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One-Pot Trifluoromethylative Functionalization of Amides: Synthesis of Trifluoromethylated Bis(indolyl)arylmethanes and Triarylmethanes

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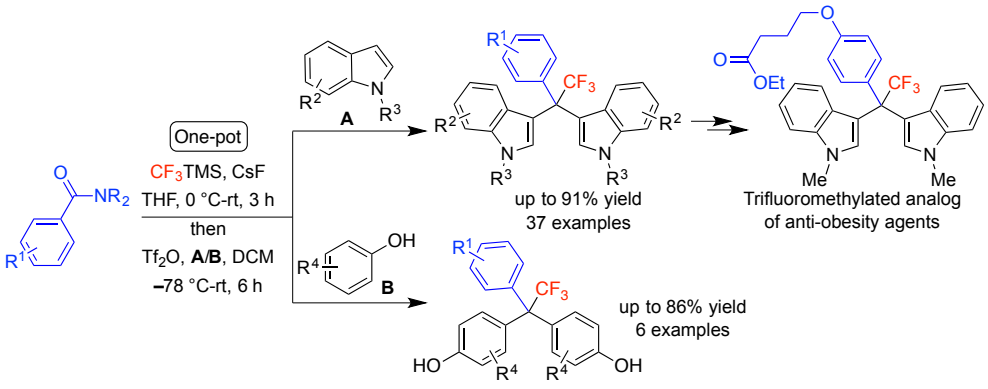


Abstract: Efficient and general one-pot trifluoromethylative functionalization of amides has been accomplished for the synthesis of various trifluoromethylated bis(indolyl)arylmethane, utilizing trifluoromethyltrimethylsilane and substituted indoles as nucleophiles. The developed reaction involves the *in-situ* generation and trapping of trifluoromethylated iminium ion, derived from trifluoromethylated hemiaminal of amide, with various substituted indoles. This method has been successfully extended to the synthesis of diverse trifluoromethylated triarylmethanes employing phenols as nucleophiles. Furthermore, the potential of the method was demonstrated *via* the two steps synthesis of trifluoromethylated analog of hypolipidemic and anti-obesity agent.

Introduction:

Substituted bisindolylmethanes (BIMs) are ubiquitous subunits present in various natural products and biologically interesting molecules. Most of the BIMs exhibit diverse therapeutic activities such as anticancer, antimicrobial, antioxidant, anti-inflammatory, and etc.[1] For example, vibrindole **1a** and streptindole **1b** are natural products containing BIM moiety and BIM **2** display broad cytotoxic activity (Figure 1). Similarly, triarylmethanes (TAMs) have also shown to possess various industrial, biological and material applications.[2]

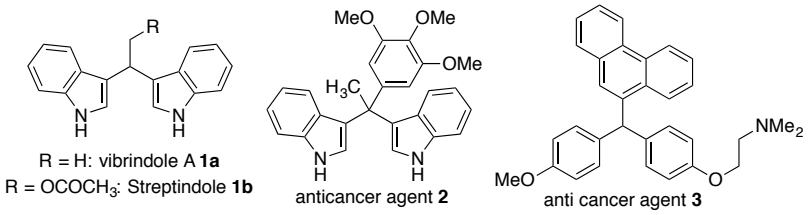


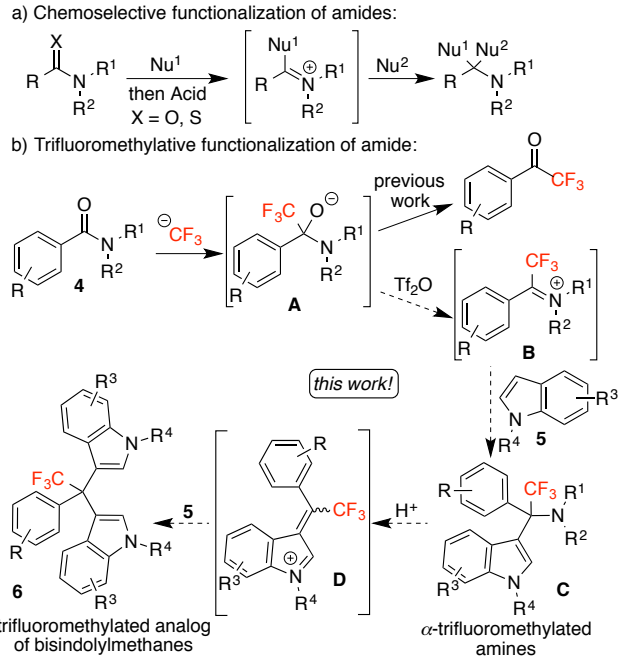
Figure 1. Examples of bioactive bisindolylmethanes

On the other hand, incorporation of trifluoromethyl group (CF_3) in therapeutically important molecules has the profound effect in their bioactivity and physicochemical properties, compared to parent molecules.[3] As a result, trifluoromethylated functionalized organic compounds have gained significant interest in various fields such as pharmaceutical, agrochemical, functional materials and etc,[4] which also triggered substantial interest in their synthesis.[5] However, the synthesis of trifluoromethylated BIMs is rather limited. The known methods for the synthesis of trifluoromethylated BIMs include the Friedel Crafts reaction of indole and trifluoromethylketones with a suitable acid promoter.[6] Due to the high potential of BIMs and 'CF_3' group, the development of general and efficient synthesis of trifluoromethylated BIMs should be highly warranted.

In general, BIMs are synthesized from aldehydes, ketones and their derivatives with substituted indoles.[7] In this context, to the best of our knowledge, amides were not utilized for the synthesis of either BIMs or trifluoromethylated derivatives[8], in spite their versatile application in the construction of various C-C bonds[9] through nucleophilic addition of organometallic reagents. Particularly, in the recent

past, various one-pot reductive functionalizations of amides to multisubstituted amines have been documented,[10] due to the potency of the carbonyl carbon to accept two nucleophiles (Scheme 1a).[11] Inspired by the one-pot reductive functionalization of amide and our continued interest in the utilization of trifluoromethylated hemiaminal in the construction of trifluoromethylated scaffolds[12], we envisioned the synthesis of potential trifluoromethylated BIMs from amides *via* trifluoromethylative functionalization. Thus, trifluoromethylation of amide to trifluoromethylated hemiaminal **A** followed by treatment with triflic anhydride (Tf_2O) would afford the trifluoromethylated iminium ion **B**, which could be functionalized with indole derivatives, in one-pot, for the synthesis of trifluoromethylated bis(indolyl)arylmethanes (BIAMs) *via* the possible generation of α-trifluoromentylated amine **C** and alkylideneindoleninium intermediate **D**[13] (Scheme 1b). We herein disclose the development of one-pot trifluoromethylative functionalization of amides for the general and efficient synthesis of trifluoromethylated BIAMs. Furthermore, the developed methodology could be easily applied in the synthesis of trifluoromethylated analog of therapeutically important molecules.

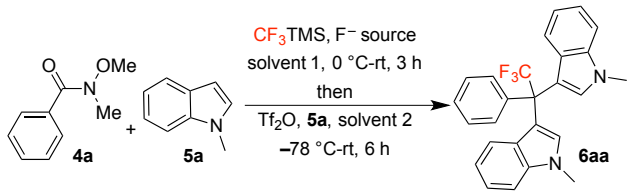
Scheme 1. Functionalization of amides



Results and Discussion

Based on the hypothesis, we initiated our studies with model substrates Weinreb amide **4a** and indole **5a**. Reaction of **4a** with trifluoromethyltrimethylsilane (CF_3TMS) in the presence of fluoride activator (CsF) at 0 °C in THF followed by changing the reaction medium to DCM and treatment with Tf_2O/**5a** afforded the trifluoromethylated BIAM **6aa** in 31% yield and no formation of α-trifluoromethylated amine derivative **C** was observed (Table 1, entry 1).[14] Various attempts to control the addition of only one indole **5a** to form α-trifluoromethylated amine derivative **C** was not successful and led to either **6aa** or no reaction, suggesting that the formed amine derivatives is not stable and highly reactive under the reaction conditions (Table 1, entries 1-6).

Table 1. One-pot trifluoromethylative functionalization of Weinreb amide **4a** with *N*-methylindole **5a**: Optimization[a]



Entry	F⁻ source	Solvent 1	5a (equiv)	Solvent 2	Yield (%)[b]
1	CsF	THF	1	DCM	31 (23)[c]
2	KF	THF	1	DCM	0
3	TBAF	THF	1	DCM	0
4	CsF	DCM	1	DCM	0
5	CsF	Toluene	1	DCM	34
6	CsF	Toluene	1	-	32
7	CsF	Toluene	2	-	72
8	CsF	Toluene	2.5	-	79
9	CsF	Toluene	2.5	DCM	81
10	CsF	THF	2.5	DCM	87

[a] Reaction conditions: **4a** (50 mg, 0.3 mmol), CF_3TMS (86 mg, 0.6 mmol, 2 equiv), F⁻ source (1 equiv), Solvent 1 (2 mL), 0 °C-rt, 3h, then Tf_2O (1.1 equiv), **5a** (equiv), Solvent (2 mL), –78 °C-rt, 6 h. [b] all are isolated yields. [c] 1.5 equivalents of CsF.

