *m*/*z* 648 [M–H]$^+$ HRMS (ES): calcd for $C_{26}H_{25}Co_2FNO_{10}$ [M–H]$^+$ 648.0132; found [648.0127].

4.4.7. Hexacarbonyl[1-{3,5-difluoro-2-[(3-methylbut-2-en-1-yl)oxy] phenyl}-3-N-Boc-methylaminoprop-2-yn-o1]dicobalt ***6h***. Following the general procedure the title compound was isolated as a red oil (1.07 g, 67%): R_f 0.22 (DCM); ν_{max} (NaCl)/cm^{-1} (thin film) 3422, 2914, 2229, 2050, 2048, 1672, 1598, 1476; ^{1}H NMR (400 MHz, $CDCl_3$): 7.12 (d, 1H, *J*=8.2 Hz, Ar–H), 6.84–6.73 (m, 1H, Ar–H), 6.15 (d, 1H, *J*=2.0 Hz, CH–OH), 5.51–5.37 (m, 1H, CH=C and NH), 4.79–4.68 (m, 1H, CH_2), 4.61 (d, 1H, *J*=2.0 Hz, OH), 4.57–4.42 (m, 2H, CH_2N), 4.29 (dd, 1H, *J*=15.7, 5.7 Hz, CH_2), 1.74 (bd s, 3H, CH_3–C=C), 1.67 (s, 3H, CH_3–C=C), 1.47 (s, 9H, $(CH_3)_3$C): ^{13}C NMR (100 MHz, $CDCl_3$): 138.9, 119.5, 115.7, 80.4, 70.4 (d, $^4J_{C-F}$=6.9 Hz), 67.9 (d, $^4J_{C-F}$=3.1 Hz), 43.3, 28.3, 25.7, 17.9; LRMS (EI): *m*/*z* 666 [M–H]$^+$ HRMS (ES): calcd for $C_{26}H_{25}Co_2F_2NO_{10}$ [M–H]$^+$ 666.0038; found [666.0033].

4.5. Preparation of hexacarbonyl {3-(1-fluoro-1-methylethyl)-4-(*N*-Boc-methylaminoethynyl)chromane} dicobalt 7a[14]

To a solution of hexacarbonyl[1-{2-[(3-methylbut-2-en-1-yl)oxy] phenyl}-3-*N*-Boc-methylaminoprop-2-yn-o1]dicobalt **6a** (1.10 g, 1.7 mmol) dissolved in dry dichloromethane (10 mL) and maintained at a temperature of 0 °C was added boron trifluouride diethyl etherate (0.25 g, 220 μL, 1.8 mmol). The reaction mixture was left to stir for about 5 min under an atmosphere of nitrogen. Analysis by TLC showed the presence of a new compound with an R_f of 0.49 (DCM). The reaction mixture was quenched by the addition of a saturated aqueous solution of sodium hydrogen carbonate (10 mL) and then partitioned with dichloromethane. The aqueous phase was extracted with dichloromethane (3×15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed in vacuo to afford the title compound as a red oil (0.55 g, 94%): ν_{max} (NaCl)/cm^{-1} (thin film) 3583, 2980, 2857, 2091, 2053, 2021, 1712, 1506; ^{1}H NMR (400 MHz, $CDCl_3$): 7.26–7.22 (m, 1H, Ar–H), 7.15 (t, 1H, *J*=7.2 Hz, Ar–H), 6.94 (t, 1H, *J*=7.2 Hz, Ar–H), 6.83 (d, 1H, *J*=8.0 Hz, Ar–H), 4.98–4.86 (m, 1H, NH), 4.62 (dd, 1H, *J*=16.1 and 6.5 Hz, CH_2), 4.47 (dd, 1H, *J*=16.1 and 6.5 Hz, CH_2), 4.39 (ddd, 1H, *J*=7.8, 3.0 and 1.3 Hz, CH_2), 4.33 (d, 1H, *J*=12.5 Hz, CH_2), 4.25 (s, 1H, Ar–CH), 2.46–2.35 (m, 1H, CH–CF) 1.45 (s, 9H, $(CH_3)_3$C), 1.44 (d, 3H, *J*=21.8 Hz, CH_3), 1.32 (d, 3H, *J*=22.3 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.5, 154.0, 130, 128.6, 124.7, 121.4, 117.3, 104.4, 97.7, 96.6 (d, $^2J_{C-F}$=165.3 Hz), 79.9, 68.1, 63.1 (d, $^4J_{C-F}$=9.2 Hz), 49.7 (d, $^3J_{C-F}$=24.2 Hz), 37.2 (d, $^4J_{C-F}$=5.4 Hz), 28.3, 25.9 (d, $^3J_{C-F}$=23.8 Hz), 24.5 (d, $^3J_{C-F}$=24.6 Hz): LRMS (EI): *m*/*z* 666.

