Highly Regioselective Synthesis of Substituted Pyrroles Utilizing Low-Valent Titanium Reagent

Daqing Shi,*[a,b] Guolan Dou,[b] Chunling Shi,[c] Zhengyi Li,[b] Shun-Jun Ji[a]

[a] College of Chemistry and Chemical Engineering, Key Laboratory of Organic Synthesis of Jiangsu Province, Suzhou University, Suzhou 215123, P. R. of China

[b] College of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou 221116, P. R. of China

[c] College of Chemistry and Chemical Engineering, Southeast University, Nanjing 210009, P. R. of China
E-mail: dqshi@263.net

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Abstract: A short and efficient synthesis of substituted pyrroles was accomplished in good yields via the novel coupling cyclization reaction of 1,3-diketones with imines promoted by low-valent titanium reagent. High regioselectivity was achieved and the structures of two of the products were confirmed by X-ray diffraction studies.

Key words: low-valent titanium, pyrrole, regioselectivity

The pyrrole ring is one of the fundamental heterocycles. It is a widely distributed structural unit in a variety of natural and biologically important molecules such as porphyrins, bile pigments, coenzymes, and alkaloids.[1] Therefore, several methods for the synthesis of substituted pyrroles have been described in the literature;[2] the Knorr[3] method being the classical method. Recently, conjugate addition reactions have been used for the synthesis of polysubstituted pyrroles.[4] These compounds can also be prepared from transition-metal intermediates,[5] reductive coupling,[6] aza-Wittig reactions,[7] and other multi-step operations.[8] For example, Rao et al.[9] have reported a facile one-pot synthesis of polyarylpyrroles from but-2-ene-1,4-diones and but-2-yne-1,4-diones under microwave irradiation. The synthesis of pyrroles via samarium-catalyzed three-component coupling reaction of aldehydes, amines and nitroalkanes was carried out by Ishii et al.[10] Ranu et al.[11] reported the one-pot synthesis of pyrroles via three-component condensation of a carbonyl compound, and amine and a nitroalkene in a molten ammonium salt. Ashwin et al.[12] have reported the synthesis of highly substituted pyrroles utilizing a one-pot sila-Stetter/Paal–Knorr strategy, and Bimal et al.[13] have conducted a simple synthesis of substituted pyrroles using iodine-catalyzed and montmorillonite KSF-clay-induced modified Paal–Knorr method. The synthesis of pyrroles on the surface of silica gel and alumina under microwave irradiation has been described by Ranu et al.[14] Some one-pot pyrroles synthesis starting from imines have been known recently. For example, Gao et al. reported the synthesis of substituted pyrroles from alkynes, imines and carbon monoxide via an organotitanium intermediate[15] as well as from alkynes, nitriles, imines, and titanium-imine complexes.[16] Lee et al. carried out a one-pot synthesis of substituted pyrroles from propargylic dithioacetals,[17] and Katritzky et al. have reported the synthesis of 1,2,3-triarylpyrroles from 1-benzylbenzotriazoles via [1+2+2] annulation.[18] However, these are not always satisfactory with respect to ease of operation, yield, reaction time, general applicability, and all the products have no regioselectivity. For this reason, we became interested in developing a novel and convenient synthetic methods for the preparation of pyrrole derivatives. Our initial studies showed that successful synthesis of substituted pyrroles from 1,3-diketones and imines could be performed at room temperature while induced by low-valent titanium ($TiCl_4$/Zn system);[19] however, the only 1,3-diketone used was dibenzoylmethane, the products had to be purified by column chromatography, and there was no regioselectivity observed. Here, we report the full results of our investigations utilizing low-valent titanium reagent to broader the scope of this method.

In a preliminary study, dibenzoylmethane (**1**) and imine **2a** were used to define the reaction conditions for the preparation of substituted pyrroles (Scheme 1).

First, different low-valent titanium system were investigated as reductive reagent for this reaction (Table 1, entries 1–8); the $TiCl_4$/Sm (1:1) system gave the best result of synthesis of **3a** (92%) (entry 5). Further optimization of the reaction conditions revealed that the use of four equivalents of $TiCl_4$/Sm can give superior results than those under the other reaction conditions (entries 9–12).

In order to apply this reaction to library synthesis, various kinds of 1,3-diketones and imines were subjected to give the corresponding 1,2,3,5-tetrarylpyrroles. When symmetrical diaroylmethane **1** and imine **2** were treated with low-valent titanium ($TiCl_4$/Sm), the coupling cyclization products **3** were obtained and purified by recrystallization from 95% ethanol in good yields (Scheme 2). Table 2 summarizes our results on the coupling cyclization of **1** with **2**.

Table 2 shows that the $TiCl_4$/Sm system could efficiently promote the reductive cyclization of 1,3-diketones and imines to give 1,2,3,5-tetrarylpyrroles with different substitution patterns. The self-coupling products of 1,3-diketone and imine-substituted 1,3-cyclohexene and substituted ethylenediamine were not obtained. Unfortunately, when pentane-2,4-dione or ethyl acetoacetate and

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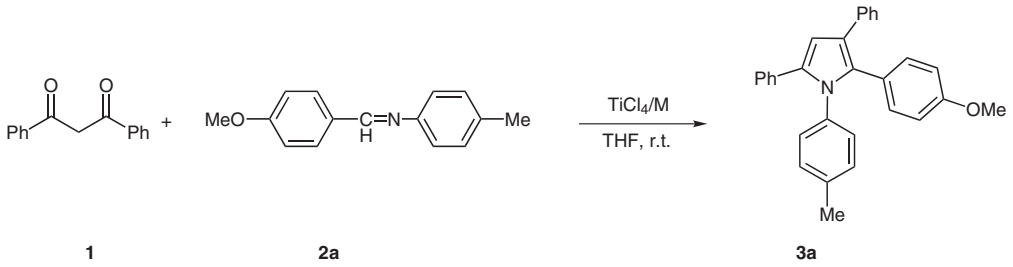
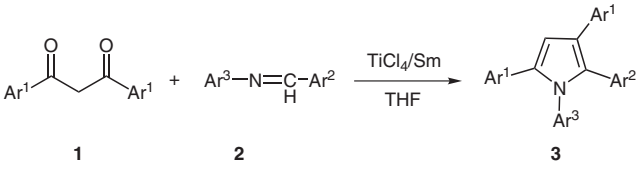


Scheme 1

Table 1 Optimization of Metal and Ratio of Low-Valent Titanium in the Synthesis of **3a**