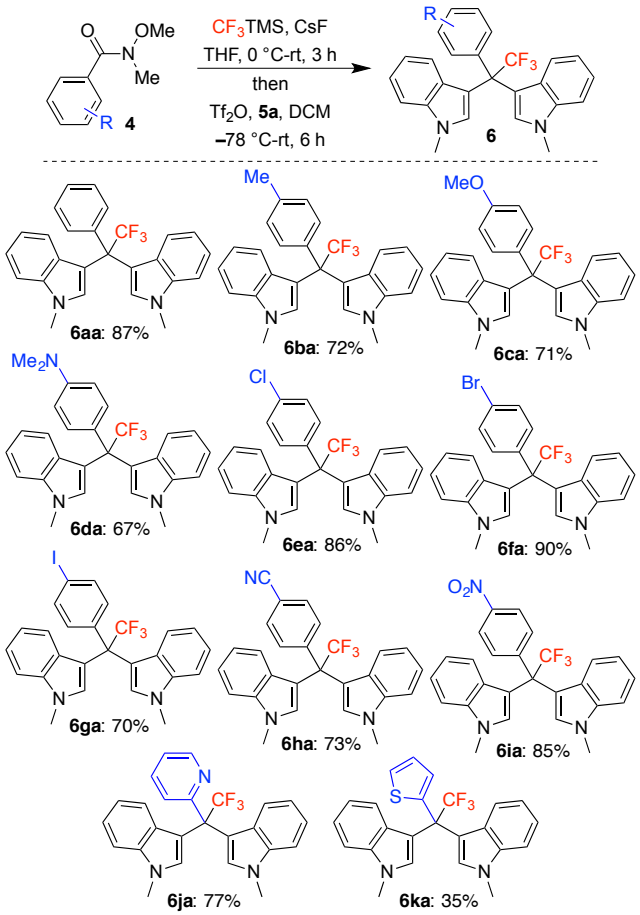
Next to increase the yield of potential trifluoromethylated BIAM **6aa**, number of equivalents of **5a** was raised to two in toluene, which gave the **6aa** in 72% yield (Table 1, entry 7). Further increase in

amount of **5a** as well as changing the solvent to DCM for iminium ion generation showed only slight improvement (Table 1, entries 8 and 9). Use of THF and DCM as solvents for the trifluoromethylation of **4a** and subsequent functionalization with Tf_2O and **5a**, respectively, gave the best result with 87% isolated yield of **6aa** (Table 1, entry 10). Having optimized the conditions for the trifluoromethylative functionalization of Weinreb amide **4**, *in-situ* NMR experiment was performed to understand and evaluate the involvement of possible intermediate. Although the formation of *N*,*O*-acetal intermediate **A** was observed after the trifluoromethylation of **4a** with CF_3TMS (see Supporting Information), the subsequent formation of neither a proposed iminium ion intermediate **B** nor 2,2,2-trifluoroacetophenone could be detected. On the other hand, to understand the possible formation of trifluoromethyl ketone as potential intermediate, 2,2,2-trifluoroacetophenone was subjected under the best-optimized conditions. This resulted in the formation **6aa** in only 56% yield, which is significantly less compared to the one-pot trifluoromethylative functionalization. Thus, these results favors the involvement of iminium ion **B** as potential intermediate in the trifluoromethylative functionalization of **4**, but the involvement of trifluoromethyl ketone could not completely ruled out.

Next, the scope and limitation of substituted amides were investigated. As can be seen in Scheme 2, various substituted aryl containing trifluoromethylated BIAMs **6** were synthesized in good to excellent yield in one-pot from substituted Weinreb amides **4**. For instance, alkyl and electron donating methoxy and *N*,*N*-dimethyl substituted Weinreb amides underwent smooth reaction to afford the corresponding products **6ba-6da** in good yield. Readily functionalizable aryl halides containing BIAMs **6ea-6ga** were synthesized in 86%, 90% and 70% yield, respectively. It is important to note that reactive and electron withdrawing cyano and nitro substituents were also well tolerated under the optimized conditions and led to the formation **6ha** and **6ia** in good yield. Pyridine and thiophene, heteroarene derived Weinreb amides were also successfully converted to corresponding product (**6ja** and **6ka**) in good to moderate yield. On the other hand, Weinreb amides derived from aliphatic carboxylic acids did not afford the expected products, which is possibly due to the low reactivity of aliphatic amide and possible

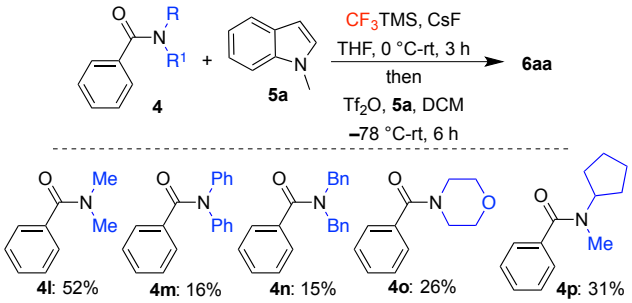
isomerization of iminium ion to enamine (see supporting information).

Scheme 2. One-pot trifluoromethylative functionalization: Scope and limitation of amide **4**



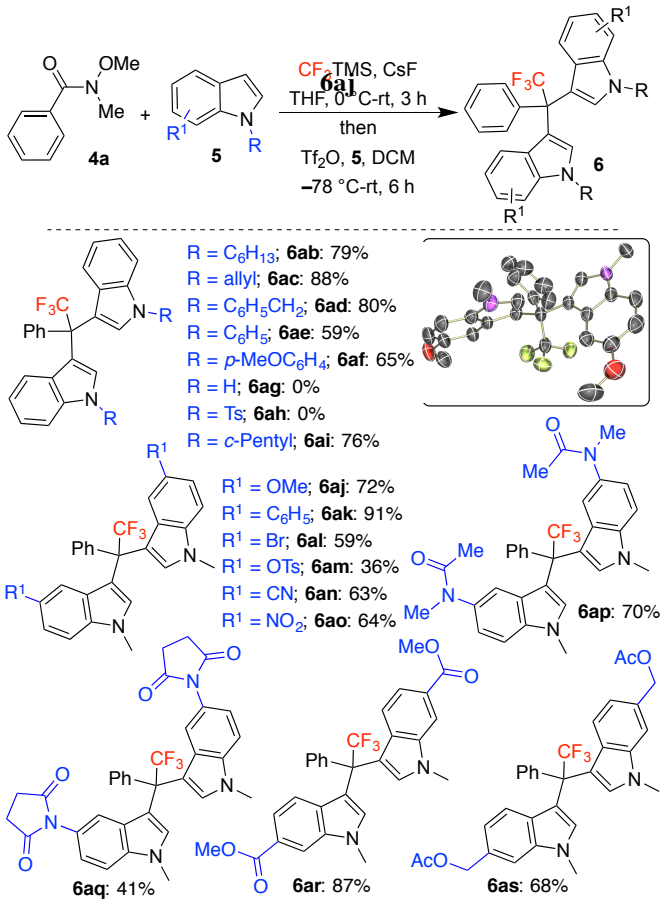
Following the successful screening of various substituted Weinreb amides, related dialkyl substituted amides was also examined to explore the generality of the amide. Trifluoromethylative functionalization of *N*,*N*-dimethylbenzamide **4l** with **5a** under the optimized conditions afforded the product **6aa** in 52% yield (Scheme 3). Bulky diphenyl and dibenzyl substitution on the nitrogen (**4m** and **4n**) decreased the reactivity and led to **6aa** in low yield. On the other hand, amide derived from morpholine (**4o**) and cyclopentylmethyl amine (**4p**) underwent smooth reaction to **6aa** in 26% and 31% yield. These results revealed the supremacy of Weinreb amide over other amides, which is possibly due to the relatively higher stability of hemiaminal derived from Weinreb amide compared to other amides.[9a,9b]

Scheme 3. One-pot trifluoromethylative functionalization of amides **4**



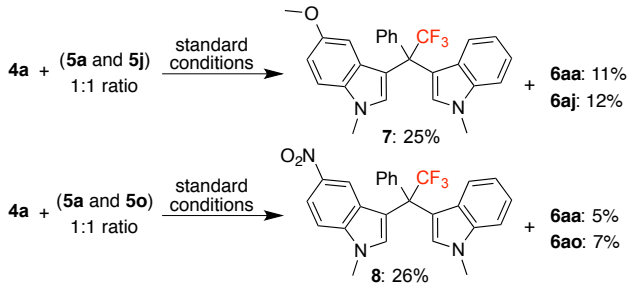
Having explored the scope and generality of amides, diverse substituted indole derivatives were screened under the optimized conditions. (Cyclo)Alkyl, allyl and benzyl substitutions on the nitrogen of indole were well tolerated to furnish the corresponding products **6ab-6ad** and **6ai** in excellent yield (Scheme 4). *N*-Aryl substituted indoles gave **6ae** and **6af** in comparable yield. On the other hand, unsubstituted indole and electron withdrawing tosyl at nitrogen did not afford the expected products (**6ag** and **6ah**). Indoles having electron rich methoxy and halo substituents at 5th position underwent smooth reaction to give trifluoromethylated BIAMs **6aj-6al** in good yield. The structure of **6aj** was unambiguously confirmed by single crystal X-ray analysis.[15] Electron withdrawing *p*-toluenesulfonyloxy, cyano and nitro at 5th position and methylester at 6th position were highly compatible with optimized conditions to give expected products (**6am-6ao** and **6ar**) in moderate to good yield. Most importantly, reactive functional groups such as amide, imide and acetate containing BIMs **6ap**, **6aq** and **6as** were also achieved in good yield. But, expected product was not observed with *N*-methyl-7-azaindole, *N*,2-dimethylindole and *N*,3-dimethylindole.

