One-Pot Synthesis of New Substituted 1,2,3,4-Tetrahydrocarbazoles via Petasis Reaction

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The one-pot synthesis of a new substituted 1,2,3,4-tetrahydrocarbazoles has been described via Petasis reactions. These tetrahydrocarbazoles exhibits various medicinal importance and might be suitable for elaboration into larger peptides at carboxy termini. The scope and limitations of this method have been examined.

Introduction

The tetrahydrocarbazole architecture widely exists in various naturally occurring alkaloids, biologically active molecules, and synthetic analogues of medicinal importance,[1−3] some of which can be potentially used as tumor growth inhibitors and protein kinase C inhibitors.[4]

It was reported[5] by Glennon et al. that 1,2,3,4-tertrahydro carbazoles (**I**) act as 5-HT_6 serotonin receptor ligands. Evidence suggests that these receptors could play a role in certain central disorders, such as schizophrenia and depression, and more recent information implicates possible involvement in cognition (but see Lindner et al.),[6c] convulsive disorders, and obesity.[6]

Recently, Gudmundsson et al. reported[7] that substituted tetrahydrocarbazoles (**II**) act as a potent activity against human papillomaviruses (HPVs) which are small nonenveloped DNA viruses that cause a wide variety of benign and premallignant epithelical tumors. Several HPVs infect the genital mucosa. HPV infection is the most common sexually transmitted disease throughout the world, with an incidence roughly twice that of herpes simplex infection.[8] There are over 5.5 million new cases of sexually transmitted HPV infection that occur in the U.S. each year, with at least 20 million people currently infected.[9]

Recently, Barf et al. also reported[10] that N-substituted-indolo carboxylic acids (**III**) act as a potent and selective adipocyte fatty-acid binding protein (A-FABP) inhibitors which are tissue-specific, ∼15 KDa cytoplasmic lipid chaperones, capable of binding and transporting endogenous fatty acids from the cell surface to the various sites of metabolism or storage.[11] Consequently, the role of fatty-acid binding proteins (FABPs) is directly linked to lipid-mediated biology such as signaling pathways, trafficking and membrane synthesis.[12]

There was a report[13] by Brown et al. that 1,2,3,4-tetrahydorcarbazoles (**IV**) show relatively good antioxidants properties.

Fabio et al.[14] and Koppitz et al.[15] also reported that substituted tetrahydrocarbazoles (**V** and **VI**, respectively) act as a new NPY-1 antagonists and as a GPCR antagonists respectively. Neuropeptide Y (NPY) is a 36-amino acid peptide isolated fromporcine brain in 1982 by Tatemoto et al.[16] NPY belongs to a family of biologically active polypeptides such as peptide YY (PYY) and pancreatic polypeptide (PP)[17] widely distributed in the central and peripheral nervous system of many mammalian species including humans.

For this reason, the development of new and efficient methods for the synthesis of tetrahydrocarbazole derivatives continues to attract considerable attention. Many elegant methods for the synthesis of various tetrahydrocarbazole derivatives have been developed in the past years,[18] including reductive cyclization of 2-nitrobiphenyl,[18q−s] Pd-catalyzed oxidation cyclization of 3-(3′-alkenyl)indoles,[18t] intramolecular arylation of N,N-diaryl amines,[18u,v] and alkyllithium-mediated intramolecular anionic cyclization.[18w] However, many of these methods involve harsh reaction conditions, expensive reagents, complex handling, and low yields of products. Thus, it was desirable to develop operationally simple, more efficient, and practical approaches for the construction of tetrahydrocarbazoles.

With the recent emergence of combinatorial chemistry and high-speed parallel synthesis in the lead discovery arena, the multicomponent reaction (MCR) has witnessed a resurgence of interest.[19] Easily automated one-pot reactions, such as Ugi,[20] Passerini,[21] Petasis[22] reactions are powerful tools for producing diverse arrays of compounds, often in one step and high yield. The Petasis boronic acid−Mannich reaction that provides a powerful and convenient method for the preparation of α-amino acids[22] is also quite useful for the synthesis of combinatorial libraries. In earlier studies, it was shown that hydrazine can participate in the Petasis boronic acid−Mannich reaction to afford various α-hydrazinocarboxylic acids.[23] Because of our interests in the synthesis of combinatorial

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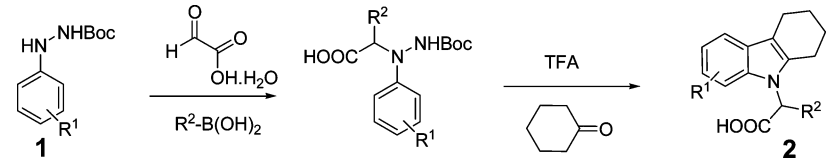
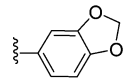
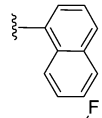
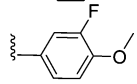
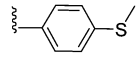
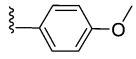
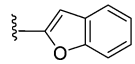
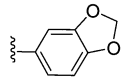
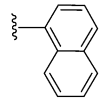
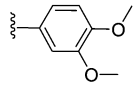
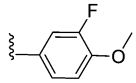
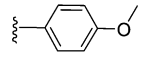
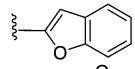
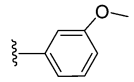
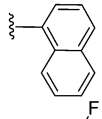
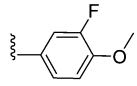
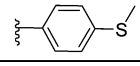
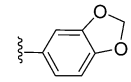
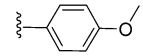
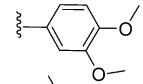
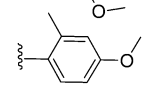
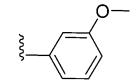
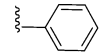
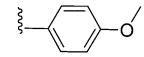
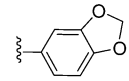
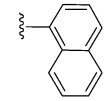
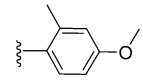
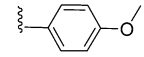
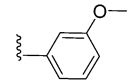
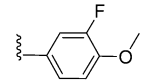
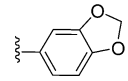
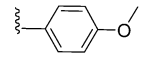
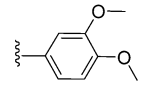
Table 1. Synthesis of 1,2,3,4-Tetrahydro Substituted Carbazole Derivatives



Product	R^1	R^2	Yield(%)[a]
2(I)	4-OMe		51
2(II)	4-OMe		51
2(III)	4-OMe		48
2(IV)	4-OMe		47
2(V)	4-OMe		46
2(VI)	4-OMe		38
2(VII)	H		44
2(VIII)	H		44
2(IX)	H		38
2(X)	H		33
2(XI)	H		28
2(XII)	H		21
2(XIII)	H		27
2(XIV)	4-F		49
2(XV)	4-F		45
2(XVI)	4-F		44
2(XVII)	4-F		44
2(XVIII)	4-F		37
2(XIX)	4-F		36
2(XX)	4-F		32
2(XXI)	4-F		31
2(XXII)	4-F		25
2(XXIII)	$4\text{-}CH_3$		27
2(XXIV)	$2\text{-}CH_3$		32
2(XXV)	$2\text{-}CH_3$		32
2(XXVI)	$2\text{-}CH_3$		31
2(XXVII)	$2\text{-}CH_3$		29
2(XXVIII)	$2\text{-}CH_3$		29
2(XXIX)	$2\text{-}CH_3$		29
2(XXX)	$3\text{-}CH_3$		31
2(XXXI)	$3\text{-}CH_3$		30
2(XXXII)	3-CH3		28

[a] All yields refer to pure, isolated products; the reactions proceed through the Petasis, removal of the Boc group, coupling, and cyclization in one pot without purification until the final product (**2**) is isolated. All compounds have been characterized by LC-MS, ^{1}H NMR, ^{13}C NMR, FAB, and HRMS.

libraries of heterocycles for drug discovery,[24,25] we have investigated further the scope and limitations of using substituted hydrazines in the Petasis boronic acid−Mannich reaction. Within this context, we wished to apply the strategy more broadly to the preparation of heterocycles, that is, druglike chemical collections, for high-throughput biological screening. Herein, we report a practical method for the synthesis of substituted 1,2,3,4-tetrahydrocarbazoles *via* multicomponent condensation reactions in one pot. However, there is no literature report available for the synthesis of 1,2,3,4-tetrahydrocarbazoles **2** via Petasis reaction.

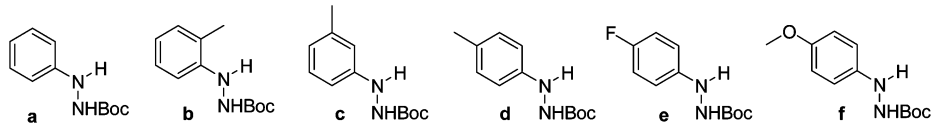


Figure 1. Substituted hydrazines.