4.5.1. Hexacarbonyl{3-(1-fluoro-1-methylethyl)-6-fluoro-4-(N-Boc-methylaminoethynyl)chromane}dicobalt ***7b***. Following the general procedure the title compound was isolated as a red oil (0.41 g, 62%): R_f 0.65 (DCM); ν_{max} (NaCl)/cm^{-1} (thin film) 3586, 2995, 2098, 2055, 1692, 1500; ^{1}H NMR (400 MHz, $CDCl_3$): 7.01 (dd, 1H, *J*=7.8, 3.0 Hz, Ar–H), 6.87 (ddd, 1H, *J*=9.0, 7.8, 3.0 Hz, Ar–H), 6.80 (dd, 1H, *J*=9.0, 4.5 Hz, Ar–H), 5.04–4.88 (m, 1H, NH), 4.64 (dd, 1H, *J*=16.1, 6.5 Hz, CH_2), 4.46 (dd, 1H, *J*=16.1, 6.5 Hz, CH_2), 4.40–4.31 (m, 1H, CH_2), 4.31–4.25 (m, 1H, CH_2), 4.23 (s, 1H, Ar–CH), 2.45–2.34 (m, 1H, CH–CF), 1.45 (s, 9H, $(CH_3)_3$C), 1.44 (d, 3H, *J*=22.1 Hz, CH_3), 1.32 (d, 3H, *J*=22.1 Hz, CH_3): ^{13}C NMR (100 MHz, $CDCl_3$): δ=126.1, 118.3, 115.4, 103.4, 97.8, 95, 80.2, 68.5, 62.8, 49.9, 37.3, 28.3, 25.6, 24.4; LRMS (EI): *m*/*z* 674 [M+Na]$^+$ HRMS (ES): calcd for $C_{26}H_{25}Co_2F_2NNaO_9$ [M+Na]$^+$ 674.0054; found [674.0047].

4.5.2. Hexacarbonyl{3-(1-fluoro-1-methylethyl)-8-fluoro-4-(N-Boc-methylaminoethynyl)chromane}dicobalt ***7c***. Following the general procedure the title compound was isolated as a red oil (1.53 g, 58%): R_f 0.60 (DCM); ν_{max} (NaCl)/cm^{-1} (thin film) 3582, 2986, 2080, 2054, 1682, 1509; ^{1}H NMR (400 MHz, $CDCl_3$): 7.08 (d, 1H, *J*=7.6 Hz, Ar–H), 6.97 (dd, *J*=8.1, 1.5 Hz, 1H, Ar–H), 6.90, (dd, 1H, *J*=7.6, 5.0 Hz, Ar–H), 4.96 (t, 1H, *J*=6.6 Hz, NH), 4.64 (dd, 1H, *J*=16.3, 6.6 Hz, CH_2), 4.51–4.39 (m, 3H, CH, CH_2), 4.30 (s, 1H, CH), 2.42 (dt, 1H, *J*=11.4, 3.2 Hz, CH_2), 1.51–1.43 (m, 12H, CH_3, $(CH_3)_3$C), 1.32 (d, 3H, *J*=22.3 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=120.8, 120.7, 115.0, 101.7, 68.9, 63.4, 43.7, 28.3, 25.3, 24.6: LRMS (EI): *m*/*z* 650 [M–H$^+$] HRMS (ES): calcd for $C_{26}H_{25}Co_2F_2NO_9$ [M–H$^+$] 650.0089; found [650.0081].