Scheme 4. One-pot trifluoromethylative functionalization: Scope and limitation of indole **5**



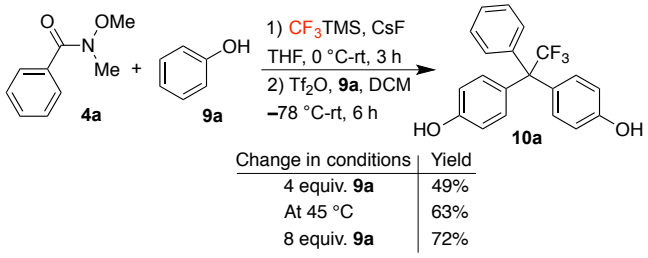
Next, synthesis of unsymmetrical bis(indolyl)arylmethane was investigated with mixture of indole derivatives **5**. Reaction of Weinreb amide **4a** with equimolar mixture of neutral and electron rich indoles **5a** and **5j** under the standard conditions afforded the mixture of trifluoromethylated BIAMs **7**, **6aa** and **6aj** in 48% yield and 2:1:1 ratio, where the formation of unsymmetrical BIAM **7** was found to be major (Scheme 5). Similarly, equimolar mixture of neutral and electron deficient indoles **5a** and **5o** were also resulted in the mixture of **8**, **6aa** and **6ao** in 38% yield and 5:1:1 ratio under the optimized conditions. Unfortunately, various attempts to further improve the yield of unsymmetrical BIAM, such as sequential addition and changing the ratio of indoles, were not successful.

Scheme 5. Synthesis of unsymmetrical trifluoromethylated bis(indolyl)arylmethanes



After successful demonstration of one-pot synthesis of trifluoromethylated BIAMs, we envisioned the use of various aryl nucleophiles to widen the scope of the present methodology. Among the various aryl nucleophiles that were studied, 4 equivalents of phenol under the optimized conditions afforded the expected trifluoromethylated TAM **10a** in 49% yield. Interestingly, the yield of the trifluoromethylated TAM **10a** could be increased by increasing either temperature or equivalents of phenol (Scheme 6). For studying the scope of the transformation, 8 equivalents of phenol derivatives were used under the optimized conditions.

Scheme 6. One-pot trifluoromethylative functionalization of **4a** with phenol **9a**:

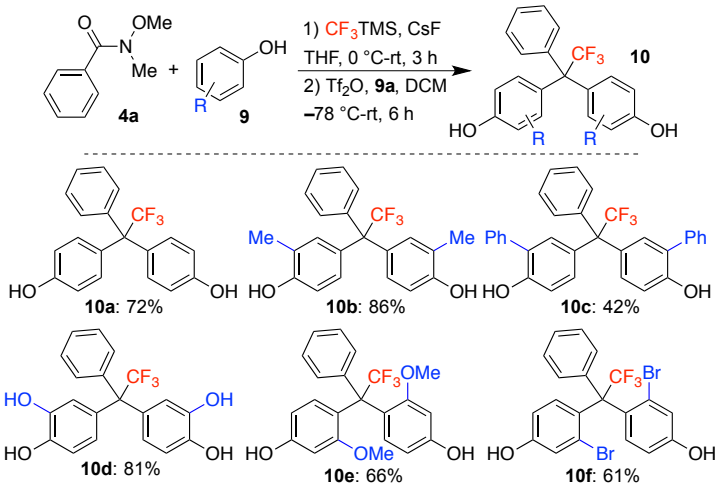


Change in conditions	Yield
4 equiv. **9a**	49%
At 45 °C	63%
8 equiv. **9a**	72%

As can be seen in Scheme 7, diverse substituted electron rich phenol derivatives were examined to demonstrate the scope and generality of the synthesis of trifluoromethylated TAMs **10**. Ortho-substituted phenols, such as *o*-cresol and 2-phenylphenol, on reaction with Weinreb amide 4a under the optimized conditions furnished the expected trifluoromethylated TAMs **10b** and **10c** in 86% and 42% yield, respectively. Similarly, catechol also gave the corresponding trifluoromethylated TAMs **10d** in 81% yield. Sterically hindered m-methoxy- and m-bromophenols also underwent smooth reaction to

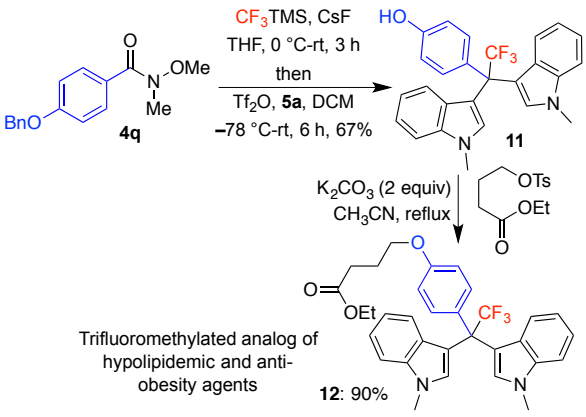
afford **10e** and **10f** in 66% and 61% yield, respectively. It is important to note that all the phenols tested afforded the product as single regioisomer, other isomers are not detected in ^{1}H NMR.

Scheme 7. One-pot synthesis of trifluoromethylated TAMs **10**.



Having demonstrated the general and efficient method for the synthesis of trifluoromethylated BIAMs **6** and TAMs **10**, potential application of the developed method was envisioned *via* the synthesis of trifluoromethylated analog of hypolipidemic and anti-obesity agent[16] **12** (Scheme 8). The synthesis of **12** started with **4q**, which on trifluoromethylative functionalization under the optimized conditions furnished the trifluoromethylated BIAM **11**, where the deprotection of benzyl group was also observed under the reaction conditions. Subsequently, alkylation of phenolic hydroxyl in **11** with ethyl 4-(tosyloxy)butanoate in the presence of K_2CO_3 furnished the expected trifluoromethyalted analog of hypolipidemic and anti-obesity agent **12**.

Scheme 8. Synthesis of trifluoromethyl analog of anti-obesity agent **10**



Conclusion

In conclusion, we have successfully demonstrated the one-pot trifluoromethylative functionalization of amides utilizing the trifluoromethyltrimethylsilane as nucleophilic 'CF_3'source. The reaction involves the *in-situ* generation of trifluoromethylated iminium ion from trifluoromethylated hemiaminal of amide and trapping with substituted indoles. Importantly, the present reaction tolerates diverse reactive and vital functional groups and allowed the synthesis of potential trifluoromethylated BIAM derivatives in good to excellent yield. Additionally, the developed methodology has been successfully extended to the synthesis of diverse trifluoromethylated triarylmethanes employing phenols as nucleophiles. Furthermore, the potential of the developed methodology was shown *via* the synthesis of trifluoromethylated analog of hypolipidemic and anti-obesity agent in two steps.

Experimental Section:

General Comments: All reactions were carried out under an atmosphere of dry nitrogen using reaction tubes and round bottom flask. Dry toluene was prepared by distilling over sodium ketyl and stored over molecular sieves 4Å under N_2 atmosphere. Dry THF was prepared by sodium ketyl, benzophenone and freshly distilled and used. Dry DCM were prepared by distilling over calcium hydride and stored over molecular sieves 4Å under N_2 atmosphere. Trifluoromethyltrimethylsilane, TBAF, triflic anhydride,

substituted benzoyl chloride, Indole and other benzoic acid were obtained from commercially available sources and they were used as received. All substituted Weinreb amides[8] and substituted indoles[17] derivatives were synthesized employing known organic synthesis procedure. Column chromatography was performed using Rankem Silicagel (100-200 mesh) and ethyl acetate/hexanes were used as solvent system, unless otherwise specified, with various percentage of polarity depending on the nature of the substrate.

Analytical Methods: NMR data were recorded on 400 and 500 MHz spectrometers. ^{13}C and ^{1}H NMR spectra were referenced to signals of deutero solvents and residual protiated solvents, respectively. ^{19}F NMR spectra were recorded on 500 MHz spectrometers using hexafluorobenzene as standard. HRMS were recorded by electron spry ionization (ESI) method on a Q-TOF Micro with lock spray source. Melting points are corrected. The crystal data were collected and integrated using a diffractometer, with graphite monochromated Mo-Kα radiation.