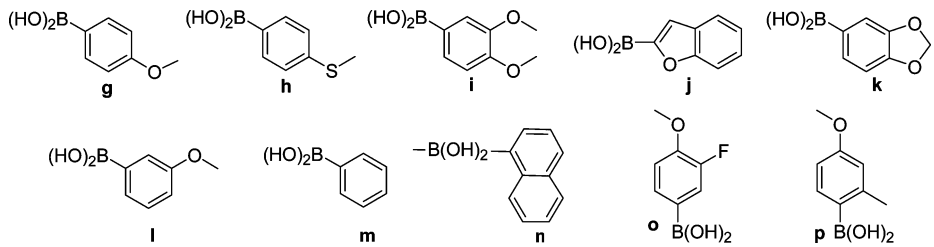
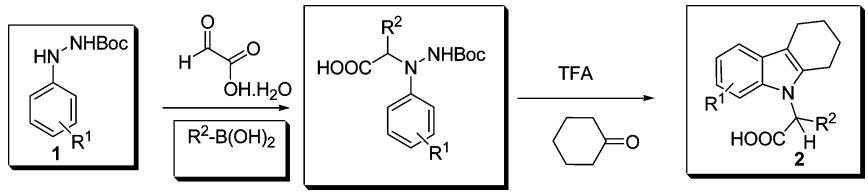


Figure 2. Substituted boronic acids.

Scheme 1. Synthesis of 1,2,3,4-Tetrahydro Substituted Carbazoles



The lack of general synthetic method may have precluded a comprehensive biological evaluation of this interesting structural class of compounds for these new substituted 1,2,3,4-tetrahydrocarbazoles. Herein, we report an efficient synthesis of substituted 1,2,3,4-tetrahydrocarbazoles **2** via multicomponent condensation reactions in one pot (Table 1).

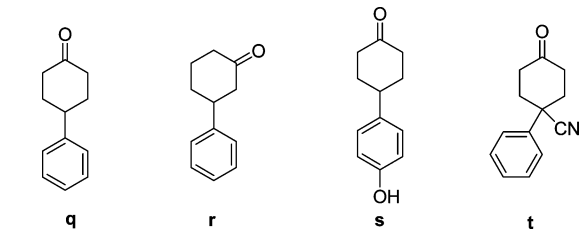
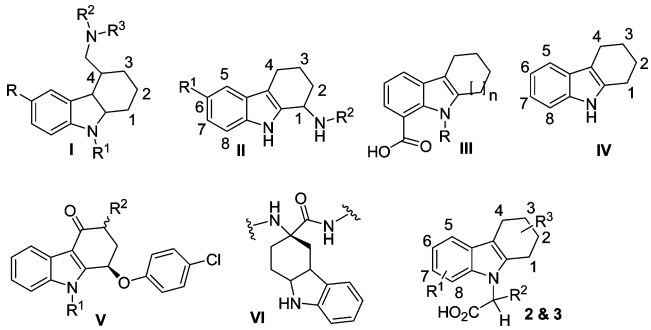


Figure 3. Substituted cyclohexanones.



Result and Discussion

A variety of *N*-1-Boc-*N*-2-(phenyl substituted)-hydrazines[23] (**1**, Figure 1) were subjected to Petasis three-component condensation reaction in presence of glyoxylic acid monohydrate and a variety of boronic acids (Figure 2) in DCM (Scheme 1). The resulting mixture was stirred at ambient temperature for 12 h and then to this reaction mixture was added cyclohexanone followed by TFA and stirred at ambient temperature for 24 h. The solvent was removed under reduced pressure and the crude reaction mixture was purified by column chromatography using silica gel to furnish the desired products (Figure 4 and 5). In Table 1, when R^1 = 4-OMe and R^2 = aryl [**2(I)**−**2(VI)**], these reactions proceeded in good yields affording 38−51% of the corresponding (1,2,3,4-tetrahydro-carbazol-9-yl)-α-phenyl acetic acid derivatives after purification by column chromatography. It is to be noted that when R^1 = H, and R^2 = aryl [**2(VII)**−**2(XIII)**], these reactions proceeded in moderate yields affording 21−44% of the corresponding desired products after purification. It is also interesting to note that when R^1 = 4-F and R^2 = aryl [**2(XIV)**−**2(XXII)**], these reactions proceeded in moderate yields affording 25−49% of the corresponding (1,2,3,4-tetrahydro-carbazol-9-yl)-α-phenyl acetic acid derivatives after purification by column chromatography. When R^1 = 4-CH_3; 2-CH_3, 3-CH_3, and R^2 = aryl [**2(XXIII)**−**2(XXXII)**], these reactions proceeded in moderate yields affording 27−32% of the corresponding desired products after purification. It is noteworthy that the reactions proceed through the Petasis, followed by removal of the Boc group and Fischer indole in one pot without purification of intermediate until the final product (**2**) is isolated (Table 1).

We explored the diversity at the ketone step with butanone, pentanone, heptanone, and piperidone to expand the scope of the reaction, but the reactions gave no tetrahydrocarbazole products. However, substituted cyclohexanone (Figure 3, Scheme 2) proceeded in moderate yields affording 30−37% of the corresponding desired

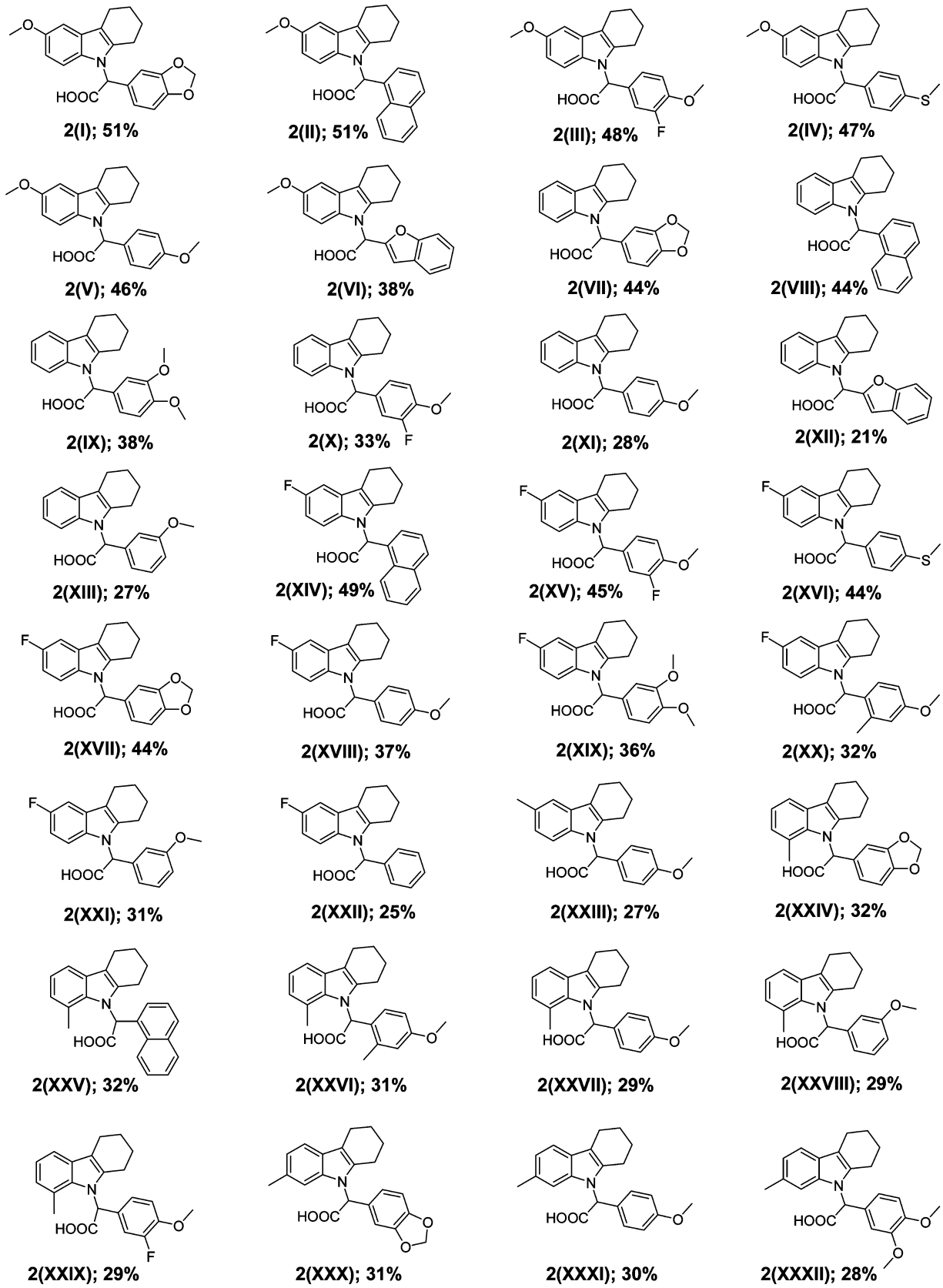


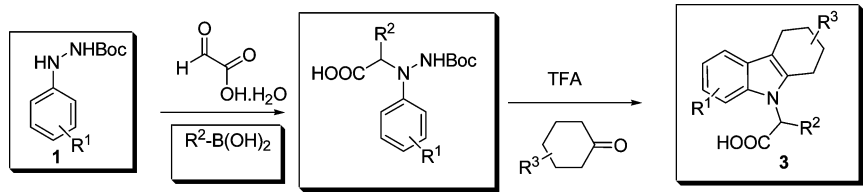
Figure 4. New substituted 1,2,3,4-tetrahydro substituted carbazoles.

products [**3(I)**−**3(IX)**] after purification (Figure 5). It is noteworthy that the reactions proceed through the Petasis, followed by removal of the Boc group and Fischer indole in one pot without purification of intermediate until the final product (**3**) is isolated (Table 2).

