A Facile One-Pot Three-Component Synthesis of 5-(Trifluoromethyl)-4,7-dihydro-[1,2,4]-triazolo[1,5-*a*]pyrimidine Derivatives in Ionic Liquid

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An efficient one-pot synthesis of 5-(trifluoromethyl)-4,7-dihydro-7-aryl-[1,2,4]triazolo[1,5-*a*]pyrimidine derivatives was performed via the reaction of aryl aldehyde, 3-amino-1,2,4-triazole and ethyl 4,4,4-trifluoro-3-oxobutanoate or 4,4,4-trifluoro-1-phenylbutane-1,3-dione in ionic liquid. This method has the advantages of short synthetic route, operational simplicities, mild reaction conditions, high yields and eco-friendliness.

Keywords multicomponent reaction, trifluoromethyl, triazolo[1,5-*a*]pyrimidine, ionic liquid

Introduction

Since many 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives possess biological activities and are used as anticancer agents,[1] inhibitors of the MDM2-p53 protein-protein interaction,[2] antituberculosis agents[3] and dehydrogenase inhibitors[4] *etc*., the structural modification of these nitrogen-containing heterocyclic scaffolds is of considerable interest for both organic and medicinal chemistry. They were synthesized by reaction of aldehydes with 3-amino-1,2,4-triazole and ethyl acetoacetate or cyclic *β*-diketones via the Biginelli-like reaction.[5-9] The introduction of a trifluoromethyl group into organic molecules often changes their physical, chemical, and physiological properties.[10] The trifluoromethylation of 1,2,4-triazolo[1,5-*a*]pyrimidine may provide a new potential biological compound library for biomedicinal screening. However, only a few studies on the synthesis of 5-(trifluoromethyl)-4,7-dihydro-[1,2,4]-triazolo[1,5-*a*]pyrimidine derivatives have been described in the literature. Pryadeina and co-workers[11] first reported the synthesis of these derivatives by the reaction of fluorinated 3-oxo esters with aldehyde and 3-amino-1,2,4-triazole or 2-benzylidene-2-fluoroacyl esters with 3-amino-1,2,4-triazole. Their procedure underwent two steps and the cyclocondensation reactions were realized by using ethanol or DMF as solvent and hydrochloric acid or sulfamic acid as catalyst. Besides, the present method has some other disadvantages such as long reaction time, complicated procedures, low yields, operational complexity and the narrow application scope of substrates. As the consequence, a simple, rapid, and efficient procedure is still highly desirable for the synthesis of these important heterocyclic compounds.

Ionic liquids as substitutes for volatile organic solvents are used as green media for various organic transformations because of their unique properties of nonvolatility, nonflammability, recyclability and homogenous media. On the other hand, multi-component reactions (MCRs) as resource- and time-effective and economically favorable processes are wildly performed in the synthesis of heterocyclic compounds.[12] Many MCRs were carried out efficiently in ionic liquids.[13] However, to the best of our knowledge, there is no report on the preparation of 5-(trifluoromethyl)-4,7-dihydro-7-aryl-[1,2,4]-triazolo[1,5-*a*]pyrimidine derivatives by MCRs in ionic liquids.

As part of our continued interests in the synthesis of heterocyclic compounds via MCR in ionic liquids,[14] herein we report an efficient one-pot three-component synthesis of 5-(trifluoromethyl)-4,7-dihydro-7-aryl-[1,2,4]-triazolo[1,5-*a*]pyrimidine derivatives by treatment of aldehydes with 3-amino-1,2,4-triazole and ethyl 4,4,4-trifluoro-3-oxobutanoate or 4,4,4-trifluoro-1-phenylbutane-1,3-dion in ionic liquid. This synthetic reaction is shown in Scheme 1.

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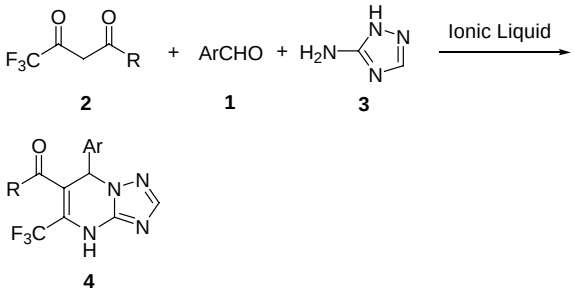
Scheme 1



Results and discussion

In order to choose the optimal solvent, the reaction of phenyl aldehyde (1 mmol) with 3-amino-1,2,4-triazole (1 mmol), and ethyl 4,4,4-trifluoro-3-oxobutanoate (1 mmol) was examined at 100 ℃ in different solvents. The results in Table 1 show that the desired product **4a** was given with higher yield (85%) in [bmim$^+$][BF_4^-] than other counterparts. Thus, [bmim$^+$][BF_4^-] was used as solvent for further optimization of reaction conditions, the same reaction was carried out at temperature ranging from 80 to 130 ℃, with an increment of 10 ℃ each time.