General procedure for the synthesis of trifluoromethylated bis(indolyl)arylmethane 6: Weinreb amide **4** (50 mg, ~0.3 mmol, 1 equiv.) and CsF (46.0 mg, 0.30 mmol, 1 equiv.) were taken in an oven dried 10 mL reaction tube, fitted with septum. Next, 2 mL dry THF (Solvent 1) was added under argon atmosphere and reaction mixture was cooled to 0 °C, at the same temperature CF_3TMS (85 mg, 0.6 mmol, 2 equiv.) was added. The reaction mixture was allowed to stir at room temperature for 3-4 hour. THF was evaporated under reduced pressure and 2 mL dry DCM (Solvent 2) was added, again the reaction mixture was cooled to –78 °C. Triflic anhydride (93 mg, 0.33 mmol, 1.1 equiv) was added at –78 °C, stirred for 20 min and then the reaction mixture was allowed to warm upto 0 °C. Indoles **5** (0.75 mmol, 2.5 equiv.) was added at 0 °C and reaction mixture allowed to stir at room temperature for 5-6 hour. After completion of reaction, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), extracted with DCM (2 x 10 mL) and the combined organic layer was dried over Na_2SO_4. Solvent was evaporated under reduced pressure and the crude product was purified by column

chromatography using hexane/ethylacetate as eluent.

6aa:[6a] 109 mg, 87% yield; brown solid; R_f = 0.46 in 85:15 hexane/ethyl acetate; Mp: 202-204 ºC; IR (KBr): 2812, 2725, 1593, 1157, 749, 714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.59-7.53 (m, 2H), 7.34-7.28 (m, 5H), 7.22-7.16 (m, 4H), 6.96-6.91 (m, 2H), 6.75 (s, 2H), 3.72 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 139.7, 137.5, 131.0, 129.7, 128.3 (q, J = 286.5 Hz), 128.0, 127.5, 126.9, 122.5, (q, J = 3.0 Hz), 121.6, 119.3, 113.9, 109.3, 56.0 (q, J = 26.5 Hz), 32.9; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.52 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{26}H_{21}N_2F_3Na$: 441.1555; found: 441.1549.

6ba: 86 mg, 72% yield; white solid; R_f = 0.62 in 85:15 hexane/ethyl acetate; Mp: 228-230 ºC; IR (KBr): 2919, 2818, 2360, 1594, 812, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.43 (d, 2H, J = 8.1 Hz), 7.32 (d, 2H, J = 8.1 Hz), 7.22-7.17 (m, 4H), 7.11 (d, 2H, J = 8.1 Hz), 6.94 (t, 2H, J = 7.6 Hz), 6.77 (s, 2H), 3.72 (s, 6H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 137.5, 137.1, 136.7, 130.9, 129.5, 128.7, 128.3 (q, J = 286.2 Hz), 127.0, 122.6, (q, J = 3.0 Hz), 121.5, 119.2, 114.1, 109.2, 55.6, (q, J = 26.4 Hz), 32.9, 21.1; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.71 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{27}H_{23}N_2F_3Na$: 455.1703; found: 455.1706.

6ca: 80 mg, 71% yield; yellow solid; R_f = 0.46 in 85:15 hexane/ethyl acetate; Mp: 238-240 ºC; IR (KBr): 2813, 2724, 1595, 1350, 1150, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.45 (d, 2H, J = 8.7 Hz), 7.32-7.28 (m, 2H), 7.21-7.15 (m, 4H), 6.93 (td, 2H, J = 8.0, 1.0 Hz), 6.74 (s, 2H), 6.81 (dd, 2H, J = 6.9, 2.2 Hz), 3.80 (s, 3H), 3.72 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 158.7, 137.5, 131.8, 130.9, 129.1, 128.3 (q, J = 285.3 Hz), 127.0, 122.6, (q, J = 3.1 Hz), 121.5, 119.3, 114.2, 113.2, 109.3, 55.3, (q, J = 26.7 Hz), 55.2, 33.0; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.50 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{27}H_{23}ON_2F_3Na$: 471.1653; found: 471.1655.

6da: 74 mg, 67% yield; white solid; R_f = 0.26 in 80:20 hexane/ethyl acetate; Mp: 270-272 ºC; IR (KBr): 2925, 2811, 1594, 1351, 1152, 812, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.36 (d, 2H, J =

8.8 Hz), 7.29 (d, 2H, *J* = 8.8 Hz), 7.24-7.13 (m, 4H), 6.92 (td, 2H, *J* = 8.0, 1.0 Hz), 6.77 (s, 2H), 6.63 (dd, 2H, *J* = 7.1, 2.0 Hz), 3.72 (s, 6H), 2.94 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 149.5, 137.5, 130.9, 130.4, 128.5 (q, *J* = 286.7 Hz), 127.3, 127.1, 122.8 (q, *J* = 3.1 Hz), 121.4, 119.1, 114.6, 111.7, 109.2, 55.1 (q, *J* = 26.5 Hz), 40.5, 32.9; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –63.07 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{28}H_{27}N_3F_3$: 462.2152; found: 462.2155.

6ea: 98 mg, 86% yield; brown solid; 90:10 hexane/ethyl acetate; Mp: 250-252 ºC; IR (KBr): 2812, 1595, 1350, 1151, 1016, 930, 815, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.48 (d, 2H, *J* = 8.5 Hz), 7.29 (d, 2H, *J* = 8.5 Hz), 7.42 (d, 2H, *J* = 8.5 Hz), 7.20-7.12 (m, 4H), 6.96-6.90 (m, 2H), 6.72 (s, 2H), 3.70 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 138.3, 137.6, 133.5, 131.2, 131.0, 128.2, 128.1 (q, *J* = 286.1 Hz), 126.7, 122.4 (q, *J* = 2.7 Hz), 121.7, 119.5, 113.4, 109.4, 55.6 (q, *J* = 27.2 Hz), 33.0; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.83 (s, 3F, CF_3)**;** HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{26}H_{20}ClN_2F_3Na$: 475.1159; found: 475.1161.

6fa: 89 mg, 90% yield; dark brown solid; R_f = 0.55 in 90:10 hexane/ethyl acetate; Mp: 248-250 ºC; IR (KBr): 2814, 1592, 1350, 1227, 1150, 1074, 813, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.46-7.40 (m, 4H), 7.32 (d, 2H, *J* = 8.2 Hz), 7.23-7.15 (m, 4H), 6.96 (td, 2H, *J* = 8.1, 1.0 Hz) 6.74 (s, 2H) 3.72 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 138.8, 137.6, 131.5, 131.1, 131.0, 128.0, (q, *J* = 286.0 Hz), 126.7, 122.4 (q, *J* = 3.0 Hz), 121.8, 121.7, 119.5, 113.3, 109.4, 55.7 (q, *J* = 27.0 Hz), 33.0; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.79 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{26}H_{20}BrN_2F_3Na$: 519.0654; found: 519.0651.

6ga: 65 mg, 70% yield; white solid; R_f = 0.62 in 80:20 hexane/ethyl acetate; Mp: 260-262 ºC; IR (KBr): 2811, 2725, 1594, 1350, 1151, 810, 768, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.65 (dd, 2H, *J* = 6.8, 1.9 Hz), 7.33-7.27 (m, 4H), 7.22-7.14 (m, 4H), 6.95 (td, 2H, *J* = 8.0, 0.9 Hz), 6.73 (s, 2H) 3.72 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 139.6, 137.6, 137.1, 131.8, 131.0, 128.0, (q, *J* = 286.6 Hz), 126.7, 122.4 (q, *J* = 3.0 Hz), 121.7, 119.5, 113.3, 109.4, 93.7, 55.8 (q, *J* = 27.1 Hz), 33.0; ^{19}F

NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.76 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{26}H_{20}IN_2F_3Na$: 567.0525; found: 567.0516.

6ha: 84 mg, 73% yield; brown solid; R_f = 0.40 in 70:30 hexane/ethyl acetate; Mp: 220-222 ºC; IR (KBr): 2928, 2815, 2237, 1597, 1350, 1154, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.71 (d, 2H, J = 8.2 Hz), 7.58 (d, 2H, J = 8.5 Hz), 7.34 (d, 2H, J = 8.2 Hz), 7.29-7.23 (m, 2H), 7.11 (d, 2H, J = 8.0 Hz), 6.98-6.93 (m, 2H), 6.74 (s, 2H), 3.74 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 145.0, 137.5, 132.9, 131.8, 131.0, 130.6, 127.8 (q, J = 287.1 Hz), 126.5, 122.1, (q, J = 2.6 Hz), 121.9, 119.7, 112.6, 111.5, 109.6, 56.2 (q, J = 27.1 Hz), 33.0; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.70 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{27}H_{20}N_3F_3Na$: 466.1505; found: 466.1502.

6ia: 90 mg, 85% yield; yellow solid; R_f = 0.44 in 70:30 hexane/ethyl acetate; Mp: 140-142 ºC; IR (KBr): 2928, 2818, 1596, 1351, 1163, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.14 (dd, 2H, J = 7.2, 1.2 Hz), 7.97 (d, 2H, J = 8.8 Hz), 7.35 (d, 2H, J = 8.2 Hz), 7.23 (td, 2H, J = 7.9, 0.6 Hz), 7.13 (d, 2H, J = 8.2 Hz), 6.97 (td, 2H, J = 7.9, 0.6 Hz), 6.76 (s, 2H), 3.75 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 147.2, 147.0, 137.6, 131.0, 130.8, 127.6 (q, J = 286.0 Hz), 126.5, 123.1, 122.1, (q, J = 2.8 Hz), 122.0, 119.7, 112.5, 109.6, 56.2 (q, J = 27.1 Hz), 33.0; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.71 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{26}H_{20}O_2N_3F_3Na$: 486.1408; found: 486.1400.