Conclusion

In summary, we have demonstrated that an efficient synthesis of substituted 1,2,3,4-tetrahydrocarbazoles have been developed from *N*-1-Boc-*N*-2-(phenyl substituted)-hydrazines utilizing multicomponent condensation reactions in one pot. All these

Scheme 2. Synthesis of 1,2,3,4-Tetrahydro Substituted Carbazoles



compounds are having three points of diversity and these can be further derivatized at the carboxy terminal to provide more elaborate peptide. To the best of our knowledge these compounds have not been synthesized previously.

Experimental Section

General Procedure for the Synthesis of (1,2,3,4-Tetrahydro-substituted carbazol-9-yl)-α-substituted Phenyl Acetic Acid Derivatives 2 (Table 1). To a stirred mixture of glyoxylic acid monohydrate (92 mg, 1 mmol) in DCM (4 mL) was added *N*-(4-methoxy phenyl)hydrazinecarboxylic acid *tert*-butyl ester (238 mg, 1 mmol), followed by 3,4-(methylenedioxy)phenylboronic acid (166 mg, 1 mmol). The resulting mixture was stirred at ambient temperature for 12 h and then to this reaction mixture was added cyclohexanone (294 mg, 3 mmol) followed by TFA (342 mg, 3 mmol) and stirred at ambient temperature for 24 h. The solvent was removed under reduced pressure and the crude reaction mixture was purified by column chromatography using silica gel (230−400 mesh) and EtOAc/hexane as eluent to furnish the desired product **2(I)** as white solid (193.5 mg, 51%).

2(I): white solid; mp (Met-Temp) 162°−164 °C (uncorrected); analytical HPLC symmetry C18 (4.6 × 75 mm, 3.5 μmparticle size), mobile phase 10 mM NH_4OAc/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 4.59 min, 98.76% purity; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.96−1.02 (m, 1H), 1.23−1.34 (m, 1H), 1.48−1.51 (m, 1H), 1.68−1.74 (m, 2H), 1.80−1.86 (m, 1H), 2.05−2.08 (m, 1H), 2.31−2.34 (m, 1H), 3.42 (s, 3H), 4.59 (s, 1H), 5.36 (s, 1H), 6.05−6.06 (m, 1H), 6.55−6.64 (m, 4H), 6.97−6.99 (d, J = 7.92, 1H), 7.16 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.97, 22.74, 31.82, 33.73, 55.21, 55.54, 79.42, 101.52, 105.32, 108.23, 110.20, 111.57, 112.53, 114.13, 124.90, 127.36, 132.84, 140.82, 147.00, 152.35, 174.61; LCMS (UV) 380.2 (M + H^+); FABMS 380 [calcd for $C_{22}H_{22}NO_5$, 380.41 (M + H^+)].

2(II): white solid; mp (Met-Temp) 83°−84 °C (uncorrected); analytical HPLC Zorbax Extend C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 0.1%TFA/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 4.71 min, 97.48% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25−1.30 (m, 1H), 1.50−1.55

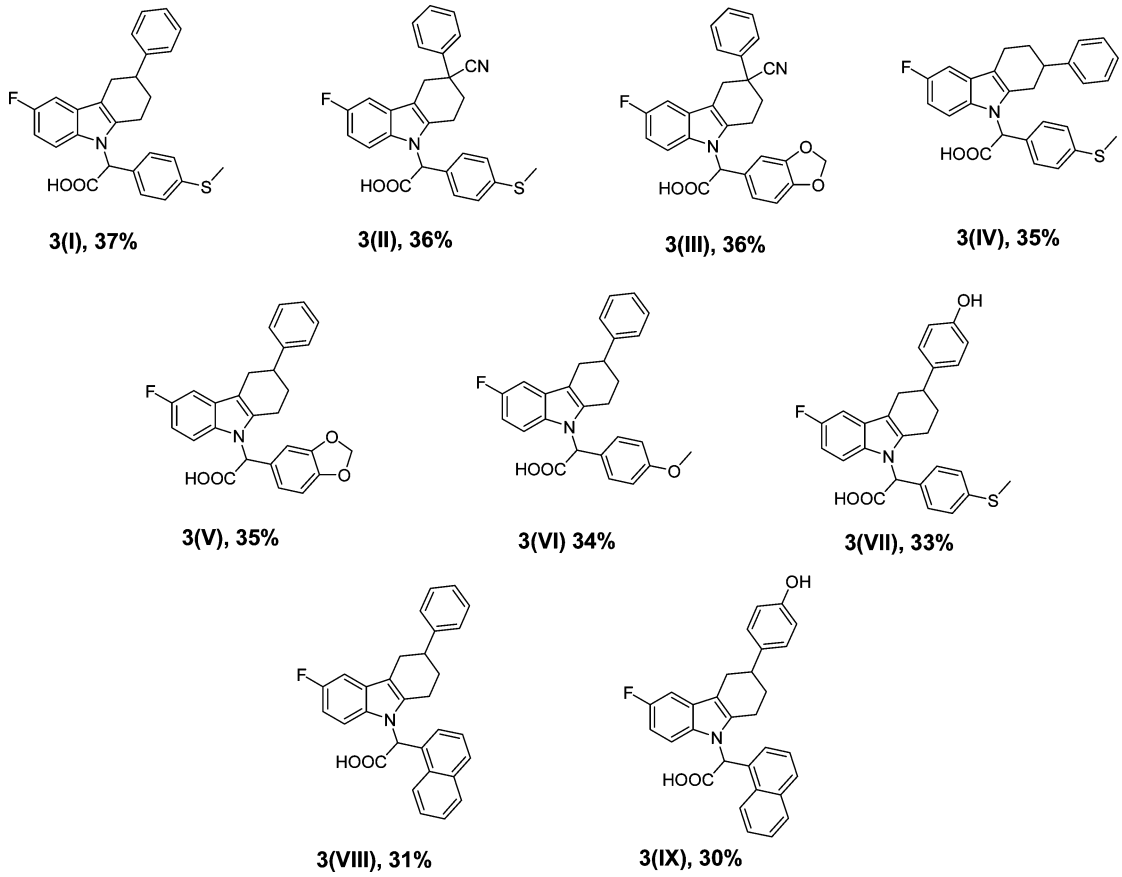
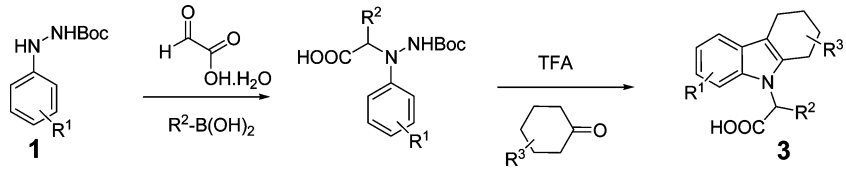
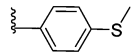
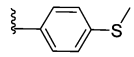
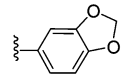
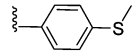
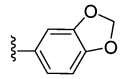
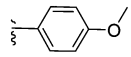
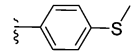
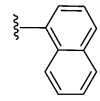
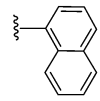


Figure 5. New substituted 1,2,3,4-tetrahydro substituted carbazoles.

Table 2. Synthesis of 1,2,3,4-tetrahydro substituted carbazole derivatives



Product	R^1	R^2	R^3	Yield(%)[a]
3(I)	4-F		4-Ph	37
3(II)	4-F		4-Ph, 4-CN	36
3(III)	4-F		4-Ph, 4-CN	36
3(IV)	4-F		3-Ph	35
3(V)	4-F		4-Ph	35
3(VI)	4-F		4-Ph	34
3(VII)	4-F		4-(4-OH)-Ph	33
3(VIII)	4-F		4-Ph	31
3(IX)	4-F		4-(4-OH)-Ph	30

[a] All yields refer to pure, isolated products; the reactions proceed through the Petasis, removal of the Boc group, coupling, and cyclization in one pot without purification until the final product (**3**) is isolated. All compounds have been characterized by LC-MS, ^{1}H NMR, and ^{13}C NMR.

(m, 1H), 1.80−1.86 (m, 2H), 1.95−2.03 (m, 2H), 2.24−2.28 (m, 1H), 2.52−2.56 (m, 1H), 3.35 (s, 3H), 5.22 (m, 2H), 6.65 (s, 2H), 7.16−7.18 (d, J = 7.28, 1H), 7.46−7.50 (m, 1H), 7.53−7.62 (m, 2H), 7.91−7.93 (d, J = 8.16, 1H), 7.95−7.97 (d, J = 7.88, 1H), 8.10−8.12 (d, J = 8.4, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.36, 22.27, 29.69, 33.31, 47.61, 55.63, 110.67, 112.79, 114.83, 122.25, 124.87, 125.63, 126.51, 128.79, 129.37, 129.41, 131.71, 132.31, 133.00, 133.75, 139.53, 153.14, 174.93; LCMS (UV) 386.2 (M + H^+); Anal. Calcd for $C_{25}H_{23}NO_3$ C 77.90, H 6.01, N 3.63; Found C 77.81, H 6.06, N 3.60.