4.5.3. Hexacarbonyl{3-(1-fluoro-1-methylethyl)-5,6-difluoro-4-(N-Boc-methylaminoethynyl)chromane}dicobalt ***7d***. Following the general procedure the title compound was isolated as a red oil (0.25 g, 95%): R_f 0.61 (DCM); ν_{max} (NaCl)/cm^{-1} (thin film) 3425, 2946, 2220, 2080, 2055, 1672, 1598; ^{1}H NMR (400 MHz, $CDCl_3$): 7.04–6.95 (m, 1H, Ar–H), 6.68–6.64, (m, 1H, Ar–H), 5.01–4.97 (m, 1H, NH), 4.53–4.46 (m, 3H, CH_2 and CH_2), 4.43 (ddd, *J*=12.3, 4.8, 2.5 Hz, 1H, CH_2), 4.33–4.29 (m, 1H, CH), 1.85–1.76 (m, 1H, CH), 1.48–1.38 (m, 12H, CH_3 and $(CH_3)_3$C), 1.32 (d, 3H, *J*=22.1 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 80.1, 62.9, 49.1, 28.3, 25.7, 24.4; LRMS (EI): *m*/*z* 668 [M–H]$^+$ HRMS (ES): calcd for $C_{26}H_{24}Co_2F_3NO_9$ [M–H]$^+$ 667.9994; found [667.9989].

4.5.4. Hexacarbonyl{3-(1-fluoro-1-methylethyl)-5,8-difluoro-4-(N-Boc-methylaminoethynyl)chromane}dicobalt ***7e***. Following the general procedure the title compound was isolated as a red oil (0.46 g, 76%): R_f 0.58 (DCM) ν_{max} (NaCl)/cm^{-1} (thin film) 2914, 2228, 2055, 2040, 1598; ^{1}H NMR (400 MHz, $CDCl_3$); 7.04–6.92 (m, 1H, Ar–H), 6.49, (br s, 1H, Ar–H), 4.97 (br s, 1H, NH), 4.56–4.44 (m, 1H, CH_2), 4.41–4.27 (m, 2H, CH and CH_2), 3.95–3.78 (m, 2H, CH_2), 1.80–1.72 (m, 1H, CH), 1.49–1.35 (m, 15H, 2×CH_3 and $(CH_3)_3$C); ^{13}C

NMR (100 MHz, $CDCl_3$): δ=116.0, 105.7,77.8, 67.1, 63.2, 48.2, 43.1, 28.3, 25.7, 24.6; LRMS (EI): *m/z* 669 $[M-H]^+$ HRMS (ES): calcd for $C_{26}H_{24}Co_2F_3NO_9$ $[M-H]^+$ 667.9994; found [667.9977].

4.5.5. Hexacarbonyl{3-(1-fluoro-1-methylethyl)-6,7-difluoro-4-(N-Boc-methylaminoethynyl)chromane}dicobalt ***7f***. Following the general procedure the title compound was isolated as a red oil (0.21 g, 39%): R_f 0.56 (DCM); ν_{max} (NaCl)/cm^{-1} (thin film) 3425, 2915, 2050, 2025, 1672, 1598; ^1H NMR (400 MHz, $CDCl_3$): 7.16 (t, 1H, *J*=9.4 Hz, Ar–H), 6.67, (dd, 1H, *J*=11.2, 6.9 Hz, Ar–H), 5.07–4.86 (m, 1H, NH), 4.65 (dd, 1H, *J*=16.3 and 6.5 Hz, CH_2), 4.44 (dd, 1H, *J*=16.3 and 6.5 Hz, CH_2), 4.33 (d, 2H, *J*=3.3 Hz, CH_2), 4.20 (s, 1H, Ar–CH), 2.40–2.30 (m, 1H, CF–CH) 1.51–1.39 (m, 12H, CH_3 and $(CH_3)_3C$) 1.31 (d, 3H, *J*=22.6 Hz, CH_3); 63.1, 43.6, 28.3, 25.9, 24.4; LRMS (EI): *m/z* 687 $[M+NH_4]^+$ HRMS (ES): calcd for $C_{26}H_{28}Co_2F_3N_2O_9$ $[M+NH_4]^+$ 687.0405; found [687.0404].