Table 1 Solvent effect on the synthesis of **4a**[a]

Entry	Solvent	Time/h	Yield/%
1	[byp$^+$][BF_4^-]	7	81
2	[bmim$^+$][BF_4^-]	7	85
3	CH_3CN	9	60
4	EtOH	7	70
5	HOAc	8	73
6	DMF	8	64

[a] [byp$^+$][BF_4^-], 1-butylpyridinium tetrafluoroborate; [bmim$^+$]• [BF_4^-], 3-butyl-1-methyl-1*H*-imidazol-3-ium tetrafluoroborate.

As shown in Table 2, the yield of product **4a** increased, and the reaction time was shortened with the temperature increasing from 80 to 110 ℃, while the yield significantly decreased when the temperature was further increased to 120 and 130 ℃. Therefore, 110 ℃ was chosen as reaction temperature for all further MCR reactions in ionic liquid.

Table 2 Temperature effect on the synthesis of **4a**

Entry	Tem./℃	Time/h	Yield/%
1	80	12	73
2	90	10	80
3	100	7	85
4	110	6	92
5	120	5	75
6	130	5	70

Under the optimal conditions ([bmim$^+$][BF_4^-], 110 ℃), a series of 5-(trifluoromethyl)-4,7-dihydro-7-aryl-[1,2,4]-triazolo[1,5-*a*]pyrimidine derivatives (Table 3, **4a**—**4m**) were synthesized with good yields via the one-pot reactions of aryl aldehydes with 3-amino-1,2,4-triazole and ethyl 4,4,4-trifluoro-3-oxobutanoate. The results reveal that both electron-rich aryl aldehyde and electron-deficient aryl aldehyde in the multicomponent reactions afforded the corresponding products with good yields efficiently under the same conditions. In order to expand the scope of this method, the replacement of ethyl 4,4,4-trifluoro-3-oxobutanoate with 4,4,4-trifluoro-1-phenylbutane-1,3-dione was examined. To our delight, the reactions proceeded steadily to afford a series of new triazolopyrimidine compounds **4n**—**4s** (Table 3) with good to excellent yields at 80 ℃. Moreover, the results also show that the electronic nature of substituents of the aromatic aldehyde had no significant effect on the reaction in the viewpoint of yields.

In this study, all of the products were characterized by IR and ^{1}H NMR spectral data as well as elemental analyses. To further elucidate the structure of products, a single crystal of compound **4k** was prepared and its structure was established by X-ray crystallographic analysis. The molecular structure of **4k** is shown in Figure 1.

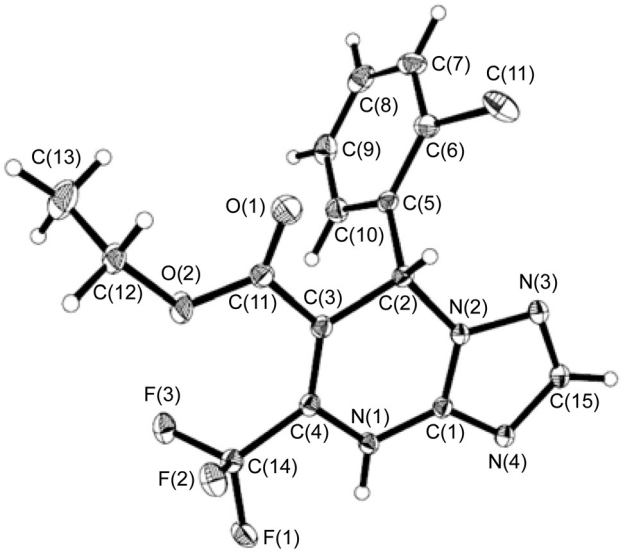


Figure 1 The structure of compound **4k**.

The recovery and reuse of solvent are highly preferable in terms of green chemistry. Therefore, with the success of the above reactions, we further studied the reuse of the reaction solvent. It turned out that the recovery and reuse of [bmim$^+$][BF_4^-] is not only convenient but also efficient. Thus, at completion monitored by TLC, the reaction mixture was cooled to room temperature, then poured into water. The solid product was collected by filtration and recrystallized from ethanol to

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Table 3 Synthesis of **4** in ionic liquid ([bmim$^+$][BF_4^-])