2(III): white solid; mp (Met-Temp) 79°−80 °C (uncorrected); analytical HPLC Zorbax Extend C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 0.1%TFA/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 4.69 min, 98.30% purity; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26−1.27 (m, 1H), 1.48−1.51 (m, 2H), 1.71−1.77 (m, 2H), 1.82−1.86 (m, 1H), 2.18 (m, 1H), 2.50 (m, 1H), 3.50 (s, 3H), 3.93 (s, 3H), 4.23 (s, 1H), 5.47 (s, 1H), 6.65 (m, 2H), 6.92−7.03 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.14, 22.36, 32.81, 33.23, 51.09, 55.97, 56.27, 104.07, 110.71, 112.53, 112.94, 114.58, 118.76, 118.95, 125.49, 127.00, 131.92, 139.63, 147.49, 150.58, 153.03, 173.75; LCMS (UV) 384.2 (M + H^+); Anal. Calcd for $C_{22}H_{22}FNO_4$ C 68.92, H 5.78, N 3.65; Found C 68.83, H 5.75, N 3.67.

2(IV): white solid; mp (Met-Temp) 86°−88 °C (uncorrected); analytical HPLC Zorbax Extend C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 0.1% TFA/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 4.53 min, 96.03% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (m, 1H), 1.42−1.48 (m, 1H), 1.57−1.59 (m, 1H), 1.71 (m, 1H), 1.78−1.82 (m, 1H), 1.85−1.86 (m, 1H), 2.19−2.22 (m, 1H), 2.44 (m, 1H), 2.47 (s, 3H), 3.46 (s, 3H), 3.79 (s, 1H), 4.27 (s, 1H), 5.43 (s, 1H), 6.64 (m, 2H), 7.12−7.14 (d, J = 8.28, 2H), 7.14 (m, 1H), 7.24−7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.81, 20.11, 22.38, 32.86, 33.06, 51.56, 55.61, 104.13, 110.66, 112.40, 114.63, 126.16, 126.46, 129.46, 130.02, 130.18, 131.48, 132.08, 138.66, 139.61, 153.40, 173.97; LCMS (UV) 382.2 (M + H^+); Anal. Calcd for $C_{22}H_{23}NO_3S$ C 69.26, H 6.08, N 3.67; Found C 69.32, H 6.10, N 3.68.

2(V): white solid; mp (Met-Temp) 192°−193 °C (uncorrected); analytical HPLC Symmetry C18 (4.6X 75 mm, 3.5 μmparticle size), mobile phase 10 mM. NH_4OAc/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 4.79 min, 99.49% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26−1.30 (m, 1H),

1.42−1.47 (m, 2H), 1.57−1.71 (m, 2H), 1.78−1.85 (m, 1H), 2.20−2.24 (m, 1H), 2.44−2.48 (m, 1H), 3.37 (s, 3H), 3.78 (s, 3H), 4.59 (s, 1H), 5.24 (s, 1H), 6.54−6.59 (m, 2H), 6.97−6.99 (d, J = 8.4, 2H), 7.04−7.06 (d, J = 8.4, 2H), 7.15 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.59, 22.39, 32.89, 33.28, 55.06, 55.35, 55.65, 103.76, 110.56, 112.59, 113.57, 114.45, 124.72, 132.17, 132.32, 139.66, 153.38, 159.45, 174.33; LCMS (UV) 366.2 (M + H$^+$); HRMS 366.1717 [Calcd for $C_{22}H_{24}NO_4$ 366.1705 (M + H$^+$)].

2(VI): brown semi solid; moisture sensitive; analytical HPLC Sunfire C18 (4.6 × 150 mm, 3.5 μmparticle size), mobile phase 10 mM NH_4OAc/CH_3CN linear gradient over 30 min, with a flow of 0.7 mL/min, one peak detected by ELS and UV at R_t = 16.89 min, 89.39% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27−1.30 (m, 1H), 1.37−1.49 (m, 1H), 1.60 (m, 1H), 1.79−1.89 (m, 3H), 2.51−2.54 (m, 1H), 2.76−2.80 (m, 1H), 3.11 (s, 3H), 4.58 (s, 1H), 5.49 (s, 1H), 6.61−6.67 (m, 2H), 6.89 (s,1H), 7.24−7.34 (m, 2H), 7.53−7.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.87, 22.28, 33.06, 33.37, 55.04, 55.51, 104.65, 107.66, 110.22, 111.09, 115.22, 121.32, 123.16, 124.44, 128.00, 132.09, 139.10, 150.88, 153.84, 154.36, 170.98; LCMS (UV) 376.2 (M + H$^+$); Anal. Calcd for $C_{23}H_{21}NO_4$ C 73.58, H 5.64, N 3.73; Found C 73.32, H 5.91, N 3.68.

2(VII): white solid; mp (Met-Temp) 194°−195 °C (uncorrected); analytical HPLC Symmetry C18 (4.6 × 75 mm, 3.5 μmparticle size), mobile phase 10 mM NH_4OAc/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 4.92 min, 98.21% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22−1.30 (m, 1H), 1.42−1.57 (m, 2H) 1.69−1.73 (m, 1H), 1.77−1.89 (m, 2H), 2.23−2.26 (m, 1H), 2.45−2.48 (m, 1H), 4.23(s, 1H), 5.95−5.99 (m, 2H), 6.03 (m, 1H), 6.586.68 (m, 3H), 6.71−6.73 (d, J = 7.76, 1H), 6.83−6.85 (d, J = 7.92, 1H), 7.06−7.10 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.51, 22.27, 32.36, 33.37, 51.73, 54.91, 101.18, 102.90, 107.96, 110.08, 111.46, 119.63, 124.55, 126.54, 128.42, 130.94, 145.85, 147.38, 174.15; LCMS (UV) 350.2 (M + H$^+$); FABMS 350 [Calcd for $C_{21}H_{20}NO_4$ 350.39 (M + H$^+$)].

2(VIII): white solid; mp (Met-Temp) 175°−176 °C (uncorrected); analytical HPLC Zorbax Extend C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 0.1%TFA/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 5.05 min, 98.53% purity; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.60−1.70 (m, 4H), −2.09−2.14 (m, 1H), 2.59−2.61 (m, 3H), 6.98−7.02 (m, 3H), 7.27−7.31 (m, 2H), 7.38−7.52 (m, 4H), 7.78−7.80 (d, J = 8.36, 1H), 7.95−7.97 (d, J = 8.16, 2H), 13.56 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.08, 22.75, 23.26, 59.10, 110.13, 110.43, 118.04, 119.39, 121.34, 123.56, 125.50, 126.16, 126.51, 127.24, 127.88, 129.22, 129.67, 131.65, 131.75, 133.82, 136.58, 136.85, 171.50; LCMS (UV) 356.2 (M + H$^+$); Anal. Calcd for $C_{24}H_{21}NO_2$ C 81.10, H 5.96, N 3.94; Found C 81.16, H 5.94, N 3.95.

2(IX): white solid; mp (Met-Temp) 193°−°C (uncorrected); analytical HPLC Symmetry C18 (4.6 × 75 mm, 3.5 μmparticle size), mobile phase 10 mM. NH_4OAc/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 4.61 min, 97.67% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22−1.30 (m, 1H), 1.43−1.50(m, 1H), 1.53−1.60 (m, 1H), 1.70−1.74 (m, 1H), 1.80−1.90 (m, 2H), 2.23−2.27 (m, 1H), 2.46−2.50 (m, 1H), 3.75 (s, 3H), 3.93 (s, 3H), 4.27 (s, 1H), 5.89−5.91 (d, J = 7.52, 1H), 6.54−6.60 (m, 2H), 6.71−6.73 (d, J = 7.8, 1H), 6.78−6.80 (m, 1H), 6.88−6.90 (d, J = 8.2, 1H), 7.05−7.09(m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.56, 22.29, 32.78, 33.35, 51.81, 54.95, 55.92, 103.17, 110.07, 110.62, 114.52, 119.37, 123.40, 125.23, 126.84, 128.46, 131.01, 145.91, 148.37, 148.94, 174.48; LCMS (UV) 366.2 (M + H$^+$); Anal. Calcd for $C_{22}H_{23}NO_4$ C 72.31, H 6.34, N 3.83; Found C 71.89, H 6.52, N 3.76.

2(X): white solid; mp (Met-Temp) 194°−195 °C (uncorrected); analytical HPLC Zorbax Extend C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 10 mM NH_4OAc/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 4.31 min, 98.91% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44−1.48 (m, 1H), 1.52−1.59 (m, 1H), 1.71−1.75 (m, 1H), 1.79−1.87 (m, 2H), 1.91 (m, 1H), 2.21−2.25 (m, 1H), 2.48−2.51 (m, 1H), 3.95 (s, 3H), 4.24 (s, 1H), 5.85−5.87 (d, J = 7.52, 1H), 6.57−6.61 (m, 1H), 6.73−6.75 (d, J = 7.8, 1H), 6.90−6.99 (m, 3H), 7.01−7.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.52, 22.31, 32.72, 33.42, 54.89, 56.30, 103.55, 110.20, 112.90, 118.85, 119.71, 125.69, 126.32, 126.94, 128.52, 130.80, 145.83, 147.54, 150.59, 153.03, 173.82; LCMS (UV) 354.2 (M + H$^+$); Anal. Calcd for $C_{21}H_{20}FNO_3$ C 71.37, H 5.70, N 3.96; Found C 71.32, H 5.73, N 3.91.