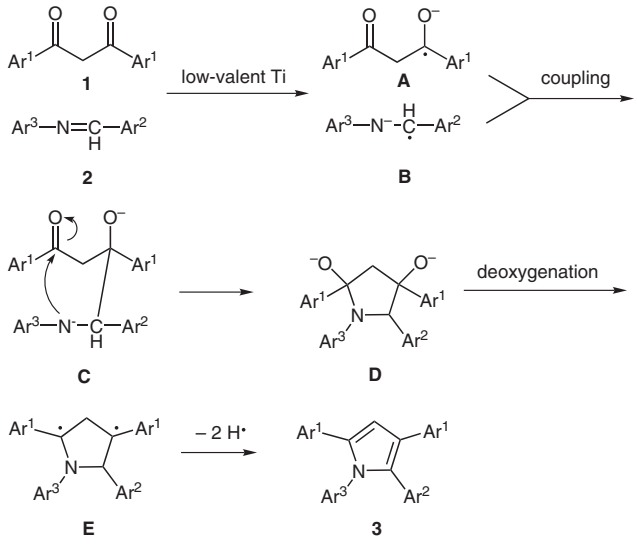
Entry	$TiCl_4$/M system	Ratio[a]	Yield (%)[b]
1	$TiCl_4$/Zn (1:2)	1:4	81
2	$TiCl_4$/Mg (1:2)	1:4	57
3	$TiCl_4$/Al (1:1)	1:4	38
4	$TiCl_4$/Fe (1:2)	1:4	20
5	$TiCl_4$/Sm (1:1)	1:4	92
6	$TiCl_4$/Sm (1:0.5)	1:4	0
7	$TiCl_4$/Sm (1:2)	1:4	86
8	$TiCl_4$/Sm (1:3)	1:4	85
9	$TiCl_4$/Sm (1:1)	1:1	37
10	$TiCl_4$/Sm (1:1)	1:2	74
11	$TiCl_4$/Sm (1:1)	1:3	81
12	$TiCl_4$/Sm (1:1)	1:5	91

[a] Ratio of **1** and $TiCl_4$.
[b] Isolated yield.



Scheme 2

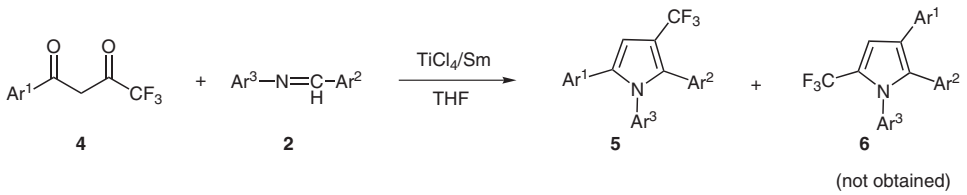
2a were treated with $TiCl_4$/Sm system under the same reaction conditions they failed to give the desired pyrrole products and only the self-coupling product of imine was obtained. It seems that 1,3-diketones should be 1,3-diaroylmethane, otherwise, the reductive cross-coupling process could not take place.



Scheme 3

A plausible mechanistic pathway to pyrrole is illustrated in Scheme 3, although the details are still unclear. Titanium(IV) chloride is reduced by Sm dust to give a low-valent titanium species. In the initial step, an electron is transferred from low-valent titanium to 1,3-diketone **1** or imine **2** to give radical anions **A** and **B**, respectively, the two radical anions then couple to form the carbon–carbon bond and generate the intermediate **C**. The ring closing then takes place by nucleophilic addition to give the intermediate **D**, which deoxygenates to form radical **E**. The radical **E** loses two hydrogen atoms to form the pyrrole **3**.

However, when unsymmetrical 1,3-diketones bearing a CF_3 group **4** and imine **2** were treated with low-valent titanium ($TiCl_4$/Sm), only one coupling cyclization product **5** were obtained, while the other isomer **6** was not obtained (Scheme 4). The products were purified by recrystallization from 95% ethanol in good yields. Table 3 summarizes our results on the coupling cyclization of **4** and **2**.



Scheme 4

Table 2 Substituted Pyrroles **3** Prepared Using Low-Valent Titanium ($TiCl_4$/Sm)

Product	Ar^1	Ar^2	Ar^3	Yield (%)[a]
3a	Ph	4-$MeOC_6H_4$	4-MeC_6H_4	91
3b	Ph	4-MeC_6H_4	4-FC_6H_4	92
3c	Ph	4-ClC_6H_4	4-FC_6H_4	82
3d	Ph	4-$MeOC_6H_4$	4-$MeOC_6H_4$	89
3e	Ph	4-BrC_6H_4	4-$MeOC_6H_4$	76
3f	Ph	4-ClC_6H_4	3-Cl,4-$CH_3C_6H_3$	77
3g	Ph	4-MeC_6H_4	3-Cl,4-$CH_3C_6H_3$	90
3h	Ph	3,4-$OCH_2OC_6H_3$	3-Cl,4-$CH_3C_6H_3$	83
3i	Ph	3,4-$OCH_2OC_6H_3$	4-FC_6H_4	92
3j	Ph	4-BrC_6H_4	4-FC_6H_4	76
3k	Ph	3,4-$OCH_2OC_6H_3$	4-$MeOC_6H_4$	93
3l	Ph	4-BrC_6H_4	4-MeC_6H_4	76
3m	Ph	4-$MeOC_6H_4$	3-Cl,4-$CH_3C_6H_3$	93
3n	Ph	4-MeC_6H_4	3-ClC_6H_4	86
3o	Ph	4-BrC_6H_4	3-ClC_6H_4	79
3p	4-ClC_6H_4	4-MeC_6H_4	4-FC_6H_4	70
3q	4-ClC_6H_4	4-ClC_6H_4	4-FC_6H_4	80
3r	4-MeC_6H_4	4-MeC_6H_4	4-FC_6H_4	74
3s	4-MeC_6H_4	4-$MeOC_6H_4$	4-$MeOC_6H_4$	81
3t	4-MeC_6H_4	4-ClC_6H_4	4-FC_6H_4	75
3u	Ph	2-thienyl	4-MeC_6H_4	83
3v	Ph	2-thienyl	4-ClC_6H_4	78
3w	Ph	2-thienyl	4-BrC_6H_4	82
3x	Ph	2-thienyl	4-IC_6H_4	79

[a] Isolated yield.