4.5.6. Hexacarbonyl{3-(1-fluoro-1-methylethyl)-7-fluoro-4-(N-Boc-methylaminoethynyl)chromane}dicobalt ***7g***. Following the general procedure the title compound was isolated as a red oil (0.46 g, 76%): R_f 0.58 (DCM); ν_{max} (NaCl)/cm^{-1} (thin film) 2935, 2210, 2045, 2025, 1645, 1598, 1476; ^1H NMR (400 MHz, $CDCl_3$): 7.51 (t, 1H, *J*=7.8 Hz, Ar–H), 6.76–6.65, (m, 1H, Ar–H), 6.64–6.52 (m, 1H, Ar–H), 5.29–5.17 (m, 1H, NH), 4.66–4.34 (m, 4H, CH_2), 4.23 (br s, 1H, CH), 2.37 (d, 1H, *J*=10.5 Hz, CH), 1.53–1.38 (m, 12H, CH_3 and $(CH_3)_3C$) 1.31 (d, 3H, *J*=21.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ=106.9, 104.5, 99.5, 80.5, 67.7, 62.9, 43.1, 36.4, 28.3, 25.8, 24.4; LRMS (EI): *m/z* 650 $[M-H^+]$ HRMS (ES): calcd for $C_{26}H_{25}Co_2F_2NO_9$ $[M-H^+]$ 650.0089; found [650.0079].

4.5.7. Hexacarbonyl{3-(1-fluoro-1-methylethyl)-6,8-difluoro-4-(N-Boc-methylaminoethynyl)chromane}dicobalt ***7h***. Following the general procedure the title compound was isolated as a red oil (0.56 g, 71%): R_f 0.57 (DCM); ν_{max} (NaCl)/cm^{-1} (thin film) 3420, 2914, 2228, 2250, 2220, 1598; ^1H NMR (400 MHz, $CDCl_3$): 6.89, (d, 1H *J*=8.3 Hz, Ar–H), 6.77 (ddd, 1H *J*=10.7, 8.3, 2.9 Hz, Ar), 5.02 (t, 1H *J*=6.5 Hz, NH), 4.66 (dd, 1H *J*=16.2, 6.5 Hz, CH_2), 4.45 (dd, 1H, *J*=16.2, 6.5 Hz, CH_2), 4.41–4.37 (m, 2H, CH_2), 4.28 (br s, 1H, CH), 2.42 (dt, 1H, *J*=11.4, 3.5 Hz, CH), 1.45 (s, 9H, $(CH_3)_3C$), 1.47 (d, 3H *J*=21.9 Hz), 1.32 (d, 3H, *J*=22.7 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.5, 120.8, 115.0, 77.2, 63.4, 43.7, 28.3, 26.1, 24.3; LRMS (EI): *m/z* 687 $[M+NH_4]^+$ HRMS (ES): calcd for $C_{26}H_{28}Co_2F_3N_2O_9$ $[M+NH_4]^+$ 687.0405; found [687.0407].

4.6. Preparation of 3-(1-fluoro-1-methylethyl)-4-(*N*-Boc-methylaminoethynyl)chromane 8a

To a solution of hexacarbonyl {3-(1-fluoro-1-methylethyl)-4-(*N*-Boc-methylaminoethynyl)chromane} dicobalt **7a** (1.28 g, 2.0 mmol) in methanol (125 mL) was added cerium ammonium nitrate (CAN) (6.03 g, 11.0 mmol). The solution was stirred at an ambient temperature for about 30 min until the evolution of gas ceased. Analysis by TLC showed the presence of a new compound with an R_f of 0.50 (ethyl acetate/hexane 3:7). The reaction mixture was quenched by the addition of a saturated aqueous solution of sodium hydrogen carbonate (50 mL). The solvent, methanol, was removed in vacuo and the resulting aqueous solution was extracted with diethyl ether (4×25 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent removed in vacuo to afford the title compound as a light brown oil (0.55 g, 79%): ν_{max} (NaCl)/cm^{-1} (thin film) 3356, 2982, 2204, 1694, 1586, 1490, 1229; ^1H NMR (400 MHz, $CDCl_3$): 7.34 (dd, 1H, *J*=7.5, 1.0 Hz, Ar–H), 7.14 (dd, 1H, *J*=7.5 and 1.4 Hz, Ar–H), 6.93 (dd, 1H, *J*=7.5, 1.0 Hz, Ar–H), 6.80 (dd, 1H, *J*=7.5, 1.4 Hz, Ar–H), 4.67–4.65 (m, 1H, NH), 4.39 (dt, 1H, *J*=11.6, 2.9 Hz, CH_2), 4.18–4.08 (m, 1H, CH_2), 3.95–3.83 (m, 3H, CH, CH_2), 2.41–2.30 (m, 1H, CHCF) 1.46 (d, *J*=21.6 Hz, 3H, CH_3), 1.45 (s, 9H, $(CH_3)_3C$), 1.39 (d, 3H, *J*=22.6 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.2, 153.8, 130, 128.2, 121.6, 121.2, 116.9, 96.3 (d, $^2J_{C-F}$=168.0 Hz), 92.8, 85.6, 78.3, 65.8, 64.2 (d, $^4J_{C-F}$=10.3 Hz), 47.4 (d, $^3J_{C-F}$=22.7 Hz), 28.3, 28.0 (d, $^4J_{C-F}$=5.1 Hz), 25.8 (d, $^3J_{C-F}$=24.9 Hz), 25.3 (d, $^3J_{C-F}$=24.2 Hz): LRMS (EI): *m/z* 365 $[M+NH_4]^+$ HRMS (ES): calcd for $C_{20}H_{30}FN_2O_3$ $[M+NH_4]^+$ 365.2235; found [365.2237].