2(XI): white solid; mp (Met-Temp) 155°−156 °C (uncorrected); analytical HPLC Symmetry C18 (4.6 × 75 mm, 3.5 μmparticle size), mobile phase 10 mM NH_4OAc/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 5.01 min, 97.24% purity; ^{1}H NMR (CD_3OD, 400 MHz) δ 1.10−1.18 (m, 1H), 1.42−1.45 (m, 1H), 1.63−1.75 (m, 2H), 1.86−1.94 (m, 2H), 2.20−2.24 (m, 1H), 2.45−2.50 (m, 1H), 3.84 (s, 3H), 4.5 (s, 1H), 5.75−5.77 (d, J = 7.48, 1H), 6.44−6.48 (m, 1H), 6.69−6.71 (d, J = 7.8, 1H), 6.94−6.96 (d, J = 8.76, 2H), 7.00−7.04 (m, 1H), 7.08−7.10 (d, J = 8.56, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ 20.35, 23.69, 33.08, 34.97, 52.52, 55.74, 110.65, 114.33, 119.58, 126.74, 127.42, 129.35, 133.37, 160.94, 176.2; LCMS (UV) 336.2 (M + H$^+$); Anal. Calcd for $C_{21}H_{21}NO_3$ C 75.20, H 6.31, N 4.18; Found C 75.68, H 6.59, N 4.21.

2(XII): white solid; mp (Met-Temp) 103°−104 °C (uncorrected); analytical HPLC Symmetry C18 (4.6 × 75 mm, 3.5 μmparticle size), mobile phase 10 mM. NH_4OAc/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 2.64 min, 96.48% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81−1.88(m, 4H), 2.74(m, 2H), 2.81−2.85 (m, 1H), 3.06−3.11(m, 1H), 5.96 (s, 1H), 6.55 (s, 1H), 7.09−7.13 (m, 1H), 7.16−7.29 (m, 4H), 7.44−7.48 (m, 2H), 7.81(broad peak, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.43, 23.23, 23.48, 23.59, 47.56, 105.79, 109.11, 110.41, 111.17, 119.36, 120.94, 121.16, 122.60, 123.91,.126.18, 128.35, 134.99, 136.07, 155.04, 155.20, 174.76; LCMS (UV) 346.2 (M + H$^+$); Anal. Calcd for $C_{22}H_{19}NO_3$ C 76.50, H 5.54, N 4.06; Found C 76.12, H 5.34, N 4.08.

2(XIII): brown semi solid; moisture sensitive; analytical HPLC Hypersil BDS C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 0.1% TFA/CH_3OH linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 5.66 min, 96.82% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82−1.89 (m, 4H), 2.44−2.48 (m, 1H), 2.63−2.68 (m, 1H), 2.75−2.76 (m, 2H), 3.75(s, 3H), 6.30 (s, 1H), 6.80−6.81 (m, 2H), 6.85−6.88 (m, 1H), 7.06−7.13 (m, 3H), 7.23−7.25 (m, 1H), 7.48−7.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.82, 22.80, 23.25, 29.60, 55.18, 55.41, 110.37, 111.32, 112.02, 113.65, 117.81, 119.75, 120.99, 121.92, 123.47, 129.50, 129.95, 136.22, 137.76, 160.12, 192.08; LCMS (UV) 336.2 (M + H$^+$); Anal. Calcd for $C_{21}H_{21}NO_3$ C 75.20, H 6.31, N 4.18; Found C 74.90, H 6.33, N 4.19.

2(XIV): white solid; mp (Met-Temp) 197°−198 °C (uncorrected); analytical HPLC Zorbax Extend C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 0.1%TFA/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 5.10 min, 99.54% purity; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.61−1.71 (m, 4H), 2.13 (m, 1H), 2.57−2.65 (m, 3H), 6.79−6.84 (m, 1H), 7.05 (s, 1H), 7.12−7.14 (d, J = 9.6, 1H), 7.23−7.30 (m, 2H), 7.42−7.53 (m, 3H), 7.75−7.77 (d, J = 8.36, 1H), 7.96−7.98 (d, J = 8.16, 2H), 13.61 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 20.63, 22.26, 22.76, 22.94, 58.97, 102.73, 108.25, 110.13, 110.77, 123.28, 125.13, 125.86, 126.08, 126.80, 127.87, 128.79, 129.29, 131.16, 133.12, 133.44, 138.38, 155.87, 158.18, 171.09; LCMS (UV) 374.2 (M + H$^+$); Anal. Calcd for $C_{24}H_{20}FNO_2$ C 77.19, H 5.40, N 3.75; Found C 77.12, H 5.35, N 3.77.

2(XV): white solid; mp (Met-Temp) 194°−195 °C (uncorrected); analytical HPLC Zorbax Extend C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 10 mM NH_4OAc/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 4.35 min, 94.64% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23−1.30 (m, 1H), 1.41−1.46 (m, 1H), 1.54−1.58 (m, 1H), 1.72−1.90 (m, 3H), 2.18−2.21 (m, 1H), 2.44−2.47 (m, 1H), 3.94 (s, 3H), 4.23 (s, 1H), 5.55−5.58 (d, J = 8.8, 1H), 6.61−6.64 (m, 1H), 6.76−6.79 (m, 1H), 6.80−7.02 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.42, 22.22, 32.70, 33.15, 50.89, 55.11, 56.32, 103.68, 110.52, 113.06, 114.80, 118.48, 125.07, 126.85, 132.28, 141.88, 147.73, 150.64, 153.09, 155.70, 158.05, 173.53; LCMS (UV) 372.2 (M + H$^+$); Anal. Calcd for $C_{21}H_{19}F_2NO_3$ C 67.92, H 5.16, N 3.77; Found C 67.85, H 5.11, N 3.82.

2(XVI): yellow solid; mp (Met-Temp) 166°−167 °C (uncorrected); analytical HPLC Zorbax Extend C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 0.1% TFA/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 5.05 min, 92.99% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82−1.91 (m, 4H), 2.34−2.38 (m, 2H), 2.48 (s, 3H), 2.60−2.69 (m, 2H), 6.22 (s, 1H), 6.73−6.78 (m, 1H), 6.92−6.95 (m, 1H), 7.09−7.12 (m, 3H), 7.16−7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.37, 20.90, 22.82, 26.92, 41.85, 59.49, 103.22, 108.71, 109.05, 111.24, 111.45, 126.21, 127.74, 128.70, 130.50, 132.41, 137.49, 139.08, 156.25, 159.36, 173.48; LCMS (UV) 370.2 (M + H$^+$); Anal. Calcd for $C_{21}H_{20}FNO_2S$ C 68.27, H 5.46, N 3.79; Found C 68.35, H 5.49, N 3.76.

2(XVII): white solid; mp (Met-Temp) 196°−198 °C (uncorrected); analytical HPLC Hypersil BDS C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 10 mM NH_4OAc/CH_3OH linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 4.64 min, 98.71% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22−1.30 (m, 1H), 1.42−1.57 (m, 2H) 1.71−1.90 (m, 3H), 2.21−2.25 (m, 1H), 2.43−2.47 (m, 1H), 4.23 (s, 1H), 5.66−5.69 (m, 1H), 6.00−6.04 (m, 2H), 6.61−6.68(m, 3H), 6.76−6.81(m, 1H), 6.85−6.87 (d, J = 7.8, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.36, 22.18, 32.66, 33.03, 51.42, 55.05, 101.23, 103.45, 108.06, 110.30, 111.19, 113.68, 114.65, 124.39, 125.69, 132.32, 141.74, 147.48, 155.65, 158.00, 173.86; LCMS (UV) 368.2 (M + H$^+$); Anal. Calcd for $C_{21}H_{18}FNO_4$ C 68.66, H 4.94, N 3.81; Found C 68.40, H 5.21, N 3.77.

2(XVIII): white solid; mp (Met-Temp) 197°−198 °C(uncorrected); analytical HPLC Symmetry C18 (4.6 × 75 mm, 3.5 μmparticle size), mobile phase 10 mM NH_4OAc/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 5.07 min, 98.74% purity; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.96−1.02 (m, 1H), 1.23−1.31 (m, 1H), 1.49−1.52 (m, 1H), 1.70−1.89 (m, 3H), 2.04−2.08 (m, 1H), 2.32−2.36 (m, 1H), 3.8 (s, 3H), 4.63 (s, 1H), 5.31−5.34 (m, 1H), 6.60−6.64 (m, 1H), 6.80−6.85 (m, 1H), 6.97−6.99 (d, J = 8.72, 2H), 7.06−7.04 (d, J = 8.6, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.44, 22.17, 31.31, 33.26, 54.73, 55.11, 104.22, 109.47, 112.87, 113.25, 114.29, 125.08, 131.89, 132.93, 143.17, 153.97, 156.28, 158.76, 173.86; LCMS (UV) 354.2 (M + H$^+$); FABMS 354 [Calcd for $C_{21}H_{21}FNO_3$ 354.39 (M + H$^+$)].

2(XIX): white solid; mp (Met-Temp) 180°−181 °C (uncorrected); analytical HPLC Hypersil BDS C18 (4.6 × 250 mm, 5 μmparticle size), mobile phase 0.1%TFA/CH_3OH linear gradient over 28 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 12.34 min, 92.74% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22−1.30 (m, 1H), 1.44−1.61 (m, 2H), 1.73−1.92 (m, 3H), 2.21−2.25 (m, 1H), 2.46−2.49 (m, 1H), 3.80 (s, 3H), 3.94 (s, 3H), 4.26 (s, 1H), 5.66−5.69 (m, 1H), 6.64−6.67 (m, 2H), 6.77−6.82 (m, 2H), 6.90−6.92 (d, J = 8.24, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.45, 22.20, 32.70, 33.08, 51.58, 55.13, 56.03, 103.43, 110.31, 111.01, 114.89, 122.07, 123.50, 124.66, 132.52, 141.90, 149.31, 155.65, 158.01, 173.95; Anal. Calcd for $C_{22}H_{22}FNO_4$ C 68.92, H 5.78, N 3.65; Found C 68.66, H 6.02, N 3.61.