Table 3 Trifluoromethyl-Substituted Pyrroles **5** Prepared Using Low-Valent Titanium ($TiCl_4$/Sm)

Product	Ar^1	Ar^2	Ar^3	Yield (%)[a]
5a	Ph	4-$MeOC_6H_4$	4-MeC_6H_4	97
5b	Ph	4-BrC_6H_4	4-ClC_6H_4	87
5c	Ph	4-ClC_6H_4	4-FC_6H_4	90
5d	Ph	4-BrC_6H_4	4-BrC_6H_4	78
5e	Ph	4-$MeOC_6H_4$	3-Cl,4-MeC_6H_3	85
5f	Ph	3,4-$OCH_2OC_6H_3$	4-$MeOC_6H_4$	92
5g	2-thienyl	4-BrC_6H_4	4-ClC_6H_4	90
5h	2-thienyl	4-ClC_6H_4	3-MeC_6H_4	89
5i	2-thienyl	3,4-$OCH_2OC_6H_3$	4-$MeOC_6H_4$	75
5j	2-thienyl	4-FC_6H_4	4-MeC_6H_4	93

[a] Isolated yield.

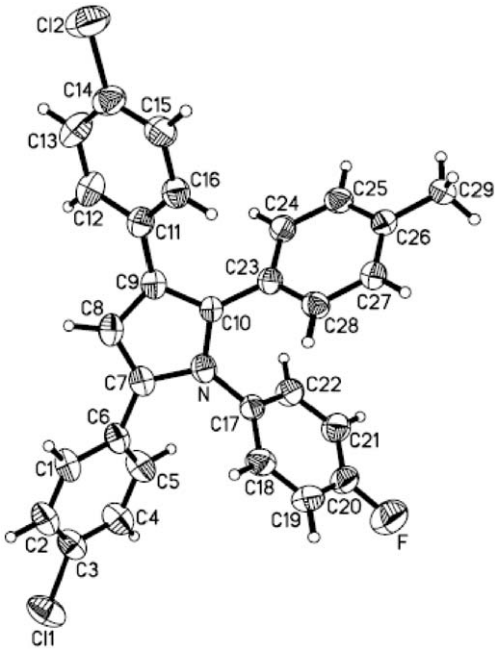


Figure 1 Molecular structure of **3p**

From Table 3, it can be seen that the reaction of aroyltrifluoroacetone and imine has high regioselectivity. Unfortunately, when other unsymmetrical 1,3-diketone such as benzoylacetone and imine **2a** were treated with $TiCl_4$/Sm system under the same reaction conditions, only a mixture of **5** and **6** (86:14) was obtained in 55% yield. It seems that only 1,3-diketones containing both aryl and CF_3 groups could give the high regioselectivity in this reaction.

The chemical structures of **3** and **5** have been established using spectroscopic data. The structures of products **3p** and **5d** have been confirmed by X-ray crystal structure analysis. The X-ray diffraction studies on a single crystal of **5d** indicate that the structures of products we obtained are 1,2,5-triaryl-3-trifluoromethylpyrroles not 1,2,3-triaryl-5-trifluoromethylpyrroles. The molecular structures of the products **3p**[20] and **5d**[21] are shown in Figure 1 and Figure 2, respectively.

In conclusion, a series of 1,2,3,5-tetrasubstituted pyrroles were synthesized via coupling cyclization of 1,3-diketones with imines induced by $TiCl_4$/Sm system. The products were only purified by recrystallization to give high purity. High regioselectivity was achieved and the structure of the products was confirmed by X-ray diffraction. This method has the advantages of high regioselectivity, easily available starting materials, short reaction time, high yields, and convenient manipulation.

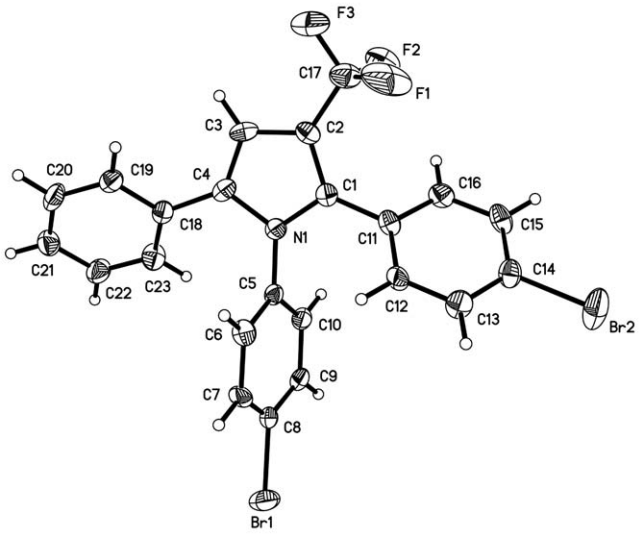


Figure 2 Molecular structure of **5d**

THF was distilled from sodium-benzophenone just prior to use. All reactions were conducted under N_2. Melting points are uncorrected. IR spectra were recorded on Tensor 27 spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR was determined on Bruker DPX-400 MHz spectrometer in DMSO-d_6 solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. Microanalyses were carried out on PerkinElmer 2400 II instruments. X-ray diffractions were recorded on a Siemens P4 or Smart-1000 diffractometer. MS were obtained on a HP 5973N GC-MS instrument using EI ionization. The starting material imines can be easily varied by condensation of aromatic aldehydes with different aromatic amines. 1,3-Diketones can be easily obtained by condensation of substituted ketones with different substituted ethyl acetates[22] or by bromination and hydrolysis from chalcone.[23]

Pyrroles 3 and 5; General Procedure

$TiCl_4$ (1.3 mL, 12 mmol) was added dropwise using a syringe to a stirred suspension of Sm powder (1.8 g, 12 mmol) in freshly distilled anhyd THF (15 mL) at r.t. under N_2. The mixture was refluxed for 2 h. The suspension of low-valent titanium reagent formed was cooled to r.t. and a solution of 1,3-diketone **1** or **4** (3 mmol) and imine **2** (3 mmol) in THF (5 mL) was added carefully. The mixture was stirred for 2 h at r.t. On completion of the reaction, most of the solvent was removed in vacuo. The residue was poured into aq 5% HCl (100 mL) and extracted with DCE (4 × 30 mL). The combined organic layers were washed with H_2O (4 × 30 mL), dried (Na_2SO_4), and the solvent was removed to give the crude product, which was purified by recrystallization from 95% EtOH to give pure **3** or **5**.

2-(4-Methoxyphenyl)-3,5-diphenyl-1-(*p*-tolyl)-1*H*-pyrrole (3a)

Solid; mp 170–171 °C.

IR (KBr): 3031, 2834, 1601, 1574, 1559, 1510, 1486, 1467, 1440, 1415, 1399, 1377, 1324, 1302, 1288, 1247, 1211, 1174, 1108, 1034, 836, 797, 765, 748, 696 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.24–7.09 (m, 10 H, ArH), 7.06–7.02 (m, 4 H, ArH), 6.97 (d, *J* = 8.4 Hz, 2 H, ArH), 6.77 (d, *J* = 8.4 Hz, 2 H, ArH), 6.71 (s, 1 H, H-4), 3.69 (s, 3 H, CH_3O), 2.23 (s, 3 H, CH_3).