4.6.1. 3-(1-Fluoro-1-methylethyl)-6-fluoro-4-(N-Boc-methylaminoethynyl)chromane ***8b***. Following the general procedure the title compound was isolated as a yellow oil (0.40 g, 97%): R_f 0.61 (ethyl acetate/hexane 3:7); ν_{max} (NaCl)/cm^{-1} (thin film) 3356, 2980, 2210, 1698, 1586, 1490, 1229; ^1H NMR (400 MHz, $CDCl_3$): 7.06 (dd, 1H, *J*=9.0, 3.0 Hz, Ar–H), 6.85 (ddd, 1H, *J*=9.0, 8.0, 3.0 Hz, Ar–H), 6.75 (dd, 1H, *J*=9.0, 4.0 Hz, Ar–H), 4.63 (br s, 1H, NH), 4.39–4.30 (m, 1H, CH_2), 4.17–4.06 (m, 1H, CH_2), 3.92 (d, 2H, *J*=4.0 Hz, CH_2), 3.85 (br s, 1H, CH), 2.38–2.24 (m, IH, CH), 1.45 (s, 9H, $(CH_3)_3C$), 1.46 (d, 3H, *J*=22.3 Hz, CH_3), 1.39 (d, 3H, *J*=23.1 Hz, CH_3): ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 157.1 (d, $^2J_{C-F}$=253.82 Hz), 123.7 (d, $^3J_{C-F}$=24.94 Hz), 122.8 (d, $^4J_{C-F}$=7.34 Hz), 119.5 (d, $^4J_{C-F}$=7.34 Hz), 117.8 (d, $^4J_{C-F}$=8.07 Hz), 115.76 (d, $^3J_{C-F}$=23.48 Hz), 96.2 (d, $^2J_{C-F}$=167.99 Hz), 93.7, 84.7, 78.8, 68.5, 64.4 (d, $^4J_{C-F}$=9.54 Hz), 47.12 (d, $^3J_{C-F}$=22.01 Hz), 28.3, 28.2, 25.7 (d, $^3J_{C-F}$=24.94 Hz), 25.3 (d, $^3J_{C-F}$=24.21 Hz); LRMS (EI): *m/z* 365 $[M]^+$ HRMS (ES): calcd for $C_{20}H_{25}F_2NO_3$ $[M]^+$ 365.1797; found [365.1800].