2(XX): white solid; mp (Met-Temp) 84°−85 °C (uncorrected); analytical HPLC Zorbax Extend C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 10 mM. NH_4OAc/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 2.93 min, 97.59% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82−1.86 (m, 4H), 2.27 (s, 3H), 2.62−2.67 (m, 4H), 3.79 (s, 3H), 5.49 (s, 1H), 6.72−6.77 (m, 3H), 6.87−6.88 (m, 1H), 7.09−7.12 (d, J = 10.68, 1H), 7.18−7.20 (d, J = 8.48, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.72, 20.77, 22.96, 23.08, 23.19, 46.19, 55.11, 102.61, 102.93, 110.26, 110.77, 111.14, 116.34, 118.61, 127.42, 127.86, 129.17, 131.84, 136.23, 138.18, 158.69,

177.72; LCMS (UV) 368.2 (M + H^+); Anal. Calcd for $C_{22}H_{22}FNO_3$ C 71.92, H 6.04, N 3.81; Found C 71.85, H 6.07, N 3.77.

2(XXI): yellow solid; mp (Met-Temp) 131 °C−132 °C (uncorrected); analytical HPLC Sunfire C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 10 mM NH_4OAc/CH_3OH linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 5.59 min, 97.24% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82−1.91 (m, 4H), 2.63 (m, 1H), 2.67−2.70 (m, 3H), 3.75(s, 3H), 6.24 (s, 1H), 6.75−6.80(m, 3H), 6.86−6.89(m, 1H), 6.95−6.98 (m, 1H), 7.09−7.12 (m, 1H), 7.24−7.28 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.97, 22.75, 22.85, 23.17, 55.49, 59.86, 103.21, 108.78, 109.04, 111.34, 113.23, 119.65, 121.62, 123.64, 128.74, 129.72, 130.04, 132.54, 137.58, 159.75, 192.27; LCMS (UV) 354.2 (M + H^+); Anal. Calcd for $C_{21}H_{20}FNO_3$ C 71.37, H 5.70, N 3.96; Found C 70.99, H 6.06; N 3.91.

2(XXII): brown semi solid; moisture sensitive; analytical HPLC Hypersil BDS C18 (4.6 × 250 mm, 5 μmparticle size), mobile phase 10 mM NH_4OAc/CH_3OH linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 14.98 min, 89.08% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81−1.93 (m, 4H), 2.46−2.50 (m, 1H), 2.62−2.71 (m, 3H), 3.98 (m, 1H), 6.28 (s, 1H), 6.73−6.78 (m, 1H), 6.93−6.96 (m, 1H), 7.10−7.13 (m, 1H), 7.20−7.22 (m, 1H), 7.33−7.39 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.92, 22.70, 29.59, 31.54, 59.88, 102.90, 103.13, 108.70, 108.95, 111.18, 127.29, 128.29, 128.60, 132.48, 134.05, 137.56, 174.62; LCMS (UV) 324.2 (M + H^+); Anal. Calcd for $C_{20}H_{18}FNO_2$ C 74.29, H 5.61, N 4.33; Found C 73.92, H 5.37, N 4.34.

2(XXIII): white solid; mp (Met-Temp) 197°−199 °C (uncorrected); analytical HPLC Symmetry C18 (4.6 × 75 mm, 3.5 μmparticle size), mobile phase 10 mM NH_4OAc/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 5.25 min, 91.77% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38−1.50 (m, 2H), 1.54−1.61 (m, 1H), 1.70−1.73(m, 1H), 1.79−1.90 (m, 2H), 2.04 (s, 3H), 2.20−2.23 (m, 1H), 2.46−2.50 (m, 1H), 3.87 (s, 3H), 4.26 (s, 1H), 5.63(s, 1H), 6.63−6.65 (d, J = 7.88, 1H), 6.87−6.89 (d, J = 7.88, 1H), 6.92−6.94 (d, J = 8.72, 2H), 7.09−7.12 (d, J = 8.68, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.62, 20.77, 22.36, 31.92, 32.83, 54.80, 55.38, 103.29, 109.74, 113.39, 124.97, 127.38, 128.63, 128.71, 131.29, 132.23, 143.46, 159.45, 174.54; LCMS (UV) 350.2 (M + H^+); Anal. Calcd for $C_{22}H_{23}NO_3$ C 75.62, H 6.63, N 3.99; Found C 75.24, H 6.80, N 3.92.

2(XXIV): white solid; mp (Met-Temp) 205 °C−206 °C (uncorrected); analytical HPLC Hypersil BDS C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 0.1%TFA/CH_3OH linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 5.44 min, 99.76% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25−1.30 (m, 1H), 1.42−1.58 (m, 2H) 1.69−1.73 (m, 1H), 1.79−1.90 (m, 2H), 2.18 (s, 3H), 2.23−2.27 (m, 1H), 2.50−2.53 (m, 1H), 4.24 (s, 1H), 5.81−5.83 (d, J = 7.52, 1H), 5.99−6.03 (m, 2H), 6.52−6.56 (m, 1H), 6.65−6.69 (m, 2H), 6.83−6.85 (d, J = 7.88, 1H),6.90−6.92 (d, J = 7.48, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.57, 19.49, 22.29, 32.80, 33.30, 51.68, 55.08, 101.11, 102.74, 107.87, 111.46, 119.29, 119.63, 123.92, 124.53, 126.28, 129.35, 130.28, 144.45, 147.26, 147.32, 174.18; LCMS (UV) 364.2 (M + H^+); Anal. Calcd for $C_{22}H_{21}NO_4$ C 72.71, H 5.82, N 3.85; Found C 72.57, H 5.71, N 3.77.

2(XXV): white solid; mp (Met-Temp) 232°−233 °C (uncorrected); analytical HPLC Zorbax Extend C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 10 mM NH_4OAc/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 3.04 min, 99.78% purity; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.49−1.52 (m, 1H), 1.62−1.70 (m, 3H), 2.24−2.29 (m, 1H), 2.41 (s, 3H), 2.68 (m, 2H), 2.83−2.87 (m, 1H), 6.24 (s, 1H), 6.62−6.64 (d, J = 7.4, 1H), 6.75−6.77 (d, J = 7.44, 1H), 6.99−7.01 (d, J = 7.12, 1H), 7.38−7.41 (m, 1H), 7.52−7.59 (m, 2H), 7.82−7.84 (d, J = 8.16, 1H), 7.96−8.00 (m, 2H), 10.68 (s, 1H), 12.70 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 16.68, 22.23, 22.62, 23.07, 23.37, 50.46, 108.00, 118.51, 118.94, 120.60, 122.87, 125.44, 125.69, 126.35, 126.49, 126.65, 127.42, 128.83, 131.36, 133.49, 134.81, 135.46, 136.13, 174.28; LCMS (UV) 370.2 (M + H^+); Anal. Calcd for $C_{25}H_{23}NO_2$ C 81.27, H 6.27, N 3.79; Found C 81.34, H 6.32, N 3.83.

2(XXVI): white solid; mp (Met-Temp) 87°−88 °C (uncorrected); analytical HPLC Zorbax Extend C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 0.1%TFA/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 4.30 min, 96.10% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.84−1.92 (m, 4H), 2.27 (s, 3H), 2.42 (s, 3H), 2.65−2.67 (m, 2H), 2.72−2.75 (m, 2H), 3.77 (s, 3H), 5.24 (s, 1H), 6.67−6.72 (m, 1H), 6.74−6.76 (m, 1H), 6.82 (s, 1H), 7.01−7.03 (d, J = 8.6, 2H), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.70, 19.77, 20.09, 21.02, 23.21, 23.26, 53.23, 55.13, 110.95, 111.06, 115.85, 116.20, 116.38, 119.64, 122.82, 127.48, 128.39, 129.52, 129.81, 134.40, 137.85, 158.44, 178.59. LCMS (UV) 364.2 (M + H^+); Anal. Calcd for $C_{23}H_{25}NO_3$ C 76.01, H 6.93, N 3.85; Found C 75.95, H 6.98, N 3.86.

2(XXVII): white semi solid; moisture sensitive; analytical HPLC YMC Pack Pro C18 (4.6 × 250 mm, 5 μmparticle size), mobile phase 0.1%TFA/CH_3CN linear gradient over 45 min, with a flow of 0.7 mL/min, one peak detected by ELS and UV at R_t = 28.57 min, 95.19% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37−1.73 (m, 3H), 1.80−1.91 (m, 2H), 2.02−2.08 (m, 1H), 2.19 (s, 3H), 2.21−2.25 (m, 1H), 2.48−2.53 (m, 1H), 3.86 (s, 3H), 4.26 (s, 1H), 5.69−5.71 (d, J = 7.52, 1H), 6.48−6.52 (m, 1H), 6.89 (s, 1H), 6.91−6.94 (d, J = 8.6, 2H), 7.09−7.11 (d, J = 8.52, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.62, 19.60, 22.37, 31.92, 32.91, 55.09, 55.32, 102.72, 113.5, 119.27, 119.60, 124.06, 124.84, 129.34, 130.55, 132.16, 144.54, 159.35, 174.49; LCMS (UV) 350.4 (M + H^+); Anal. Calcd for $C_{22}H_{23}NO_3$ C 75.62, H 6.63, N 4.01; Found C 75.82, H 6.71, N 4.02.