Product No.	Ar	R	Time/h	Yield[a]/%	m.p./℃
4a	C_6H_5	OC_2H_5	6	92	145—146 (Ref 11: 157—159)
4b	2,4-$Cl_2C_6H_3$	OC_2H_5	7	85	180—182
4c	4-$NO_2C_6H_4$	OC_2H_5	6	87	245—246
4d	4-FC_6H_4	OC_2H_5	6	85	209—211
4e	3-BrC_6H_4	OC_2H_5	7	86	193—195
4f	4-BrC_6H_4	OC_2H_5	7	88	241—242
4g	3-FC_6H_4	OC_2H_5	6	86	182—184
4h	3-$NO_2C_6H_4$	OC_2H_5	7	84	248—249
4i	2-FC_6H_4	OC_2H_5	7	88	156—157
4j	3,4-(OCH_2O)C_6H_3	OC_2H_5	6	87	197—199
4k	2-ClC_6H_4	OC_2H_5	6	86	191—193
4l	3-ClC_6H_4	OC_2H_5	6	85	184—186
4m	2,4-$(NO_2)_2C_6H_3$	OC_2H_5	7	85	214—216
4n	4-$NO_2C_6H_4$	C_6H_5	9	85	222—223
4o	C_6H_5	C_6H_5	8	82	231—233
4p	3,4-(OCH_2O)C_6H_3	C_6H_5	9	86	248—249
4q	3-BrC_6H_4	C_6H_5	8	82	222—224
4r	4-FC_6H_4	C_6H_5	9	83	232—234
4s	3-FC_6H_4	C_6H_5	8	84	265—266

[a] Isolated yields.

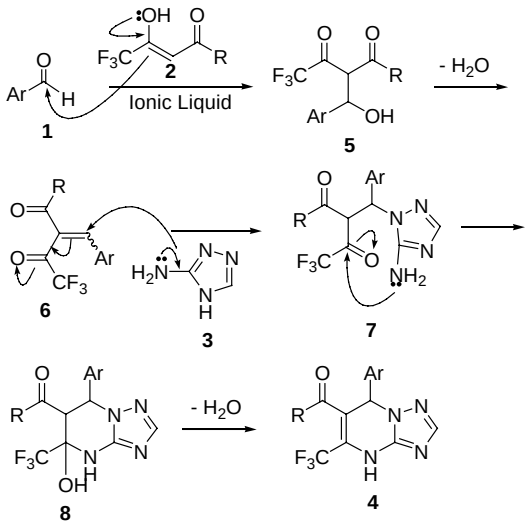
give the pure product. The filtrate was washed with acetic ester, concentrated under reduced pressure, and dried *in vacuo* at 100 ℃ for several hours to obtain the reusable solvent. Studies by using phenyl aldehyde, 3-amino-1,2,4-triazole and ethyl 4,4,4-trifluoro-3-oxobutanoate as model substrates show that the recovered solvent could be successively recycled in subsequent reactions without remarkable decrease in its efficiency. The results of the reuse of the ionic liquid are summarized in Table 4. Even in the fourth round, the yield of the product **4a** is fairly high.

Table 4 Study on the reuse of ionic liquid ([bmim$^+$][BF_4^-])

Round	1	2	3	4
4a yield/%	92	89	84	78

Although the detailed mechanism of the above reaction remains to be fully clarified, the formation of trifluoromethylated 1,2,4-triazolo[1,5-*a*]pyrimidine **4** could be explained by the reaction sequence presented in Scheme 2.[15] Knoevenagel condensation between aryl aldehyde and trifluoromethylated building block **2** gave intermediate **6**. Michael addition between **6** and **3** then afforded the intermediate **7**, which subsequently underwent intramolecular cyclization and dehydration to give the ultimate compounds **4**.

Scheme 2



Conclusions

In summary, we have developed an efficient and environmentally benign procedure for synthesizing 5-(trifluoromethyl)-4,7-dihydro-7-aryl-[1,2,4]-triazolo[1,5-*a*]pyrimidine derivatives in ionic liquid medium [bmim$^+$][BF_4^-]. This protocol has the advantages of short synthetic route, operational simplicities, mild reaction conditions and high yields. Furthermore, the ionic liquid was chosen as a kind of green solvent, which could be reused for several rounds without significant loss of activity.

Experimental

All chemicals were purchased from commercial sources and purified by recrystallization or distillation.

Infrared (IR) spectra were recorded on a TENSOR 27 spectrophotometer in KBr pellet and are reported in terms of frequency of absorption (cm^{-1}). ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 with chemical shift (δ) relative to TMS as internal standard. Elemental analyses were determined by using a Perkin-Elmer 240c elemental analysis instrument. Melting points were determined in open capillaries and are uncorrected. The single crystal diffraction data were gathered on a Rigaku Saturn diffractometer.