4.6.2. 3-(1-Fluoro-1-methylethyl)-8-fluoro-4-(N-Boc-methylaminoethynyl)chromane ***8c***. Following the general procedure the title compound was isolated as a yellow oil (0.22 g, 76%): R_f 0.54 (ethyl acetate/hexane 3:7); ν_{max} (NaCl)/cm^{-1} (thin film) 3480, 2914, 2228, 1680, 1599, 1476; ^1H NMR (400 MHz, $CDCl_3$): 7.10 (d, 1H, *J*=7.9 Hz, Ar–H), 6.96–6.90 (m, 1H, Ar–H), 6.83 (dd, 1H, *J*=7.9, 5.1 Hz, Ar–H), 4.72 (br s, 1H, NH), 4.43 (dt, 1H, *J*=11.8, 3.0 Hz, CH_2), 4.22 (dd, 1H, *J*=11.8, 5.1 Hz, CH_2), 3.90 (d, 3H, *J*=5.1 Hz, CH, CH_2), 2.38–2.24 (m, IH, CH), 1.50 (d, 3H, *J*=12.0 Hz, CH_3), 1.43 (s, 9H, $(CH_3)_3C$), 1.36 (d, 3H, *J*=22.8 Hz, CH_3): ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6 (d, $^2J_{C-F}$=248.69 Hz), 152.6 (d, $^3J_{C-F}$=19.07 Hz), 151.3, 142.2 (d, $^3J_{C-F}$=11.53 Hz), 124.8 (d, $^4J_{C-F}$=3.08 Hz), 120.4 (d, $^4J_{C-F}$=6.92 Hz), 114.4 (d, $^3J_{C-F}$=17.68 Hz), 96.1 (d, $^2J_{C-F}$=169.12 Hz), 93.7, 84.9, 78.8, 68.8, 64.4 (d,$^4J_{C-F}$=9.99 Hz), 47.1 (d, $^3J_{C-F}$=22.29 Hz), 28.2, 28.29–28.13 (m), 25.5 (d, $^3J_{C-F}$=25.35 Hz), 25.4 (d, $^3J_{C-F}$=24.60 Hz); LRMS (EI): *m/z* 365 $[M]^+$ HRMS (ES): calcd for $C_{20}H_{25}F_2NO_3$ $[M]^+$ 365.1797; found [365.1799].

4.6.3. 3-(1-Fluoro-1-methylethyl)-5,6-difluoro-4-(N-Boc-methylaminoethynyl)chromane ***8d***. Following the general procedure the title compound was isolated as a yellow oil (1.10 g, 96%): R_f 0.52 (ethyl acetate/hexane 3:7); ν_{max} (NaCl)/cm^{-1} (thin film) 3422, 2920, 2228, 1685, 1599, 1476; ^1H NMR (400 MHz, $CDCl_3$): 6.97 (dd, 1H, *J*=9.4, 9.2 Hz, Ar–H), 6.55 (ddd, 1H, *J*=9.2, 3.8 and 1.8 Hz), 4.65–4.54 (m, 1H, NH), 4.37–4.25 (m, 2H, CH_2), 4.02 (br s, 1H, CH), 3.91 (m, 3H, CH, CH_2), 1.44 (s, 9H, $(CH_3)_3C$), 1.42 (d, 3H, *J*=21.6 Hz, CH_3), 1.28 (d, 3H, *J*=23.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 150.0 (dd, $^4J_{C-F}$=5.13, 2.20 Hz), 148.3 (dd, $^2J_{C-F}$=248.69, $^3J_{C-F}$=13.94 Hz), 144.8 (dd, $^2J_{C-F}$=240.62, $^3J_{C-F}$=12.47 Hz), 115.8 (dd, $^3J_{C-F}$=19.07, $^4J_{C-F}$=1.47 Hz), 112.0 (d, $^3J_{C-F}$=15.41 Hz), 111.7 (dd, $^4J_{C-F}$=5.87, 3.67 Hz), 95.9 (d, $^2J_{C-F}$=169.46 Hz), 83.6, 80.1, 78.0, 65.8, 63.4 (d, $^4J_{C-F}$=8.07 Hz), 46.5 (d, $^3J_{C-F}$=23.47 Hz), 30.7 (bd s) 28.3, 25.8 (d, $^3J_{C-F}$=23.48 Hz), 24.9 (d, $^3J_{C-F}$=24.94 Hz): LRMS (EI): *m/z* 401 $[M+NH_4]^+$ HRMS (ES): calcd for $C_{20}H_{24}F_3NO_3$ $[M+NH_4]^+$ 401.2047; found [401.2049].