6ja: 97 mg, 77% yield; brown solid; R_f = 0.42 in 70:30 hexane/ethyl acetate; Mp: 212-214 ºC; IR (KBr): 2933, 2814, 2360, 1593, 1350, 1153, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.58 (d, 1H, J = 5.2 Hz), 7.39 (d, 1H, J = 1.7 Hz), 7.29 (d, 2H, J = 8.2 Hz), 7.23 (ddd, 1H, J = 5.2, 3.4, 1.9 Hz), 7.16 (td, 2H, J = 7.9, 0.9 Hz), 7.06 (d, 2H, J = 8.1 Hz) 6.92-6.86 (m, 5H), 3.72 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 161.1, 149.4, 144.4, 137.4, 130.8, 127.5 (q, J = 287.1 Hz), 126.8, 125.1, 122.9, 122.1, 121.7, 119.4, 112.1, 109.4, 57.8 (q, J = 26.4 Hz), 33.0; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$,

24 °C): δ –63.25 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + K]^+$ calcd. for $C_{25}H_{20}N_3F_3K$: 458.1246; found: 458.1241.

6ka: 43 mg, 35% yield; black solid; R_f = 0.33 in 80:20 hexane/ethyl acetate; Mp: 236-238 ºC; IR (KBr): 2932, 2814, 1594, 1350, 1237, 1154, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.31-7.21 (m, 4H), 7.17-7.06 (m, 4H), 6.99-6.92 (m, 3H), 6.86 (t, 2H, J = 7.6 Hz), 3.74 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 144.3, 137.4, 130.2, 128.1, 127.6 (q, J = 285.8 Hz), 126.9, 126.2, 125.6, 122.3, (q, J = 2.4 Hz), 121.6, 119.3, 113.5, 109.3, 53.1 (q, J = 28.1 Hz), 33.0; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –66.57 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{24}H_{19}SN_2F_3Na$: 447.1113; found: 447.1110.

6ab: 133 mg, 79% yield; yellow liquid; R_f = 0.40 in 90:10 hexane/ethyl acetate; IR (Neat): 2955, 2929, 1465, 1236, 1151, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.53 (dd, 2H, J = 7.9, 2.1 Hz), 7.34-7.27 (m, 5H), 7.17-7.12 (m, 4H), 6.88 (td, 2H, J = 8.0, 0.9 Hz), 6.78 (s, 2H), 4.03 (t, 4H, J = 7.1 Hz), 1.76 (t, 4H, J = 7.1 Hz), 1.25 (brs, 12H), 0.85 (t, 6H, J = 6.7 Hz); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 139.8, 137.7, 130.2, 129.7, 128.3 (q, J = 286.6 Hz), 128.0, 127.4, 127.1, 122.6 (q, J = 3.0 Hz), 121.3, 119.1, 113.7, 109.8, 56.0 (q, J = 26.8 Hz), 46.4, 31.4, 30.1, 26.6, 22.6, 14.1; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.57 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{36}H_{41}N_2F_3Na$: 581.3120; found: 581.3097.

6ac: 124 mg, 88% yield; yellow solid; R_f = 0.33 in 90:10 hexane/ethyl acetate; Mp: 114-116 ºC IR (KBr): 2928, 2809, 1595, 1349, 1147, 930, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.60-7.53 (m, 2H), 7.36-7.27 (m, 5H), 7.21-7.12 (m, 4H), 6.94-6.88 (m, 2H), 6.85 (s, 2H), 6.01-5.91 (m, 2H), 5.18 (d, 2H, J = 10.4 Hz), 5.02 (d, 2H, J = 17.1 Hz), 4.68 (dd, 4H, J = 3.5, 1.2 Hz); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 139.5, 136.9, 133.4, 130.1, 129.7, 128.2 (q, J = 286.3 Hz), 128.0, 127.5, 127.2, 122.6, 121.6, 119.4, 117.1, 114.2, 109.7, 56.0 (q, J = 26.3 Hz), 48.8; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.67 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{30}H_{25}N_2F_3Na$: 493.1862; found:

493.1866.

6ad: 138 mg, 80% yield; yellow solid; %; R_f = 0.30 in 90:10 hexane/ethyl acetate; Mp: 106-108 ºC; IR (KBr): 2811, 2724, 1593, 1350, 1151, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.60-7.53 (m, 2H), 7.31-7.27 (m, 4H), 7.25-7.18 (m, 6H), 7.15 (d, 2H, J = 8.3 Hz), 7.03 (t, 3H, J = 7.7 Hz), 7.02 (d, 4H, J = 6.8 Hz), 6.93(s, 2H), 6.86 (t, 2H, J = 7.7 Hz), 5.25 (s, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 139.3, 137.4, 137.1, 130.6, 129.7, 128.8, 128.2 (q, J = 286.4 Hz), 128.1, 127.6, 127.3, 126.5, 126.0, 122.6 (q, J = 3.0 Hz), 121.8, 119.5, 114.3, 109.9, 55.9 (q, J = 26.9 Hz), 50.1; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.82 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{38}H_{29}N_2F_3Na$: 593.2175; found: 593.2177.

6ae: 97 mg, 59% yield as yellow viscous liquid; R_f = 0.44 in 85:15 hexane/ethyl acetate; IR (neat): 3060, 2925, 1500, 1458, 1150, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.72-7.64 (m, 2H), 7.56 (d, 2H, J = 8.3 Hz), 7.52-7.44 (m, 8H), 7.39-7.31 (m, 7H), 7.19 (td, 2H, J = 8.0, 0.8 Hz), 7.14 (s, 2H), 7.02 (td, 2H, J = 8.0, 0.8 Hz); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 139.4, 139.0, 136.9, 130.2, 129.7, 128.7, 128.3 (q, J = 285.9 Hz), 128.2, 127.8, 127.7, 126.8, 124.8, 122.8, (q, J = 3.0 Hz), 122.5, 120.4, 116.1, 110.6, 56.2 (q, J = 26.9 Hz); ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.84 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{36}H_{25}N_2F_3Na$: 565.1862; found: 565.1858.

6af: 117 mg, 65% yield; white solid; R_f = 0.42 in 85:15 hexane/ethyl acetate; Mp: 180-182 ºC; IR (KBr): 2932, 2836, 1597, 1248, 1149, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.64 (dd, 2H, J = 5.9, 3.0 Hz), 7.42 (d, 2H, J = 8.3 Hz), 7.37-7.27 (m, 9H), 7.15 (td, 2H, J = 7.9, 1.0 Hz), 7.03 (s, 2H), 7.01-6.94 (m, 6H), 3.85 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 158.5, 139.2, 137.3, 132.3, 130.6, 129.7, 128.2 (q, J = 286.3 Hz), 128.1, 127.7, 127.3, 126.4, 122.7, 122.2, 120.1, 115.6, 114.7, 110.5, 56.1 (q, J = 26.6 Hz), 55.6; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.25 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + K]^+$ calcd. for $C_{38}H_{29}O_2N_2F_3K$: 641.1813; found: 641.1824.

6ai: 121 mg, 76% yield; yellow liquid; R_f = 0.40 in 90:10 hexane/ethyl acetate; IR (neat): 2959, 2873, 1536, 1462, 1150, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.56 (dd, 2H, J = 5.5, 2.4 Hz), 7.41 (d, 2H, J = 8.1 Hz), 7.33-7.28 (m, 3H), 7.18-7.12 (m, 4H), 6.93-6.90 (m, 2H), 6.89 (s, 2H), 4.78 (qt, 2H, J = 6.9 Hz), 2.20-2.11 (m, 4H), 1.90-1.78 (m, 4H), 1.77-1.66 (m, 8H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 139.8, 136.9, 129.6, 128.3 (q, J = 286.3 Hz), 127.9, 127.4, 127.2, 127.1, 122.5 (q, J = 3.0 Hz), 121.2, 119.1, 113.7, 109.9, 57.0, 56.0 (q, J = 26.4 Hz), 32.5, 23.9; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.50 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{34}H_{33}N_2F_3Na$: 549.2488; found: 549.2490.

6aj: 105 mg, 72% yield; brown solid; R_f = 0.23 in 80:20 hexane/ethyl acetate; Mp: 218-220 ºC; IR (KBr): 2952, 2833, 1594, 1492, 1223, 1150, 792 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.61-7.55 (m, 2H), 7.33-7.28 (m, 3H), 7.20 (s, 1H), 7.18 (s, 1H), 6.84 (dd, 2H, J = 8.9, 2.4 Hz), 6.78 (s, 2H), 6.48 (d, 2H, J = 2.2 Hz), 3.70 (s, 6H), 3.51 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 153.6, 139.5, 132.8, 131.2, 129.9, 128.4 (q, J = 286.2 Hz), 128.0, 127.6, 127.4, 113.2, 112.0, 109.9, 104.2, (q, J = 2.6 Hz), 55.8 (q, J = 26.4 Hz), 55.6, 33.1; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.87 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{28}H_{25}O_2N_2F_3Na$: 501.1760; found: 501.1760.