MS: *m*/*z* = 415 (M^+, 100%).

Anal. Calcd for $C_{30}H_{25}NO$: C, 86.71; H, 6.06; N, 3.37. Found: C, 86.95; H, 5.93; N, 3.58.

1-(4-Fluorophenyl)-3,5-diphenyl-2-(*p*-tolyl)-1*H*-pyrrole (3b)

Solid; mp 168–170 °C.

IR (KBr): 3061, 3027, 2914, 1601, 1573, 1503, 1478, 1450, 1407, 1377, 1335, 1264, 1218, 1180, 1151, 1112, 1093, 1068, 1027, 1012, 945, 913, 844, 816, 763, 746, 712, 699 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.26–6.98 (m, 18 H, ArH), 6.76 (s, 1 H, H-4), 2.24 (s, 3 H, CH_3).

MS: *m*/*z* = 403 (M^+, 100%).

Anal. Calcd for $C_{29}H_{22}FN$: C, 86.32; H, 5.50; N, 3.47. Found: C, 86.11; H, 5.63; N, 3.29.

2-(4-Chlorophenyl)-1-(4-fluorophenyl)-3,5-diphenyl-1*H*-pyrrole (3c)

Solid; mp 200–202 °C.

IR (KBr): 3060, 2917, 2861, 1614, 1507, 1405, 1375, 1330, 1216, 1183, 1150, 1111, 1091, 1020, 844, 816, 789, 737 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.30–7.09 (m, 18 H, ArH), 6.77 (s, 1 H, H-4).

Anal. Calcd for $C_{28}H_{19}ClFN$: C, 79.33; H, 4.52; N, 3.30. Found: C, 79.60; H, 4.33; N, 3.45.

1,2-Bis(4-methoxyphenyl)-3,5-diphenyl-1*H*-pyrrole (3d)

Solid; mp 190–191 °C.

IR (KBr): 3056, 3013, 2929, 2834, 1598, 1557, 1510, 1485, 1462, 1432, 1407, 1378, 1339, 1287, 1244, 1177, 1105, 1066, 1026, 942, 911, 836, 799, 752, 694 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.24–7.10 (m, 10 H, ArH), 7.04 (d, *J* = 8.0 Hz, 4 H, ArH), 6.79 (d, *J* = 7.6 Hz, 2 H, ArH), 6.77 (d, *J* = 7.6 Hz, 2 H, ArH), 6.73 (s, 1 H, H-4), 3.70 (s, 3 H, CH_3O), 3.68 (s, 3 H, CH_3O).

Anal. Calcd for $C_{30}H_{25}NO_2$: C, 83.50; H, 5.84; N, 3.25. Found: C, 83.72; H, 5.95; N, 3.09.

2-(4-Bromophenyl)-1-(4-methoxyphenyl)-3,5-diphenyl-1*H*-pyrrole (3e)

Solid; mp 219–220 °C.

IR (KBr): 3027, 2996, 2961, 1838, 1602, 1510, 1475, 1463, 1444, 1408, 1390, 1379, 1294, 1243, 1207, 1183, 1167, 1107, 1070, 1034, 1009, 945, 913, 839, 801, 766, 752, 723, 698 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.40 (d, *J* = 8.4 Hz, 2 H, ArH), 7.27–7.12 (m, 10 H, ArH), 7.07–7.03 (m, 4 H, ArH), 6.81 (d, *J* = 8.8 Hz, 2 H, ArH), 6.73 (s, 1 H, H-4), 3.71 (s, 3 H, CH_3O).

Anal. Calcd for $C_{29}H_{22}BrNO$: C, 72.50; H, 4.62; N, 2.92. Found: C, 72.67; H, 4.83; N, 3.16.

1-(3-Chloro-4-methylphenyl)-2-(4-chlorophenyl)-3,5-diphenyl-1*H*-pyrrole (3f)

Solid; mp 172–174 °C.

IR (KBr): 3056, 3027, 1600, 1567, 1497, 1479, 1441, 1408, 1393, 1370, 1332, 1179, 1092, 1066, 1048, 1028, 1013, 1000, 888, 841, 827, 769, 757, 729, 719, 697 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.23–7.12 (m, 16 H, ArH), 7.00 (dd, *J* = 2.0, 8.0 Hz, 1 H, ArH), 6.77 (s, 1 H, H-4), 2.26 (s, 3 H, CH_3).

MS: *m*/*z* = 453 (M^+, 100%).

Anal. Calcd for $C_{29}H_{21}Cl_2N$: C, 76.65; H, 4.66; N, 3.08. Found: C, 76.80; H, 4.43; N, 3.26.

1-(3-Chloro-4-methylphenyl)-3,5-diphenyl-2-(*p*-tolyl)-1*H*-pyrrole (3g)

Solid; mp 187–188 °C.

IR (KBr): 3057, 3029, 2919, 1600, 1567, 1495, 1450, 1371, 1330, 1257, 1210, 1176, 1066, 1050, 1030, 998, 943, 920, 906, 879, 842, 820, 771, 757, 702, 691 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.28–7.15 (m, 11 H, ArH), 7.13–7.08 (m, 1 H, ArH), 7.07–6.96 (m, 5 H, ArH), 6.74 (s, 1 H, H-4), 2.24 (s, 6 H, 2 × CH_3).

Anal. Calcd for $C_{30}H_{24}ClN$: C, 83.03; H, 5.57; N, 3.23. Found: C, 83.28; H, 5.41; N, 3.05.

2-(Benzo[*d*][1,3]dioxol-6-yl)-1-(3-chloro-4-methylphenyl)-3,5-diphenyl-1*H*-pyrrole (3h)
Solid; mp 188–189 °C.

IR (KBr): 3057, 3026, 2891, 1599, 1559, 1501, 1485, 1462, 1444, 1371, 1330, 1234, 1178, 1140, 1106, 1088, 1042, 999, 939, 905, 880, 861, 842, 823, 773, 757, 702, 690 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.28–7.10 (m, 12 H, ArH), 7.02 (dd, *J* = 2.0, 8.0 Hz, 1 H, ArH), 6.79 (d, *J* = 8.0 Hz, 1 H, ArH), 6.74 (d, *J* = 8.4 Hz, 1 H, ArH), 6.73 (s, 1 H, H-4), 6.64 (dd, *J* = 1.6, 8.0 Hz, 1 H, ArH), 5.99 (s, 2 H, OCH_2O), 2.26 (s, 3 H, CH_3).