4.6.4. 3-(1-Fluoro-1-methylethyl)-5,8-difluoro-4-(N-Boc-methylaminoethynyl)chromane ***8e***. Following the general procedure the title compound was isolated as a yellow oil (0.19 g, 73%): R_f 0.50 (ethyl acetate/hexane 3:7); ν_{max} (NaCl)/cm^{-1} (thin film) 2914, 2230,

1686, 1598; ^{1}H NMR (400 MHz, $CDCl_3$): 6.93 (ddd, 1H, J=9.5, 9.0, 5.0 Hz, Ar–H), 6.58 (ddd, J=9.5, 9.0, 3.5 Hz, 1H, Ar–H) 6.61 (br s, 1H, NH), 4.49–4.39 (m, 2H, CH_2), 4.02 (br s, 1H, CH), 3.90 (br s, 2H, CH_2), 2.34 (bd d, IH, J=13.3 Hz, CH), 1.49–1.39 (m, 12H, CH_3, $(CH_3)_3C$), 1.28 (d, 3H, J=22.3 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4, 150.8, 131.0, 128.8, 114.3, 110.8, 106.2, 96.7, 92.5, 88.8, 80.2, 68.1, 63.7 (d, $^3J_{C-F}$=8.1 Hz), 46.6 (d, $^3J_{C-F}$=22.7, Hz), 28.9, 28.3, 25.9 (d,$^3J_{C-F}$=24.2 Hz), 24.8 (d, $^3J_{C-F}$=24.9 Hz); LRMS (EI): m/z 383 $[M]^+$ HRMS (ES): calcd for $C_{20}H_{25}F_3NO_3$ $[M]^+$ 383.1703; found [383.1699].

4.6.5. 3-(1-Fluoro-1-methylethyl)-6,7-difluoro-4-(N-Boc-methylaminoethynyl)chromane ***8f***. Following the general procedure the title compound was isolated as a yellow oil (0.07 g, 91%): R_f 0.52 (ethyl acetate/hexane 3:7); ν_{max} (NaCl)/cm^{-1} (thin film) 3445, 3321, 2918, 2228, 1678, 1602, 1476; ^{1}H NMR (400 MHz, $CDCl_3$): 7.14 (dd, 1H, J=10.2, 9.2 Hz, Ar–H), 6.62 (dd, 1H, J=11.3, 7.0 Hz, Ar–H) 4.63 (br s, 1H, NH), 4.35 (dt, 1H, J=11.5, 2.8 Hz, CH_2), 4.10 (dd, 1H, J=11.5, 5.6 Hz, CH_2), 3.92 (d, 2H, J=2.5 Hz, CH_2), 3.80 (d, 1H, J=2.5 Hz, CH), 2.37–2.25 (m, 1H, CH), 1.45 (s, 9H, $(CH_3)_3C$), 1.46 (d, 3H, J=21.8 Hz, CH_3), 1.39 (d, 3H, J=22.6 Hz, CH_3): ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 148.3 (dd, $^2J_{C-F}$=248.69, $^3J_{C-F}$=14.67 Hz), 148.8 (dd, $^2J_{C-F}$=241.35, $^3J_{C-F}$=13.20 Hz), 144.8 (dd, $^2J_{C-F}$=240.62, $^3J_{C-F}$=12.47 Hz), 115.8 (dd, $^3J_{C-F}$=19.07, $^4J_{C-F}$=1.47 Hz), 112.0 (d, $^3J_{C-F}$=16.14 Hz), 111.7 (dd, $^4J_{C-F}$=5.87, 4.47 Hz), 95.9 (d, $^2J_{C-F}$=167.99 Hz), 83.6, 80.1, 78.0, 65.8, 63.4 (d,$^4J_{C-F}$=8.80 Hz), 46.5 (d, $^3J_{C-F}$=22.74 Hz), 32.8, 28.3, 25.8 (d, $^3J_{C-F}$=24.21 Hz), 24.9 (d, $^3J_{C-F}$=22.74 Hz); LRMS (EI): m/z 401 $[M+NH_4]^+$ HRMS (ES): calcd for $C_{20}H_{24}F_3NO_3$ $[M+NH_4]^+$ 401.2047; found [401.2048].