6ak: 157 mg, 91% yield; yellow solid; R_f = 0.40 in 85:15 hexane/ethyl acetate; Mp: 256-258 ºC; IR (KBr): 2810, 2723, 1595, 1349, 1146, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.64 (dd, 2H, J = 6.0, 1.9 Hz), 7.46 (dd, 2H, J = 8.5, 1.6 Hz), 7.38 (s, 1H), 7.37-7.30 (m, 14H), 7.25-7.21 (m, 2H), 6.85 (s, 2H), 3.75 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 142.6, 139.7, 137.1, 132.7, 131.4, 129.9, 128.6, 128.3 (q, J = 286.0 Hz), 128.1, 127.7, 127.5, 127.4, 126.2, 121.4, 121.1, (q, J = 3.0 Hz), 114.3, 109.5, 56.0 (q, J = 27.3 Hz), 33.1; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.84 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{38}H_{29}N_2F_3Na$: 593.2175; found: 593.2175.

6al: 103 mg, 59% yield; black solid; R_f = 0.55 in 80:20 hexane/ethyl acetate; Mp: 268-270 ºC; IR (KBr): 2923, 2725, 1597, 1475, 1351, 1145, 796, 722, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ

7.45 (d, 2H, *J* = 7.3 Hz), 7.36-7.28 (m, 3H), 7.25 (dd, 2H, *J* = 8.6, 1.7 Hz), 7.21 (s, 2H), 7.16 (d, 2H, *J* = 8.6 Hz), 6.70 (s, 2H), 3.70 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 138.8, 136.3, 132.0, 129.5, 128.4, 128.3, 128.0, 127.9 (q, *J* = 286.4 Hz), 124.8, 124.6 (q, *J* = 3.2 Hz), 113.3, 113.1, 110.9, 55.7 (q, *J* = 27.1 Hz), 33.2; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.61 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{26}H_{19}Br_2N_2F_3Na$: 596.9759; found: 596.9757.

6am: 83 mg, 36% yield; yellow solid; R_f = 0.24 in 80:20 hexane/ethyl acetate; Mp: 212-214 ºC; IR (KBr): 2925, 2814, 1596, 1484, 1358, 1153, 938, 773, 552 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.36 (d, 4H, *J* = 8.2 Hz), 7.32-7.21 (m, 5H), 7.15 (d, 2H, *J* = 8.8 Hz), 7.09 (d, 4H, *J* = 8.2 Hz), 6.79 (dd, 2H, *J* = 8.9, 2.2 Hz), 6.77 (s, 2H), 6.53 (d, 2H, *J* = 1.9 Hz), 3.72 (s, 6H), 2.32 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 144.9, 143.2, 138.5, 135.9, 132.3, 132.2, 129.5, 129.3, 128.4, 128.2, 127.9, 127.7 (q, *J* = 285.4 Hz), 126.7, 116.5, 115.2, 113.6, 110.0, 55.3 (q, *J* = 26.8 Hz), 33.3, 21.6; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –63.56 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{40}H_{33}O_6S_2N_2F_3Na$: 781.1624; found: 781.1625.

6an: 88 mg, 63% yield; brown solid; R_f = 0.22 in 80:20 hexane/ethyl acetate; Mp: 248-250 ºC IR (KBr): 2925, 2812, 2219, 1488, 1349, 1148, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.41-7.36 (m, 7H), 7.36-7.31 (m, 4H), 6.93 (s, 2H), 3.81 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 139.0, 138.1, 132.8, 129.1, 128.5, 128.4, 127.7 (q, *J* = 286.7 Hz), 127.6 (q, *J* = 2.6 Hz), 126.4, 124.8, 120.7, 114.3, 110.7, 102.9, 55.4 (q, *J* = 27.0 Hz), 33.4; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –63.17 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{28}H_{19}N_4F_3Na$: 491.1454; found: 491.1460.

6ao: 100 mg, 64% yield; brown solid; R_f = 0.15 in 70:30 hexane/ethyl acetate; Mp: 220-222 ºC; IR (KBr): 2925, 2812, 1594, 1332, 1146, 1049, 737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.05 (dd, 2H, *J* = 9.1, 2.1 Hz), 7.89 (d, 2H, *J* = 2.1 Hz), 7.45 (d, 2H, *J* = 7.2 Hz), 7.39-7.31 (m, 5H), 7.03 (s, 2H), 3.85 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 141.8, 140.3, 138.0, 133.6, 129.2, 128.7, 128.6, 127.6 (q, *J* = 285.8 Hz), 126.0, 119.0 (q, *J* = 2.8 Hz), 117.7, 115.8, 109.8, 55.5 (q, *J* = 27.1 Hz),

33.6; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –63.44 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{26}H_{19}O_4N_4F_3Na$: 531.1251; found: 531.1245.

6ap: 118 mg, 70% yield; R_f = 0.17 in ethyl acetate; brown solid; Mp: 222-224 ºC; IR (KBr): 2929, 2811, 1597, 1491, 1349, 1147, 722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.51 (dd, 2H, *J* = 8.4, 1.9 Hz), 7.35-7.25 (m, 5H), 6.99 (s, 2H), 6.91 (dd, 2H, *J* = 8.4, 1.9 Hz), 6.61, (s, 2H), 3.80 (s, 6H), 3.02 (s, 6H), 1.42 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, 24 °C): δ 171.1, 139.0, 136.7, 136.2, 131.7, 129.2, 128.3, 128.1, 128.0 (q, *J* = 286.3 Hz), 127.6, 120.6, 120.5, 113.6, 110.4, 55.3 (q, *J* = 26.4 Hz), 37.5, 33.3, 22.1; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –63.83 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{33}H_{31}O_2N_4F_3Na$: 583.2291; found: 583.2291.

6aq: 76 mg, 41% yield; white solid; R_f = 0.22 in 80:20 hexane/ethyl acetate; Mp: 198-200 ºC; IR (KBr): 2927, 2812, 1777, 1493, 1357, 1146, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.50 (dd, 2H, *J* = 6.2, 2.2 Hz), 7.38 (d, 2H, *J* = 8.6 Hz), 7.34-7.29 (m, 3H), 7.09 (s, 2H), 7.03 (dd, 2H, *J* = 8.6, 1.7 Hz), 6.79 (s, 2H), 3.73 (s, 6H), 2.80 (s, 8H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, 24 °C): δ 176.9, 138.8, 137.3, 132.8, 129.4, 128.3, 128.0, (q, *J* = 286.3 Hz), 127.7, 126.6, 123.6, 121.6, 120.1, 114.1, 110.1, 55.8 (q, *J* = 26.7 Hz), 33.1, 28.4; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.34 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{34}H_{27}O_4N_4F_3Na$: 635.1877; found: 635.1877.

6ar: 139 mg, 87% yield; white solid; R_f = 0.33 in 80:20 hexane/ethyl acetate; Mp: 180-182 ºC; IR (KBr): 2946, 2808, 1720, 1595, 1240, 1145, 768, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.08 (d, 2H, *J* = 1.0 Hz), 7.57 (dd, 2H, *J* = 8.6, 1.4 Hz), 7.49 (d, 2H, *J* = 6.8 Hz), 7.34-7.26 (m, 3H), 7.09 (d, 2H, *J* = 8.6 Hz), 6.91 (s, 2H), 3.91 (s, 6H), 3.80 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, 24 °C): δ 168.0, 139.0, 137.0, 133.8, 130.4, 129.4, 128.2, 127.9, 127.7 (q, *J* = 286.3 Hz), 123.5, 121.9 (q, *J* = 2.9 Hz), 120.4, 114.1, 111.9, 55.7 (q, *J* = 26.6 Hz), 52.2, 33.2; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.95 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{30}H_{25}O_4N_2F_3Na$: 557.1659; found: 557.1656.

6as: 115 mg, 68% yield; white solid; R_f = 0.40 in 80:20 hexane/ethyl acetate; Mp: 80-82 ºC; IR (KBr): 2811, 2723, 1738, 1591, 1350, 1147, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.51 (dd, 2H, J = 7.7, 1.0 Hz), 7.35-7.27 (m, 5H), 7.13 (d, 2H, J = 8.3 Hz), 6.93 (dd, 2H, J = 8.4, 1.4 Hz), 6.76 (s, 2H), 5.20 (s, 4H), 3.73 (s, 6H), 2.10 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 171.2, 139.4, 137.4, 131.7, 129.6, 129.2, 128.1 (q, J = 286.5 Hz), 128.0, 127.6, 126.9, 122.6 (q, J = 3.0 Hz), 120.2, 113.9, 109.8, 67.3, 55.8 (q, J = 26.6 Hz), 33.0, 21.3; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.75 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{32}H_{29}O_4N_2F_3Na$: 585.1972; found: 585.1976.