Anal. Calcd for $C_{30}H_{22}ClNO_2$: C, 77.66; H, 4.78; N, 3.02. Found: C, 77.42; H, 4.56; N, 3.21.

2-(Benzo[*d*][1,3]dioxol-6-yl)-1-(4-fluorophenyl)-3,5-diphenyl-1*H*-pyrrole (3i)
Solid; mp 164–166 °C.

IR (KBr): 3067, 3029, 2898, 1600, 1560, 1504, 1482, 1467, 1438, 1397, 1381, 1324, 1230, 1179, 1150, 1107, 1036, 938, 914, 881, 864, 844, 813, 762, 727, 696 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.27–7.09 (m, 14 H, ArH), 6.78 (d, *J* = 8.0 Hz, 1 H, ArH), 6.76 (s, 1 H, H-4), 6.69 (d, *J* = 1.6 Hz, 1 H, ArH), 6.61 (dd, *J* = 1.6, 8.0 Hz, 1 H, ArH), 5.98 (s, 2 H, OCH_2O).

MS: *m*/*z* = 433 (M^+, 100%).

Anal. Calcd for $C_{29}H_{20}FNO_2$: C, 80.35; H, 4.65; N, 3.23. Found: C, 80.14; H, 4.40; N, 3.32.

2-(4-Bromophenyl)-1-(4-fluorophenyl)-3,5-diphenyl-1*H*-pyrrole (3j)
Solid; mp 181–182 °C.

IR (KBr): 3055, 3027, 1600, 1510, 1475, 1440, 1407, 1376, 1226, 1199, 1179, 1150, 1072, 1010, 942, 911, 843, 820, 757, 716, 696 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.42 (d, *J* = 8.4 Hz, 2 H, ArH), 7.28–7.10 (m, 14 H, ArH), 7.04 (d, *J* = 8.4 Hz, 2 H, ArH), 6.77 (s, 1 H, H-4).

Anal. Calcd for $C_{28}H_{19}BrFN$: C, 71.80; H, 4.09; N, 2.99. Found: C, 71.93; H, 3.98; N, 3.37.

2-(Benzo[*d*][1,3]dioxol-6-yl)-1-(4-methoxyphenyl)-3,5-diphenyl-1*H*-pyrrole (3k)
Solid; mp 162–163 °C.

IR (KBr): 3051, 2969, 2890, 1601, 1556, 1512, 1470, 1436, 1403, 1373, 1342, 1290, 1231, 1176, 1137, 1106, 1085, 1069, 1037, 974, 933, 876, 864, 840, 816, 767, 749, 699 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.26–7.10 (m, 10 H, ArH), 7.07 (d, *J* = 8.8 Hz, 2 H, ArH), 6.81 (d, *J* = 8.8 Hz, 2 H, ArH), 6.76 (d, *J* = 7.6 Hz, 1 H, ArH), 6.72 (s, 1 H, H-4), 6.68 (d, *J* = 1.6 Hz, 1 H, ArH), 6.60 (dd, *J* = 1.6, *J* = 8.0 Hz, 1 H, ArH), 5.98 (s, 2 H, OCH_2O), 3.70 (s, 3 H, CH_3O).

MS: *m*/*z* = 445 (M^+, 100%).

Anal. Calcd for $C_{30}H_{23}NO_3$: C, 80.88; H, 5.20; N, 3.14. Found: C, 80.92; H, 5.06; N, 3.31.

2-(4-Bromophenyl)-3,5-diphenyl-1-(*p*-tolyl)-1*H*-pyrrole (3l)
Solid; mp 183–184 °C.

IR (KBr): 3057, 3030, 2922, 1599, 1513, 1488, 1481, 1460, 1405, 1376, 1333, 1298, 1247, 1202, 1181, 1106, 1073, 1028, 1010, 943, 914, 825, 810, 758, 696 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.40 (d, *J* = 8.4 Hz, 2 H, ArH), 7.26–7.12 (m, 10 H, ArH), 7.07 (d, *J* = 8.0 Hz, 2 H, ArH), 7.03 (d, *J* = 8.4 Hz, 2 H, ArH), 6.99 (d, *J* = 8.4 Hz, 2 H, ArH), 6.74 (s, 1 H, H-4), 2.25 (s, 3 H, CH_3).

Anal. Calcd for $C_{29}H_{22}BrN$: C, 75.00; H, 4.77; N, 3.02. Found: C, 75.21; H, 4.59; N, 2.96.

1-(3-Chloro-4-methylphenyl)-2-(4-methoxyphenyl)-3,5-diphenyl-1*H*-pyrrole (3m)
Solid; mp 164–166 °C.

IR (KBr): 3059, 3028, 2930, 2832, 1601, 1569, 1559, 1508, 1491, 1464, 1437, 1371, 1286, 1246, 1174, 1068, 1051, 1031, 917, 882, 844, 829, 797, 774, 760, 699 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.25–7.16 (m, 11 H, ArH), 7.13–7.09 (m, 1 H, ArH), 7.07 (d, *J* = 8.8 Hz, 2 H, ArH), 6.99 (d, *J* = 8.4 Hz, 1 H, ArH), 6.81 (d, *J* = 8.8 Hz, 2 H, ArH), 6.75 (s, 1 H, H-4), 3.71 (s, 3 H, CH_3O), 2.24 (s, 3 H, CH_3).

MS: *m*/*z* = 449 (M^+, 100%).

Anal. Calcd for $C_{30}H_{24}ClNO$: C, 80.08; H, 5.38; N, 3.11. Found: C, 79.94; H, 5.20; N, 3.17.

1-(3-Chlorophenyl)-2-(4-methylphenyl)-3,5-diphenyl-1*H*-pyrrole (3n)
Solid; mp 151–153 °C.

IR (KBr): 3060, 3027, 2916, 1592, 1508, 1479, 1450, 1428, 1367, 1319, 1184, 1103, 1075, 1020, 913, 886, 825, 789, 770, 758, 698 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.32–7.11 (m, 13 H, ArH), 7.08–7.01 (m, 5 H, ArH), 6.77 (s, 1 H, H-4), 2.25 (s, 3 H, CH_3).

MS: *m*/*z* = 419 (M^+, 100%).

Anal. Calcd for $C_{29}H_{22}ClN$: C, 82.94; H, 5.28; N, 3.34. Found: C, 83.16; H, 5.08; N, 3.50.

2-(4-Bromophenyl)-1-(3-chlorophenyl)-3,5-diphenyl-1*H*-pyrrole (3o)
Solid; mp 144–146 °C.