2(XXVIII): brown solid; mp (Met-Temp) 88 °C-89 °C (uncorrected); analytical HPLC Hypersil BDS C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 10 mM NH_4OAc/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 4.12 min, 93.52% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42−1.89

(m, 5H), 2.04−2.11 (m, 1H), 2.43−2.47 (m, 1H), 2.65 (s, 3H), 2.74 (m, 1H), 3.75 (s, 3H), 6.73−6.78 (m, 2H), 6.84−6.86 (m, 2H), 6.87−6.97 (m, 2H), 7.21−7.24 (m, 1H), 7.35−7.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.67, 21.06, 22.72, 23.55, 29.70, 55.27, 60.69, 112.38, 113.10, 113.20, 116.26, 119.40, 119.70, 121.63, 123.65, 125.33, 128.77, 129.58, 136.71, 137.45, 159.71, 192.29; LCMS (UV) 350.2 (M + H$^+$); Anal. Calcd for $C_{22}H_{23}NO_3$ C 75.62, H 6.63, N 4.01; Found C 75.40, H 6.47; N 4.05.

2(XXIX): white solid; mp (Met-Temp) 184°−185 °C (uncorrected); analytical HPLC Zorbax Extend C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 10 mM NH_4OAc/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 4.69 min, 96.93% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22−1.30 (m, 1H), 1.45−1.58 (m, 2H), 1.71−1.74 (m, 1H), 1.79−1.91 (m, 2H), 2.18 (s, 3H), 2.23 (m, 1H), 2.50−2.53 (m, 1H), 3.93 (s, 3H), 4.24 (s, 1H), 5.69−5.71 (d, J = 7.52, 1H), 6.49−6.53 (m, 1H), 6.90−6.99 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.59, 19.54, 22.41, 32.78, 33.48, 51.27, 55.19, 56.31, 103.68, 112.88, 118.69, 119.55, 119.87, 123.76, 125.62, 126.96, 129.56, 130.23, 144.41, 147.44, 150.58, 153.02, 174.13; LCMS (UV) 368.2 (M + H$^+$); Anal. Calcd for $C_{22}H_{22}FNO_3$ C 71.92, H 6.04, N 3.81; Found C 71.98, H 6.09, N 3.83.

2(XXX): white solid; mp (Met-Temp) 194°−195 °C (uncorrected); analytical HPLC Zorbax Extend C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 0.1% TFA/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 4.57 min, 98.99% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23−1.29 (m, 1H), 1.44−1.45 (m, 1H), 1.53−1.57 (m, 1H), 1.68 (m, 1H), 1.79−1.87 (m, 2H), 2.20 (m, 1H), 2.25 (s, 3H), 2.44−2.48 (m, 1H), 4.21 (s, 1H), 5.84−5.86 (d, J = 7.64, 1H), 5.99−6.03 (m, 2H), 6.41−6.43 (d, J = 7.68, 1H), 6.54−6.57 (m, 2H), 6.64−6.69 (m, 2H), 6.82−6.85 (d, J = 7.92, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.56, 21.48, 22.32, 32.77, 33.49, 51.78, 54.65, 101.13, 102.68, 107.20, 107.93, 108.39, 110.85, 111.11, 120.42, 124.56, 126.23, 128.17, 128.41, 138.50, 146.09, 147.03, 174.28. LCMS (UV) 364.2 (M + H$^+$); Anal. Calcd for $C_{22}H_{21}NO_4$ C 72.71, H 5.82, N 3.85; Found C 72.80, H 5.78, N 3.83.

2(XXXI): white solid; mp (Met-Temp) 148°−149 °C (uncorrected); analytical HPLC Zorbax Extend C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 0.1% TFA/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 4.73 min, 98.14% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23−1.27 (m, 1H), 1.42−1.45 (m, 1H), 1.54−1.59 (m, 2H), 1.69−1.73 (m, 1H), 1.82−1.90 (m, 1H), 2.20 (m, 1H), 2.46 (s, 3H), 2.49 (m, 1H), 3.86 (s, 3H), 4.24 (s, 1H), 5.73−5.75 (d, J = 7.64, 1H), 6.37−6.42 (m, 1H), 6.53−6.56 (m, 1H), 6.85−6.87 (d, J = 8.68, 1H), 6.91−6.93 (d, J = 8.68, 1H), 7.06−7.03 (d, J = 8.6, 1H), 7.09−7.12 (d, J = 8.68, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.49, 19.63, 21.49, 22.44, 32.81, 51.34, 55.33, 107.22, 110.87, 113.50, 114.15, 120.44, 123.17, 124.93, 126.31, 128.44, 132.12, 138.45, 146.05, 146.97, 159.33, 174.46; LCMS (UV) 350.2 (M + H$^+$); Anal. Calcd for $C_{22}H_{23}NO_3$ C 75.62, H 6.63, N 4.01; Found C 75.69, H 6.57, N 4.05.

2(XXXII): white solid, mp (Met-Temp) 189°−190 °C (uncorrected), analytical HPLC Hypersil BDS C18 (4.6 × 50 mm, 5 μmparticle size), mobile phase 10 mM NH_4OAc/CH_3CN linear gradient over 12 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 4.30 min, 97.73% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20−1.28 (m, 2H), 1.42−1.46 (m, 1H), 1.52−1.59 (m, 1H), 1.69−1.78 (m, 1H), 1.79−1.89 (m, 1H), 2.21 (m, 1H), 2.24 (s, 3H), 2.45−2.48 (m, 1H), 3.65 (s, 3H), 3.93 (s, 3H), 4.23 (s, 1H), 5.79−5.81 (d, J = 7.68, 1H), 6.37−6.38 (d, J = 7.16, 1H), 6.55 (s, 1H), 6.62 (s, 1H), 6.76−6.79 (m, 1H), 6.86−6.88 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.56, 22.43, 22.27, 32.77, 33.36, 51.71, 54.61, 55.85, 103.09, 110.47, 110.78, 114.36, 120.12, 123.35, 125.21, 126.49, 128.19, 138.51, 146.05, 148.25, 148.79, 174.35; LCMS (UV) 380.2 (M + H$^+$); Anal. Calcd for $C_{23}H_{25}NO_4$ C 72.80, H 6.64, N 3.69; Found C 72.88, H 6.69, N 3.63.

3(I): white solid; mp (Met-Temp) 142°−144 °C (uncorrected); analytical HPLC Hypersil BDS C18 (250 × 4.6) mm, 5 μmparticle size), mobile phase 0.1%. HCOOH in H_2O/CH_3OH linear gradient over 38 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at R_t = 16.53 min, 99.28% purity; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46−1.51 (m, 1H), 1.78−1.87 (m, 1H), 2.02−2.13 (m, 2H), 2.35−2.45 (m, 1H), 2.52 (s, 3H), 2.60−2.65 (m, 1H), 2.94−3.02 (m, 1H), 4.45 (s, 1H), 5.53−5.57 (d, J = 8.76, 1H), 6.66−6.70 (m, 1H), 6.78−6.84 (m, 1H), 7.11−7.14 (d, J = 8.31, 2H), 7.22−7.36 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.68, 29.82, 33.29, 37.72, 40.96, 51.69, 56.12, 103.10, 110.66, 113.75, 114.00, 114.95, 115.19, 126.22, 126.85, 128.56, 128.76, 131.27, 132.12, 139.25, 141.78, 144.01, 155.76, 158.12, 173.34; LCMS (UV) 446.2 (M + H$^+$); Anal. Calcd for $C_{27}H_{24}FNO_2S$ C 72.78, H 5.43, N 3.14; Found C, 72.87, H 5.48, N 3.20.

3(II): white solid; mp (Met-Temp) 251°−252 °C (uncorrected); analytical HPLC Hypersil BDS C18 (50 × 4.6) mm, 5 μmparticle size, mobile phase 0.1% TFA in H_2O/CH_3OH linear gradient over 14 min, with a flow of 1 mL/min, one peak detected by ELS and UV at R_t = 5.71 min, 99.39% purity; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.38−2.42 (m, 1H), 2.51 (s, 3H), 2.55−2.57 (m, 1H), 2.87−2.91 (m, 1H), 2.97−3.05 (m, 1H), 3.16−3.19 (m, 1H), 3.31−3.35 (m, 1H), 5.21 (s, 1H), 7.05−7.07 (d, J = 6.32, 1H), 7.21−7.25 (m, 6H), 7.38−7.42 (m, 1H), 7.46−7.49 (m, 2H), 7.63−7.65 (d, J = 7.68, 2H), 10.95 (s,1H), 12.75 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 15.23, 21.54, 32.88, 33.84, 42.25, 50.40, 79.65, 102.98, 103.23, 106.34, 111.64, 120.48, 120.66, 123.30, 126.24, 126.32, 126.52, 128.52, 129.46, 129.82, 132.95, 135.28, 135.68, 137.20, 140.56, 154.21, 156.53, 173.74; LCMS (UV) 471.2 (M + H$^+$); Anal. Calcd for $C_{28}H_{23}FN_2O_2S$ C 71.47, H 4.93, N 5.95; Found C, 71.52, H 4.95, N 5.97.