General procedure for the synthesis of unsymmetrical trifluoromethylated bisindolylmethanes 7 and 8: Unsymmetrical trifluoromethylated bisindolylmethane **7** and **8** was synthesized employing standard procedure. Weinreb amide **4a** (100 mg, 0.60 mmol) and CsF (91.0 mg, 0.60 mmol) were taken in an oven dried 10 mL reaction tube, fitted with septum. Next, 4 mL dry THF (Solvent 1) was added under argon atmosphere and reaction mixture was cooled to 0 °C, at the same temperature CF_3TMS (170 mg, 1.20 mmol) was added. The reaction mixture was allowed to stir at room temperature for 3-4 hour. THF was evaporated under reduced pressure and 4 mL dry DCM (Solvent 2) was added, again reaction mixture was cooled to –78 °C. Triflic anhydride (Tf_2O, 186.12 mg, 0.66 mmol) was added at –78 °C, stirred for 20 min and then the reaction mixture was allowed to warm upto 0 °C. Next, equimolar mixture of indoles **5a** and **5j** (or **5a** and **5o**) (1.50 mmol) were added at 0 °C and reaction mixture allowed to stirred at room temperature for 5-6 hour. After completion of reaction, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), extracted with DCM (2 x 10 mL) and the combined organic layer was dried over Na_2SO4. Solvent was evaporated under reduced pressure and the crude product was purified by column chromatography using hexane/ethyl acetate as eluent.

7: 67 mg, 25% yield; light blue solid; R_f = 0.22 in 90:10 hexane/ethyl acetate; Mp: 172-174 ºC; IR (KBr): 2926, 2853, 1592, 1491, 1384, 1344, 1224, 806, 1147, 747, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.94-7.87 (m, 2H), 7.69-7.61 (m, 4H), 7.57-7.49 (m, 3H), 7.32-7.25 (m, 1H), 7.17 (dd,

1H, *J* = 8.8, 2.2 Hz), 7.13-7.05 (m, 2H), 6.81 (s, 1H), 4.06 (s, 3H), 4.04 (s, 3H), 3.85 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 153.6, 139.6, 137.6, 132.8, 131.2, 131.1, 129.8, 128.3 (q, *J* = 288.0 Hz), 128.0, 127.5, 127.3, 127.0, 122.7 (q, *J* = 3.3 Hz), 121.6, 119.3, 113.8, 113.3, 112.0, 109.9, 109.3, 104.1 (q, *J* = 3.3 Hz), 55.7 (q, *J* = 26.6 Hz), 55.6, 33.1, 32.8; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.73 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{27}H_{23}ON_2F_3Na$: 471.1660; found: 471.1642.

8: 72 mg, 26% yield; yellow solid; R_f = 0.26 in 85:15 hexane/ethyl acetate; Mp: 218-220 ºC; IR (KBr): 2925, 2853, 1592, 1329, 1384, 1161, 1068, 740, 716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.05 (dd, 1H, *J* = 9.0, 2.0 Hz), 8.01 (s, 1H), 7.50 (d, 2H, *J* = 7.0 Hz), 7.36-7.28 (m, 5H), 7.18 (t, 1H, *J* = 7.3 Hz), 7.08 (d, 1H, *J* = 8.1 Hz), 7.01 (s, 1H), 6.91 (t, 1H, *J* = 7.3 Hz), 6.74 (s, 1H), 3.79 (s, 3H), 3.75 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 141.7, 140.2, 138.8, 137.6, 133.8, 130.8, 129.4, 128.3, 128.1, 128.0 (q, *J* = 287.0 Hz), 126.7, 126.2, 122.1 (q, *J* = 3.0 Hz), 121.9, 119.6, (q, *J* = 3.0 Hz), 119.5, 117.4, 116.8, 113.1, 109.6, 109.4, 55.7 (q, *J* = 26.8 Hz), 33.5, 33.0; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.98 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{26}H_{20}O_2N_3F_3Na$: 486.1405; found: 486.1383.

General procedure for the synthesis of triaryltrifluoromethylmethane 10: Weinreb amide **4a** (50 mg, 0.30 mmol) and CsF (45.60 mg, 0.30 mmol) were taken in an oven dried 5 mL reaction tube, fitted with septum. Next, 2 mL dry THF (Solvent 1) was added under argon atmosphere and reaction mixture was cooled to 0 °C, at the same temperature CF_3TMS (85 mg, 0.60 mmol) was added. The reaction mixture was allowed to stir at room temperature for 3-4 hour. THF was evaporated under reduced pressure and 2 mL dry DCM (Solvent 2) was added, again reaction mixture was cooled to –78 °C. Triflic anhydride (Tf_2O, 94.38 mg, 0.33 mmol) was added at –78 °C, stirred for 20 min and then the reaction mixture was allowed to warm upto 0 °C. Next, phenols **9** (2.40 mmol) were added at 0 °C and reaction mixture allowed to stirred at room temperature for 5-6 hour. After completion of reaction, the

reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), extracted with EtOAc (2 x 10 mL) and the combined organic layer was dried over Na_2SO_4. Solvent was evaporated under reduced pressure and the crude product was purified by column chromatography using hexane/ethyl acetate as eluent.

10a:[18] 75 mg, 72% yield; light yellow solid; R_f = 0.30 in 70:30 hexane/ethyl acetate; Mp: 224-226 ºC; IR (KBr): 3474, 2958, 2930 2809, 1510, 1444, 1244, 828 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 24 °C): δ 9.60 (brs, 2H), 7.39-7.30 (m, 3H), 7.05 (d, 2H, J = 7.1 Hz), 6.82 (d, 4H, J = 8.7 Hz), 6.74 (d, 4H, J = 8.8 Hz); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6, 24 °C): δ 156.7, 140.4, 130.5, 129.9, 129.2, 128.4 (q, J = 284.4 Hz), 128.1, 127.6, 114.9, 63.2 (q, J = 22.9 Hz); ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –58.17 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{20}H_{15}O_2F_3Na$: 367.0922; found: 367.0957.

10b: 96 mg, 86% yield; light yellow solid; R_f = 0.40 in 70:30 hexane/ethyl acetate; Mp: 169-171 ºC; IR (KBr): 3466, 2927, 2857, 1506, 1228, 1139, 819, 624 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 24 °C): δ 9.52 (brs, 2H), 7.39-7.29 (m, 3H), 7.04 (d, 2H, J = 7.4 Hz), 6.78-6.70 (m, 4H), 6.64-6.55 (m, 2H), 2.03 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, 24 °C): δ 154.8, 140.5, 131.4, 129.9, 129.3, 128.2 (q, J = 286.6 Hz), 128.1, 128.0, 127.5, 123.3, 114.0, 63.3 (q, J = 23.1 Hz), 16.4; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –57.82 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{22}H_{20}O_2F_3$: 373.1415; found: 373.1410.

10c: 63 mg, 42% yield; white solid; R_f = 0.28 in 70:30 hexane/ethyl acetate; Mp: 72-74 ºC; IR (KBr): 3474, 3233, 2926, 1494, 1437, 1232, 1142, 706, 621 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.48-7.43 (m, 4H), 7.42-7.36 (m, 6H), 7.34-7.30 (m, 3H), 7.28-7.22 (m, 2H), 7.17-7.12 (m, 2H), 7.02 (dd, 2H, J = 8.6, 2.2 Hz), 6.92 (d, 2H, J = 8.7 Hz), 5.37 (brs, 2H); $^{13}C\{^1H\}$ NMR (100 MHz $CDCl_3$, 24 °C): δ 151.9, 140.5, 136.9, 132.7, 131.9, 130.9, 129.9, 129.4, 129.1, 128.3, 128.2 (q, J = 286.3 Hz), 128.1, 127.8, 127.6, 115.5, 64.2 (q, J = 23.9 Hz); ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –58.73 (s, 3F,

CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{32}H_{23}O_2F_3Na$: 519.1548; found: 519.1526.

10d:[19] 92 mg, 81% yield; brown solid; R_f = 0.14 in 60:40 hexane/ethyl acetate; Mp: 116-118 ºC; IR (KBr): 3416, 2929, 2858, 1527, 1418, 1262, 1139, 812, 620 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 24 °C): δ 9.06 (brs, 2H), 9.01 (brs, 2H), 7.44-7.26 (m, 3H), 7.13-6.99 (m, 2H), 6.69 (d, 2H, J = 7.6 Hz), 6.56-6.46 (m, 2H), 6.25 (d, 2H, J = 6.7 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, 24 °C): δ 144.7, 144.6, 140.6, 130.6, 129.3, 128.2 (q, J = 285.9 Hz), 128.0, 127.5, 120.6, 117.2, 114.9, 63.4 (q, J = 23.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –57.77 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{20}H_{15}O_4F_3Na$: 399.0820; found: 399.0859.

10e: 81 mg, 66% yield; colourless liquid; R_f = 0.75 in 90:10 hexane/ethyl acetate; IR (neat): 3435, 2946, 2857, 1521, 1230, 1143, 812, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.41 (d, 2H, J = 7.8 Hz), 7.37-7.27 (m, 3H), 6.77 (d, 2H, J = 8.8 Hz), 6.71 (d, 2H, J = 2.6 Hz), 6.56 (dd, 2H, J = 8.8, 2.6 Hz), 3.82 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 160.6, 152.5, 142.1, 132.5, 129.7, 128.2, 127.2, 126.5 (q, J = 284.2 Hz), 113.2, 110.4, 100.7, 55.5, 53.1 (q, J = 26.4 Hz); ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –76.93 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{22}H_{20}O_4F_3$: 405.1308; found: 405.1325.