IR (KBr): 3058, 3026, 1590, 1508, 1493, 1480, 1401, 1388, 1374, 1322, 1179, 1099, 1072, 1028, 1009, 944, 912, 886, 829, 787, 758, 740, 718, 696 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.44 (d, *J* = 8.4 Hz, 2 H, ArH), 7.36–7.15 (m, 13 H, ArH), 7.10–7.06 (m, 3 H, ArH), 6.78 (s, 1 H, H-4).

MS: *m*/*z* = 485 (M^+ + 2, 100%).

Anal. Calcd for $C_{28}H_{19}BrClN$: C, 69.37; H, 3.95; N, 2.89. Found: C, 69.24; H, 4.07; N, 2.83.

3,5-Bis(4-chlorophenyl)-1-(4-fluorophenyl)-2-(*p*-tolyl)-1*H*-pyrrole (3p)
Solid; mp 228–229 °C.

IR (KBr): 3050, 3025, 2921, 1554, 1503, 1485, 1429, 1401, 1374, 1328, 1264, 1222, 1204, 1176, 1151, 1091, 1039, 1011, 966, 944, 843, 797, 762, 726 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.30 (d, J = 8.8 Hz, 2 H, ArH), 7.27 (d, J = 8.4 Hz, 2 H, ArH), 7.22–7.08 (m, 8 H, ArH), 7.05 (d, J = 8.4 Hz, 2 H, ArH), 6.99 (d, J = 8.0 Hz, 2 H, ArH), 6.83 (s, 1 H, H-4), 2.25 (s, 3 H, CH_3).

Anal. Calcd for $C_{29}H_{20}Cl_2FN$: C, 73.74; H, 4.27; N, 2.97. Found: C, 73.86; H, 4.52; N, 3.16.

2,3,5-Tris(4-chlorophenyl)-1-(4-fluorophenyl)-1*H*-pyrrole (3q)
Solid; mp 260–261 °C.

IR (KBr): 3072, 1596, 1571, 1551, 1508, 1474, 1429, 1398, 1368, 1330, 1266, 1220, 1207, 1180, 1152, 1090, 1012, 944, 830, 799, 770, 727 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.34–7.27 (m, 6 H, ArH), 7.23–7.10 (m, 10 H, ArH), 6.84 (s, 1 H, H-4).

Anal. Calcd for $C_{28}H_{17}Cl_3FN$: C, 68.24; H, 3.48; N, 2.84. Found: C, 68.45; H, 3.62; N, 2.93.

1-(4-Fluorophenyl)-2,3,5-tri(*p*-tolyl)-1*H*-pyrrole (3r)
Solid; mp 192–193 °C.

IR (KBr): 3027, 2917, 1861, 1614, 1507, 1405, 1375, 1330, 1216, 1183, 1150, 1111, 1091, 1020, 844, 816, 789, 737 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.77–6.95 (m, 16 H, ArH), 6.65 (s, 1 H, H-4), 2.23 (s, 9 H, 3 × CH_3).

Anal. Calcd for $C_{31}H_{26}FN$: C, 86.28; H, 6.07; N, 3.25. Found: C, 86.09; H, 6.01; N, 3.40.

1,2-Bis(4-methoxyphenyl)-3,5-di(*p*-tolyl)-1*H*-pyrrole (3s)
Solid; mp 169–171 °C.

IR (KBr): 3030, 2996, 2952, 2929, 2834, 1610, 1574, 1556, 1507, 1453, 1434, 1376, 1288, 1243, 1175, 1105, 1062, 1029, 943, 825, 790, 742 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.08 (d, J = 8.0 Hz, 2 H, ArH), 7.03–6.90 (m, 10 H, ArH), 6.78 (d, J = 8.8 Hz, 2 H, ArH), 6.77 (d, J = 8.8 Hz, 2 H, ArH), 6.62 (s, 1 H, H-4), 3.69 (s, 6 H, 2 × CH_3O), 2.23 (s, 6 H, 2 × CH_3).

MS: m/z = 459 (M^+, 100%).

Anal. Calcd for $C_{32}H_{29}NO_2$: C, 83.63; H, 6.36; N, 3.05. Found: C, 83.74; H, 6.52; N, 3.17.

2-(4-Chlorophenyl)-1-(4-fluorophenyl)-3,5-di(*p*-tolyl)-1*H*-pyrrole (3t)
Solid; mp 201–202 °C.

IR (KBr): 3031, 3026, 2919, 1603, 1570, 1541, 1511, 1485, 1441, 1396, 1376, 1331, 1229, 1181, 1150, 1112, 1090, 1012, 944, 845, 830, 812, 797, 747, 722, 697 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.27 (d, J = 8.4 Hz, 2 H, ArH), 7.18–7.01 (m, 14 H, ArH), 6.66 (s, 1 H, H-4), 2.24 (s, 6 H, 2 × CH_3).

Anal. Calcd for $C_{30}H_{23}ClFN$: C, 79.72; H, 5.13; N, 3.10. Found: C, 79.58; H, 5.09; N, 3.32.

3,5-Diphenyl-2-(thiophen-2-yl)-1-(*p*-tolyl)-1*H*-pyrrole (3u)
Solid; mp 166–167 °C.

IR (KBr): 3023, 1600, 1540, 1513, 1487, 1453, 1395, 1376, 1342, 1239, 1216, 1167, 1115, 1075, 1032, 846, 826, 758, 698 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.48 (d, J = 8.0 Hz, 1 H, ArH), 7.30 (d, J = 6.8 Hz, 2 H, ArH), 7.27–7.21 (m, 4 H, ArH), 7.19–7.14 (m, 4 H, ArH), 7.10–7.03 (m, 4 H, ArH), 6.94–6.87 (m, 2 H, ArH), 6.76 (s, 1 H, H-4), 2.26 (s, 3 H, CH_3).

Anal. Calcd for $C_{27}H_{21}NS$: C, 82.83; H, 5.41; N, 3.58. Found: C, 82.79; H, 5.23; N, 3.40.

1-(4-Chlorophenyl)-3,5-diphenyl-2-(thiophen-2-yl)-1*H*-pyrrole (3v)
Solid; mp 166–167 °C.

IR (KBr): 3068, 1603, 1558, 1540, 1508, 1493, 1457, 1375, 1250, 1174, 1106, 1031, 834, 761, 697 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.80 (s, 1 H, ArH), 7.53–7.51 (m, 1 H, ArH), 7.37–7.31 (m, 4 H, ArH), 7.29–7.24 (m, 4 H, ArH), 7.22–7.17 (m, 6 H, ArH), 6.99–6.93 (m, 2 H, ArH + H-4).

Anal. Calcd for $C_{26}H_{18}ClNS$: C, 75.81; H, 4.40; N, 3.40. Found: C, 75.91; H, 4.26; N, 3.61.