3(III): white solid; mp (Met-Temp) 148°−150 °C (uncorrected); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.40−2.48 (m, 1H), 2.49−2.53 (m, 1H), 2.91−2.98 (m, 1H), 3.01 (m, 1H), 3.12−3.16 (m, 1H), 3.29−3.33 (m, 2H), 5.15 (s, 1H), 5.99 (s, 2H), 6.75−6.78 (d, J = 8.01, 1H), 6.78−6.89 (m, 2H),

7.04−7.06 (d, $J = 6.33$, 1H), 7.18−7.21 (d, $J = 11.04$, 1H), 7.35−7.48 (m, 3H), 7.61−7.64 (d, $J = 7.68$, 2H), 10.92 (s, 1H), 12.65 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.06, 32.36, 33.38, 41.78, 49.94, 100.97, 102.41, 102.73, 105.84, 105.89, 108.08, 109.11, 110.97, 120.16, 121.95, 122.73, 125.71, 128.01, 128.95, 132.07, 132.41, 134.75, 140.10, 146.18, 147.25, 153.29, 156.37, 173.31; LCMS (UV) 469.2 ($M + H^+$); Anal. Calcd for $C_{28}H_{21}FN_2O_4$ C 71.79, H 4.52, N 5.98; Found C, 71.66, H 4.59, N 5.91.

3(IV): white solid; mp (Met-Temp) 136°−138 °C (uncorrected); analytical HPLC Hypersil BDS C18 (250 × 4.6) mm, 5 μmparticle size), mobile phase 0.1% HCOOH in H_2O/CH_3OH linear gradient over 38 min, with a flow of 0.8 mL/min, one peak detected by ELS and UV at $R_t = 14.91$ min, 99.75% purity; ^{1}H NMR ($CDCl_3$, 40 MHz) δ 1.36−1.39 (m, 2H), 1.69−1.71 (m, 2H), 2.01 (m, 1H), 2.27−2.30 (m, 1H), 2.52 (m, 1H), 2.56 (s, 3H), 4.32 (s, 1H), 6.67−6.72 (m, 3H), 6.85−6.91 (m, 2H), 7.12−7.19 (m, 3H), 7.27−7.31 (d, $J =$ 8.32, 2H), 7.39−7.41 (d, $J = 8.8$, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.91, 28.14, 34.37, 37.82, 41.25, 55.10, 56.78, 110.38, 110.99, 115.14, 115.38, 126.47, 126.53, 127.04, 128.43, 129.92, 131.06, 137.58, 137.66, 139.18, 140.63, 144.53, 156.83, 159.20, 174.89; LCMS (UV) 446.2 ($M + H^+$); Anal. Calcd for $C_{27}H_{24}FNO_2S$ C 72.78, H 5.43, N 3.14; Found C, 72.85, H 5.39, N 3.22.

3(VI): white solid; mp (Met-Temp) 131°−132 °C (uncorrected); analytical HPLC Hypersil BDS C18 (50 × 4.6) mm, 5 μmparticle size, mobile phase 0.1% TFA in H_2O/CH_3OH linear gradient over 14 min, with a flow of 1.0 mL/min, one peak detected by ELS and UV at $R_t = 6.03$ min, 99.07% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.05−2.22 (m, 2H), 2.72−2.87 (m, 3H), 2.96−3.12 (m, 2H), 5.33 (s, 1H), 5.94 (s, 2H), 6.77−6.87 (m, 3H), 7.07−7.15 (m, 2H), 7.23−7.39 (m, 5H), 7.70 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.33, 29.05, 29.62, 30.17, 40.99, 49.74, 101.11, 102.95, 103.20, 108.31, 109.34, 110.71, 110.75, 119.23, 126.27, 126.96, 127.25, 128.47, 131.10, 132.32, 136.02, 146.30, 146.98, 147.89, 154.35, 156.69, 173.02; LCMS (UV) 444.2 ($M + H^+$); Anal. Calcd for $C_{27}H_{22}FNO_4$ C 73.13, H 5.00, N 3.16; Found C, 73.01, H 5.05, N 3.13.

3(VI): white solid; mp (Met-Temp) 165°−167 °C (uncorrected); analytical HPLC Hypersil BDS C18 (50 × 4.6 mm), mobile phase 0.1% TFA in H_2O/CH_3OH linear gradient over 14 min, with a flow of 1 mL/min, one peak detected by ELS and UV at $R_t = 6.00$ min, 94.8% purity; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.04 (m, 2H), 2.64−2.67 (m, 1H), 2.72−2.91 (m, 3H), 2.96−2.99 (m, 1H), 3.74 (s, 3H), 5.16 (s, 1H), 6.91−6.93 (d, $J = 8.4$, 2H), 6.97−6.99 (m, 1H), 7.08−7.10 (m, 2H), 7.21−7.23 (m, 3H), 7.29−7.33 (m, 5H), 10.72 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 23.00, 29.07, 29.96, 49.59, 55.12, 102.13, 102.37, 108.56, 110.84, 113.87, 119.69, 119.88, 126.01, 126.11, 126.97, 128.39, 129.88, 130.44, 132.34, 136.22, 146.58, 146.61, 153.67, 155.99, 158.27, 173.71; LCMS (UV) 430.2 ($M + H^+$); Anal. Calcd for $C_{27}H_{24}FNO_3$ C 75.51, H 5.63, N 3.26; Found C, 75.69, H 5.68, N 3.23.

3(VII): white solid; mp (Met-Temp) 202°−204 °C (uncorrected); analytical HPLC Hypersil BDS C18 (50 × 4.6) mm, 5 μmparticle size), mobile phase 0.1% TFA in H_2O/CH_3OH linear gradient over 14 min, with a flow of 1 mL/min, one peak detected by ELS and UV at $R_t = 5.35$ min, 94.14% purity; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.09−1.12 (m, 1H), 1.52−1.61 (m, 1H), 1.81−1.84 (m, 1H), 2.07−2.14 (m, 2H), 2.50 (s, 3H), 2.55 (m, 1H), 3.15−3.21 (m, 1H), 4.91 (s, 1H), 5.33−5.35 (d, $J = 8.88$, 1H), 6.67−6.69 (d, $J = 8.28$, 3H), 6.83−6.88 (m, 1H), 7.04−7.11 (m, 4H), 7.33−7.35 (s, $J = 8.12$, 2H), 9.19 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 15.04, 30.15, 32.41, 35.33, 42.38, 50.77, 56.33, 104.49, 110.19, 113.01, 113.34, 114.76, 115.06, 115.66, 125.71, 128.09, 129.98, 131.82, 133.07, 135.56, 138.43, 143.62, 154.15, 156.18, 157.24, 173.88; LCMS (UV) 462.2 ($M + H^+$); Anal. Calcd for $C_{27}H_{24}FNO_3S$ C 70.26, H 5.24, N 3.03; Found C, 70.33, H 5.28, N 3.07.

3(VIII): brown solid; mp (Met-Temp) 122°−124 °C (uncorrected); analytical HPLC Hypersil BDS (250 × 4.6) mm, 5 μmparticle size, mobile phase 0.1% HCOOH in H_2O/CH_3OH linear gradient over 30 min, with a flow of 1.0 mL/min, one peak detected by ELS and UV at $R_t = 16.67$ min, 92.05% purity; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.92−2.09 (m, 4H), 2.66−2.79 (m, 2H), 2.93−2.96 (m, 1H), 6.84−6.85 (m, 1H), 7.06−7.54 (m, 12H), 7.69−7.83 (m, 1H), 7.94−7.99 (m, 2H), 14.2 (br, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 22.98, 23.46, 29.04, 29.95, 59.56, 79.24, 102.51, 108.53, 109.99, 110.69, 123.24, 123.45, 125.59, 126.09, 126.67, 126.73, 126.96, 127.45, 127.54, 127.63, 128.32, 128.80, 129.16, 131.51, 131.72, 133.51, 138.18, 146.36, 155.85, 158.16, 174.90. LCMS (UV) 450.2 ($M + H^+$); Anal. Calcd for $C_{30}H_{24}FNO_2$ C 80.16, H 5.38, N 3.12; Found C, 80.25, H 5.42, N 3.16.

3(IX): white solid; mp (Met-Temp) 138°−140 °C (uncorrected); analytical HPLC Hypersil BDS C18 (50 × 4.6) mm, 5 μmparticle size, mobile phase 0.1% TFA in H_2O/CH_3OH linear gradient over 14 min, with a flow of 1 mL/min, one peak detected by ELS and UV at $R_t = 5.88$ min, 95.62% purity; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.96−2.07 (m, 4H), 2.71−2.80 (m, 2H), 2.97−3.01 (m, 1H), 6.72−6.92 (m, 4H), 7.07−7.27 (m, 4H), 7.40−7.69 (m, 5H), 7.90−7.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.25, 23.69, 29.27, 30.45, 39.24, 59.58, 103.42, 109.16, 109.42, 115.35, 122.56, 124.85, 126.20, 127.00, 127.36, 128.04, 128.50, 129.13, 129.48, 130.07, 131.56, 133.37, 133.52, 133.87, 135.45, 136.77, 137.74, 138.48, 153.82, 156.79, 174.27. LCMS (UV) 466.2 ($M + H^+$); Anal. Calcd for $C_{30}H_{24}FNO_3$ C 77.40, H 5.20, N 3.01; Found C, 77.31, H 5.13, N, 3.08.

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Supporting Information Available. Detailed experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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