10f: 93 mg, 61% yield; white solid; R_f = 0.71 in 95:5 hexane/ethyl acetate; Mp: 202-204 ºC; IR (KBr): 3414, 2926, 2867, 1472, 1237, 1159, 933, 626 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.38 (d, 2H, J = 1.9 Hz), 7.36-7.33 (m, 5H), 7.13 (dd, 2H, J = 8.4, 1.9 Hz), 6.73 (d, 2H, J = 8.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 151.6, 140.8, 133.1, 129.7, 128.6, 127.8, 126.9, 125.8 (q, J = 285.0 Hz), 123.3, 119.9, 119.7, 53.6 (q, J = 25.6 Hz); ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –69.67 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{20}H_{13}O_2Br_2F_3Na$: 522.9132; found: 522.9130.

General procedure for the synthesis of trifluoromethylated analogue of hypolipidemic and antiobesity agents 12: Compound **11** was synthesized employing general experimental procedure in 67% yield as white solid. On the other hand, compound **B** was synthesized from lactone in two steps,

first ring opening followed by tosylation of hydroxy group with tosyl chloride in presence of DMAP and Et_3N in DCM. Compound **11** (1 equiv), compound **B** (1.1 equiv) and K_2CO_3 (2 equiv) were dissolved in Dry CH_3CN and refluxed for 6 h. After 6 h, reaction mixture was cooled to room temperature and solvent was evaporated under reduce pressure. Next, the reaction mixture was dissolved in ethyl acetate and washed twice with water. The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography to yield the desired final product **12**.

11: 105 mg, 67% yield; white solid; R_f = 0.31 in 80:20 hexane/ethyl acetate; Mp: 210-212 ºC; IR (KBr): 3477, 2814, 2725, 1352, 1168, 821, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.40 (d, 2H, J = 8.5 Hz), 7.31 (d, 2H, J = 8.5 Hz), 7.22-7.15 (m, 4H), 6.93 (t, 2H, J = 7.9 Hz), 6.25 (m, 2H), 6.76 (d, 2H, J = 8.7 Hz), 4.98 (brs, 1H), 3.71 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 154.8, 137.5, 132.0, 131.1, 130.9, 128.3 (q, J = 286.0 Hz), 126.9, 122.6 (q, J = 3.0 Hz), 121.5, 119.3, 114.8, 114.1, 109.3, 55.3 (q, J = 26.9 Hz), 32.9; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –63.04 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{26}H_{21}ON_2F_3Na$: 457.1498; found: 457.1505.

12: 57 mg, 90% yield as white solid; R_f = 0.48 in 85:15 hexane/ethyl acetate; Mp: 170-172 ºC; IR (KBr): 2812, 2725, 1734, 1597, 1351, 826, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.44 (d, 2H, J = 8.7 Hz), 7.30 (d, 2H, J = 8.7 Hz), 7.22-7.15 (m, 4H), 6.95-6.90 (m, 2H), 6.79 (dd, 2H, J = 6.9, 2.2 Hz), 6.75 (s, 2H), 4.15 (q, 2H, J = 7.6 Hz), 4.00 (t, 2H, J = 6.1 Hz), 3.71 (s, 6H), 2.25 (t, 2H, J = 7.2 Hz), 2.11 (qt, 2H, J = 6.3 Hz), 1.26 (t, 3H, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 173.3, 158.0, 137.5, 131.8, 130.9, 130.0, 128.3 (q, J = 286.9 Hz), 126.9, 122.6 (q, J = 2.5 Hz), 121.5, 119.3, 114.2, 113.7, 109.2, 66.7, 60.5, 55.3 (q, J = 26.8 Hz), 32.9, 30.9, 24.8, 14.3; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$, 24 °C): δ –62.99 (s, 3F, CF_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{32}H_{31}O_3N_2F_3Na$: 571.2179; found: 571.2170.

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References:

(1) a) Shiri, M.; Zolfigol, M. A.; Kruger, H. G.; Tanbakouchian, Z. *Chem. Rev.* **2010**, *110*, 2250; b) Ichite, N.; Chougule, M. B.; Jackson, T.; Fulzele, S. V.; Safe, S.; Singh, M. *Clin. Cancer Res.* **2009**, *15*, 543; c) Marrelli, M.; Cachet, X.; Conforti, F.; Sirianni, R.; Chimento, A.; Pezzi, V.; Michel, S.; Statti, G. A.; Menichini, F. *Nat. Prod. Res.* **2013**, *27*, 2039.

(2) a) Cho, S. D.; Yoon, K.; Chintharlapalli, S.; Abdelrahim, M.; Lei, P.; Hamilton, S.; Khan, S.; Ramaiah, S. K.; Safe, S. *Cancer Res.* **2007**, *67*, 674; b) Chen, X.; Pradhan, T.; Wang, F.; Kim, J. S.; Yoon, J. *Chem. Rev.* **2012**, *112*, 1910; c) Mondal, S.; Panda, G. *RSC Adv.* **2014**, *4*, 28317.

(3) a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320; b) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305; c) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529.

(4) a) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH Verlag GmbH, Weinheim, 2013; b) Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.

(5) a) Chu, L.; Qing, F.-L. *Acc. Chem. Res.* **2014**, *47*, 1513; b) Egami, H.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 8294; c) Charpentier, J.; Fruh, N.; Togni, A. *Chem.*

Rev. **2015**, *115*, 650; d) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem*. *Rev*. **2015**, *115*, 683 and references cited therein.

(6) a) Wang, Y.; Yuan, Y.; Xing, C.-H.; Lu, L. *Tetrahedron Lett*. **2014**, *55*, 1045; b) Sasaki, S.; Ikekame, Y.; Tanayama, M.; Yamauchi, T.; Higashiyama, K. *Synlett* **2012**, *23*, 2699.

(7) For reivew see: a) Praveen, P. J.; Parameswaran, P. S.; Majik, M. S. *Synthesis* **2015**, *47*, 1827; For selected references see: b) He, Y.-Y.; Sun, X.-X.; Li, G.-H.; Mei, G.-J.; Shi, F. *J*. *Org*. *Chem*. **2017**, *82*, 2462; c) Badigenchala, S.; Ganapathy, D.; Das, A.; Singh, R.; Sekar, G. *Synthesis* **2014**, *46*, 101; d) Chinta, B. S.; Baire, B. *Tetrahedron* **2016**, *72*, 8106.

(8) Rudzinski, D. M.; Kelly, C. B.; Leadbeater, N. E. *Chem*. *Commun*. **2012**, *48*, 9610.

(9) a) Bechara, W. S.; Pelletier, G.; Charette, A. B. *Nature Chem*. **2012**, *4*, 228; b) Pace, V.; Holzer, W.; Olofsson, B. *Adv*. *Synth*. *Catal*. **2014**, *356*, 3697; c) Balasubramaniam, S.; Aidhen, I. S. *Synthesis* **2008**, *2008*, 3707.

(10) For reviews see: a) Seebach, D. *Angew*. *Chem*., *Int*. *Ed*. **2011**, *50*, 96; b) Murai, T.; Mutoh, Y. *Chem*. *Lett*. **2011**, *41*, 2; c) Sato, T.; Chida, N. *Org*. *Biomol*. *Chem*. **2014**, *12*, 3147.

(11) Selected references on conversion of amide to amines *via* nucleophilic addition: a) Jäkel, M.; Qu, J.; Schnitzer, T.; Helmchen, G. *Chem*. *–Eur*. *J*. **2013**, *19*, 16746; b) Vincent, G.; Karila, D.; Khalil, G.; Sancibrao, P.; Gori, D.; Kouklovsky, C. *Chem*. *–Eur*. *J*. **2013**, *19*, 9358; c) Xiao, K.-J.; Luo, J.-M.; Xia, X.-E.; Wang, Y.; Huang, P.-Q. *Chem*. *–Eur*. *J*. **2013**, *19*, 13075; d) Nakajima, M.; Sato, T.; Chida, N. *Org*. *Lett*. **2015**, *17*, 1696 and references cited therein.

(12) a) Pandey, V. K.; Anbarasan, P. *J*. *Org*. *Chem*. **2014**, *79*, 4154; b) Pandey, V. K.; Anbarasan, P. *RSC Adv*. **2016**, *6*, 18525.

(13) Palmieri, A.; Petrini, M.; Shaikh, R. R. *Org*. *Biomol*. *Chem*. **2010**, *8*, 1259.

(14) Liu, X.-R.; Zhou, Y.-L. *Acta Crystallogr., Sect. E* **2014**, *70*, o1156.

(15) CCDC 1508846 contains the supplementary crystallographic data for the compound **6aj**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

(16) Sashidhara, K. V.; Kumar, M.; Sonkar, R.; Singh, B. S.; Khanna, A. K.; Bhatia, G. *J. Med. Chem.* **2012**, *55*, 2769.

(17) Nemoto, K.; Tanaka, S.; Konno, M.; Onozawa, S.; Chiba, M.; Tanaka, Y.; Sasaki, Y.; Okubo, R.; Hattori, T. *Tetrahedron* **2016**, *72*, 734 and references cited therein.

(18) Shaver, A. T.; Yin, K.; Borjigin, H.; Zhang, W.; Choudhury, S. R.; Baer, E.; Mecham, S. J.; Riffle, J. S.; McGrath, J. E. *Polymer* **2016**, *83*, 199.

(19) Tao, L.; Yang, H.; Liu, J.; Fan, L.; Yang, S. *Synth. Commun.* **2013**, *43*, 2319.