1-(4-Bromophenyl)-3,5-diphenyl-2-(thiophen-2-yl)-1*H*-pyrrole (3w)
Solid; mp 171–172 °C.

IR (KBr): 3050, 2909, 1600, 1540, 1507, 1489, 1452, 1396, 1374, 1343, 1316, 1069, 1013, 834, 771, 697 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.63 (d, J = 8.4 Hz, 2 H, ArH), 7.53–7.51 (m, 1 H, ArH), 7.32–7.14 (m, 10 H, ArH), 6.98–6.93 (m, 4 H, ArH), 6.79 (s, 1 H, H-4).

Anal. Calcd for $C_{26}H_{18}BrNS$: C, 68.42; H, 3.98; N, 3.07. Found: C, 68.35; H, 4.09; N, 3.23.

1-(4-Iodophenyl)-3,5-diphenyl-2-(thiophen-2-yl)-1*H*-pyrrole (3x)
Solid; mp 193–195 °C.

IR (KBr): 3064, 2909, 1637, 1601, 1560, 1510, 1487, 1451, 1393, 1373, 1344, 1313, 1241, 1221, 1167, 1102, 1075, 1053, 1010, 844, 825, 754, 701 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.54–7.46 (m, 3 H, ArH), 7.33–7.12 (m, 12 H, ArH), 6.99–6.97 (m, 1 H, ArH), 6.95–6.93 (m, 1 H, ArH), 6.80 (s, 1 H, H-4).

Anal. Calcd for $C_{26}H_{18}INS$: C, 62.03; H, 3.60; N, 2.78. Found: C, 62.22; H, 3.68; N, 2.54.

3-(Trifluoromethyl)-2-(4-methoxyphenyl)-5-phenyl-1-(*p*-tolyl)-1*H*-pyrrole (5a)
Solid; mp 120–122 °C.

IR (KBr): 3039, 2956, 2837, 1611, 1600, 1576, 1531, 1504, 1474, 1453, 1431, 1289, 1251, 1215, 1199, 1176, 1130, 1100, 1072, 1033, 973, 951, 922, 827, 815, 767, 757, 735, 697 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.23–6.98 (m, 11 H, ArH), 6.83 (d, J = 8.4 Hz, 2 H, ArH), 6.74 (s, 1 H, H-4), 3.72 (s, 3 H, CH_3O), 2.22 (s, 3 H, CH_3).

Anal. Calcd for $C_{25}H_{20}F_3NO$: C, 73.70; H, 4.95; N, 3.44. Found: C, 73.83; H, 5.07; N, 3.20.

2-(4-Bromophenyl)-1-(4-chlorophenyl)-3-(trifluoromethyl)-5-phenyl-1*H*-pyrrole (5b)
Solid; mp 182–183 °C.

IR (KBr): 3075, 1599, 1568, 1492, 1472, 1450, 1427, 1402, 1288, 1268, 1226, 1199, 1161, 1134, 1101, 1067, 968, 949, 841, 823, 766, 745, 729, 698 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.53 (d, J = 8.4 Hz, 2 H, ArH), 7.35 (d, J = 8.4 Hz, 2 H, ArH), 7.28–7.13 (m, 9 H, ArH), 6.83 (s, 1 H, H-4).

Anal. Calcd for $C_{23}H_{14}BrClF_3N$: C, 57.95; H, 2.96; N, 2.94. Found: C, 58.14; H, 3.08; N, 2.85.

2-(4-Chlorophenyl)-3-(trifluoromethyl)-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrrole (5c)
Solid; mp 165–166 °C.

IR (KBr): 3074, 3030, 1901, 1604, 1572, 1509, 1492, 1473, 1451, 1431, 1403, 1378, 1289, 1225, 1198, 1163, 1139, 1095, 1069, 1015, 949, 846, 839, 819, 764, 729, 699, 655 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.39–7.37 (m, 2 H, ArH), 7.27–7.22 (m, 7 H, ArH), 7.15–7.10 (m, 4 H, ArH), 6.83 (s, 1 H, H-4).

Anal. Calcd for $C_{23}H_{14}ClF_4N$: C, 66.44; H, 3.39; N, 3.37. Found: C, 66.31; H, 3.58; N, 3.50.

1,2-Bis(4-bromophenyl)-3-(trifluoromethyl)-5-phenyl-1*H*-pyrrole (5d)
Solid; mp 179–180 °C.

IR (KBr): 3072, 1637, 1601, 1568, 1521, 1490, 1427, 1400, 1286, 1268, 1163, 1138, 1038, 950, 922, 838, 824, 764, 728, 698, 652 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.53 (d, *J* = 8.4 Hz, 2 H, ArH), 7.48 (d, *J* = 8.4 Hz, 2 H, ArH), 7.30–7.10 (m, 9 H, ArH), 6.83 (s, 1 H, H-4).

Anal. Calcd for $C_{23}H_{14}Br_2F_3N$: C, 53.01; H, 2.71; N, 2.69. Found: C, 53.27; H, 2.82; N, 2.78.

1-(3-Chloro-4-methylphenyl)-3-(trifluoromethyl)-2-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole (5e)
Solid; mp 141–143 °C.

IR (KBr): 3057, 2960, 2836, 1601, 1581, 1531, 1503, 1474, 1452, 1430, 1415, 1391, 1289, 1249, 1201, 1181, 1135, 1103, 1036, 1012, 955, 884, 843, 834, 814, 802, 758, 766, 734, 711, 697 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.25–7.13 (m, 9 H, ArH), 7.01 (d, *J* = 7.6 Hz, 1 H, ArH), 6.86 (d, *J* = 8.4 Hz, 2 H, ArH), 6.76 (s, 1 H, H-4), 3.73 (s, 3 H, CH_3O), 2.23 (s, 3 H, CH_3).

Anal. Calcd for $C_{25}H_{19}ClF_3NO$: C, 67.95; H, 4.33; N, 3.17. Found: C, 68.13; H, 4.26; N, 3.09.

2-(Benzo[*d*][1,3]dioxol-6-yl)-3-(trifluoromethyl)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole (5f)
Solid; mp 138–140 °C.

IR (KBr): 2952, 2894, 2837, 1609, 1585, 1513, 1490, 1473, 1455, 1433, 1293, 1248, 1224, 1197, 1153, 1131, 1094, 1064, 1042, 983, 878, 866, 834, 824, 760, 729, 698 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.24–7.22 (m, 3 H, ArH), 7.14–7.07 (m, 4 H, ArH), 6.84–6.72 (m, 6 H, ArH + H-4), 6.01 (s, 2 H, CH_2), 3.69 (s, 3 H, CH_3O).