4.6.6. 3-(1-Fluoro-1-methylethyl)-7-fluoro-4-(N-Boc-methylaminoethynyl)chromane ***8g***. Following the general procedure the title compound was isolated as a yellow oil (0.57 g, 98%): R_f 0.45 (ethyl acetate/hexane 3:7); ν_{max} (NaCl)/cm^{-1} (thin film) 3328, 2916, 2228, 1685, 1605, 1478; ^{1}H NMR (400 MHz, $CDCl_3$): 7.42 (d, J=7.4 Hz, 1H, Ar–H), 6.62–6.51 (m, 1H, Ar–H), 6.52 (dd, 1H J=10, 2.3 Hz, Ar–H), 4.64 (br s, 1H, NH), 4.49 (d, 2H, J=6.0 Hz, CH_2), 4.30 (d, J=11.5 Hz, 1H, CH_2), 4.09–4.01 (m, 1H, CH_2), 3.76 (br s, 1H, CH), 2.31–2.17 (m, IH, CH), 1.41–1.33 (m, 12H, $(CH_3)_3C$, CH_3), 1.30 (d, 3H, J=22.8 Hz CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5 (d, $^2J_{C-F}$=245.76 Hz), 161.0 (d, $^2J_{C-F}$=248.69 Hz), 155.2, 130.95 (d, $^4J_{C-F}$=9.54 Hz), 128.9 (d, $^3J_{C-F}$=10.27 Hz), 124.8 (d, $^4J_{C-F}$=3.67 Hz), 108.6 (d, $^3J_{C-F}$=22.01 Hz), 106.9 (d, $^3J_{C-F}$=20.54 Hz), 96.2 (d, $^2J_{C-F}$=167.99 Hz), 85.2, 82.5, 78.6, 65.6, 63.3 (d, $^3J_{C-F}$=10.27 Hz), 47.1 (d, $^3J_{C-F}$=22.74 Hz), 28.3, 27.6 (d, $^4J_{C-F}$=5.14 Hz), 25.8 (d, $^3J_{C-F}$=24.94 Hz), 25.3 (d, $^3J_{C-F}$=24.94 Hz); LRMS (EI): m/z 365 $[M]^+$ HRMS (ES): calcd for $C_{20}H_{25}F_2NO_3$ $[M]^+$ 365.1797; found [365.1806].

4.6.7. 3-(1-Fluoro-1-methylethyl)-6,8-difluoro-4-(N-Boc-methylaminoethynyl)chromane ***8h***. Following the general procedure the title compound was isolated as a yellow oil (0.18 g, 52%): R_f 0.45 (ethyl acetate/hexane 3:7); ν_{max} (NaCl)/cm^{-1} (thin film) 3445, 3248, 2922, 2218, 1686, 1598, 1484; ^{1}H NMR (400 MHz, $CDCl_3$): 6.88 (dd, J=8.6, 2.5 Hz, 1H, Ar–H), 6.74 (ddd, J=10.8, 8.6, 3.0 Hz, 1H, Ar–H), 6.64 (br s, 1H, NH), 4.41 (dt, J=11.7, 2.6, Hz, 1H, CH_2), 4.20 (dd, J=11.7 and 5.3 Hz, 1H, CH_2), 3.92 (d, J=3.8 Hz, 2H, CH_2), 3.87 (br s, 1H, CH), 2.41–3.31 (m, IH, CH), 1.52–1.44 (m, 12H, CH_3, $(CH_3)_3C$), 1.38 (d, 3H, J=22.9 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 162.0, 155.7 (d, $^3J_{C-F}$=12.47 Hz), 138.9 (dd, $^3J_{C-F}$=11.74, $^4J_{C-F}$=2.93 Hz), 110.9 (dd, $^3J_{C-F}$=23.47, $^4J_{C-F}$=2.93 Hz), 107.5 (dd,$^3J_{C-F}$=23.47, $^4J_{C-F}$=3.67 Hz), 103.5 (dd, $^3J_{C-F}$=27.14, 21.27 Hz), 96.9, 94.5 (d, $^2J_{C-F}$=171.66 Hz), 90.3, 83.3, 68.4 (d, $^4J_{C-F}$=8.07 Hz), 64.9 (d, $^4J_{C-F}$=10.27 Hz), 47.3 (d, $^3J_{C-F}$=22.74 Hz), 28.7 (bd s), 27.9 (d, $^3J_{C-F}$=22.74 Hz), 25.8 (d, $^3J_{C-F}$=24.21 Hz), 25.3 (d, $^3J_{C-F}$=24.21 Hz); LRMS (EI): m/z 383 $[M]^+$ HRMS (ES): calcd for $C_{20}H_{24}F_3NO_3$ $[M]^+$ 383.1703; found [383.1707].

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