Anal. Calcd for $C_{25}H_{18}F_3NO_3$: C, 68.65; H, 4.15; N, 3.20. Found: C, 68.92; H, 3.97; N, 3.05.

2-(4-Bromophenyl)-1-(4-chlorophenyl)-3-(trifluoromethyl)-5-(thiophen-2-yl)-1*H*-pyrrole (5g)
Solid; mp 182–184 °C.

IR (KBr): 3133, 1573, 1539, 1494, 1475, 1438, 1421, 1398, 1340, 1276, 1241, 1219, 1179, 1137, 1102, 1040, 1013, 968, 922, 831, 806, 748, 728, 712 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.51 (d, *J* = 8.4 Hz, 2 H, ArH), 7.44–7.42 (m, 3 H, ArH), 7.36–7.24 (m, 2 H, ArH), 7.22 (d, *J* = 8.4 Hz, 2 H, ArH), 6.98–6.96 (m, 1 H, ArH), 6.93 (s, 1 H, H-4), 6.90–6.89 (m, 1 H, ArH).

MS: *m*/*z* = 481 (M^+, 100%).

Anal. Calcd for $C_{21}H_{12}BrClF_3NS$: C, 52.25; H, 2.51; N, 2.90. Found: C, 52.29; H, 2.62; N, 3.04.

2-(4-Chlorophenyl)-3-(trifluoromethyl)-5-(thiophen-2-yl)-1-(*m*-tolyl)-1*H*-pyrrole (5h)
Solid; mp 163–164 °C.

IR (KBr): 3093, 1607, 1577, 1540, 1496, 1473, 1438, 1399, 1341, 1278, 1188, 1176, 1137, 1113, 1098, 1081, 1014, 969, 936, 839, 804, 755, 727, 712 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.40–7.34 (m, 3 H, ArH), 7.30–7.20 (m, 4 H, ArH), 7.13–7.08 (m, 2 H, ArH), 6.94–6.92 (m, 1 H, ArH), 6.90 (s, 1 H, H-4), 6.84 (dd, *J* = 1.2, 3.6 Hz, 1 H, ArH), 2.21 (s, 3 H, CH_3).

MS: *m*/*z* = 417 (M^+, 100%).

Anal. Calcd for $C_{22}H_{15}ClF_3NS$: C, 63.23; H, 3.62; N, 3.35. Found: C, 63.48; H, 3.50; N, 3.21.

2-(Benzo[*d*][1,3]dioxol-6-yl)-3-(trifluoromethyl)-1-(4-methoxyphenyl)-5-(thiophen-2-yl)-1*H*-pyrrole (5i)
Solid; mp 128–130 °C.

IR (KBr): 3094, 3061, 2954, 2889, 2838, 1610, 1585, 1513, 1494, 1475, 1442, 1417, 1387, 1340, 1229, 1238, 1216, 1181, 1152, 1130, 1099, 1058, 1043, 981, 933, 866, 848, 826, 805, 719, 713 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.37 (d, *J* = 5.2 Hz, 1 H, ArH), 7.22 (d, *J* = 8.8 Hz, 2 H, ArH), 6.94–6.92 (m, 1 H, ArH), 6.89 (d, *J* = 8.8 Hz, 2 H, ArH), 6.85–6.81 (m, 4 H, ArH + H-4), 6.75–6.73 (m, 1 H, ArH), 6.00 (s, 2 H, OCH_2O), 3.74 (s, 3 H, OCH_3).

MS: *m*/*z* = 443 (M^+, 100%).

Anal. Calcd for $C_{23}H_{16}F_3NO_3S$: C, 62.30; H, 3.64; N, 3.16. Found: C, 62.39; H, 3.43; N, 3.06.

3-(Trifluoromethyl)-2-(4-fluorophenyl)-5-(thiophen-2-yl)-1-(*p*-tolyl)-1*H*-pyrrole (5j)
Solid; mp 156–157 °C.

IR (KBr): 3109, 3038, 2926, 1592, 1547, 1508, 1475, 1439, 1423, 1404, 1380, 1341, 1279, 1242, 1217, 1179, 1163, 1136, 1081, 1040, 968, 922, 841, 815, 732, 708, 698 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.39 (d, *J* = 5.2 Hz, 1 H, ArH), 7.32–7.29 (m, 2 H, ArH), 7.17–7.10 (m, 6 H, ArH), 6.93 (t, *J* = 4.8 Hz, 1 H, ArH), 6.87 (s, 1 H, H-4), 6.84–6.83 (m, 1 H, ArH), 2.27 (s, 3 H, CH_3).

MS: *m*/*z* = 401 (M^+, 100%).

Anal. Calcd for $C_{22}H_{15}F_4NS$: C, 65.83; H, 3.77; N, 3.49. Found: C, 65.98; H, 3.90; N, 3.23.

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(20) Crystal data for **3p**: $C_{19}H_{20}Cl_2FN$; M = 472.36, colorless block crystal, 0.52 × 0.38 × 0.18 mm, monoclinic, space group $P2_1/n$, a = 10.432 (2) Å, b = 9.744 (2) Å, c = 24.034 (5) Å, β = 99.51 (2)°, V = 2409.5 (8) Å^3, Z = 4, Dc = 1.738 g.cm^{-3}, F(000) = 976, μ(MoK$_\alpha$) = 0.294 mm^{-1}. Intensity data were collected on a Siemens P4 diffractometer with graphite monochromated *MoK*$_\alpha$ radiation (λ = 0.71073 Å) using the ω scan mode with 3.10° < θ < 25.50°. 5222 unique reflections were measured and reflections with $I > 2\sigma(I)$ were used in the Fourier techniques. The final refinement was converged to R = 0.0544 and wR = 0.1911.

(21) Crystal data for **5d**: $C_{23}H_{14}Br_2F_3N$; M = 521.17, colorless block crystal, 0.54 × 0.16 × 0.09 mm, monoclinic, space group P2/c, a = 19.480 (3) Å, b = 5.76800(18) Å, c = 19.430 (3) Å, β = 114.186 (3)°, V = 1991.5 (4) Å^3, Z = 4, Dc = 1.738 g.cm^{-3}, F(000) = 1024, μ(MoK$_\alpha$) = 4.107 mm^{-1}. Intensity data were collected on a Smart-1000 diffractometer with graphite monochromated MoK$_\alpha$ radiation (λ = 0.71073 Å) using the ω scan mode with 2.298° < θ < 21.182°. 9670 unique reflections were measured and reflections with $I > 2\sigma(I)$ were used in the Fourier techniques. The final refinement was converged to R = 0.0621 and wR = 0.1450.

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