General procedure for the synthesis of benzo[4,5]-imidazo[1,2-*a*]pyrimidine derivatives (4a—4x)

Aryl aldehyde **1** (1 mmol), ethyl 4,4,4-trifluoro-3-oxobutanoate or 4,4,4-trifluoro-1-phenylbutane-1,3-dione **2** (1 mmol) and 3-amino-1,2,4-triazole **3** (1 mmol) were mixed in 3 mL [$bmim^+$][BF_4^-]. Then, the mixture was stirred for a certain time (monitored by TLC) at 110 ℃ or 80 ℃. The result mixture was cooled to room temperature and poured into 20 mL of water. The solid product was collected by filtration and recrystallized from ethanol to give the pure compound **4**. The filtrate was washed with acetic ester for several times, concentrated under reduced pressure, and dried *in vacuo* at 100 ℃ for several hours to give the reusable solvent.

Compound 4a ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.00 (t, J=7.6 Hz, 3H, CH_3), 4.00 (q, J=6.8 Hz, 2H, CH_2), 6.45 (s, 1H, CH), 7.25—7.27 (m, 2H, ArH), 7.32—7.39 (m, 3H, ArH+CH), 7.79 (s, 1H, ArH), 11.62 (br, 1H, NH); IR (KBr) v: 3218, 3112, 2983, 2869, 1712, 1600, 1458, 1416, 1369, 1305, 1256, 1207, 1180, 1171, 1142, 1115, 1024, 993, 880, 843, 749, 723, 708, 697, 675 cm^{-1}. Anal. calcd for $C_{15}H_{13}F_3N_4O_2$: C 53.26, H 3.87, N 16.56; found C 53.20, H 3.76, N 16.63.

Compound 4b ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.00 (t, J=6.8 Hz, 3H, CH_3), 3.94—4.01 (m, 2H, CH_2), 6.90 (s, 1H, CH), 7.44—7.49 (m, 2H, ArH), 7.64 (s, 1H, CH), 7.80 (s, 1H, ArH), 11.74 (br, 1H, NH); IR (KBr) v: 3218, 3107, 2981, 2805, 1712, 1602, 1540, 1475, 1419, 1390, 1368, 1336, 1269, 1201, 1139, 1105, 1007, 991, 875, 832, 810,785, 721, 715, 682, 641 cm^{-1}. Anal. calcd for $C_{15}H_{11}Cl_2F_3N_4O_2$: C 44.25, H 2.72, N 13.76; found C 44.32, H 2.52, N 13.70.

Compound 4c ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.00 (t, J=6.8 Hz, 3H, CH_3), 4.00 (q, J=6.8 Hz, 2H, CH_2), 6.62 (s, 1H, CH), 7.54 (d , J=8.0 Hz, 2H, ArH), 7.68 (s, 1H, CH), 8.24 (d, J=8.0 Hz, 2H, ArH), 12.68 (br, 1H, NH); IR (KBr) v: 3218, 3107, 2986, 2873, 2814, 1717, 1600, 1520, 1473, 1453, 1418, 1394, 1352, 1305, 1269, 1207, 1186, 1158, 1142, 1105, 1021, 992, 873, 851, 822, 800, 727,715, 695, 675, 646 cm^{-1}. Anal. calcd for $C_{15}H_{12}F_3N_5O_4$: C 47.00, H 3.16, N 18.27; found C 47.12, H 3.06, N 18.30.

Compound 4d ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.00 (t, J=6.8 Hz, 3H, CH_3), 4.00 (q, J=6.8 Hz, 2H, CH_2), 6.49 (s, 1H, CH), 6.85 (s, 1H, CH), 7.05 (d, J=7.6 Hz, 2H, ArH), 7.32 (d, J=7.6 Hz, 2H, ArH), 12.68 (br, 1H, NH); IR (KBr) v: 3374, 3220, 3104, 2983, 2814, 2361, 2341, 1723, 1600, 1530, 1509, 1489, 1453, 1418, 1394, 1373, 1350, 1305, 1207, 1184, 1139, 1100, 1072, 1011, 992, 881, 836, 805, 784, 728, 715, 705, 647 cm^{-1}. Anal. calcd for $C_{15}H_{12}F_4N_4O_2$: C 50.57, H 3.39, N 15.73; found C 50.55, H 3.41, N 15.80.

Compound 4e ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.00 (t, J=7.6 Hz, 3H, CH_3), 4.00 (q, J=6.8 Hz, 2H, CH_2), 6.48 (s, 1H, CH), 7.25 (s, 1H, CH), 7.34 (s, 1H, ArH), 7.54 (d, J=7.6 Hz, 2H, ArH), 7.82 (s, 1H, ArH), 12.63 (br, 1H, NH); IR (KBr) v: 3220, 3106, 2990, 2877, 2813, 2361, 1719, 1662, 1600, 1559, 1475, 1435, 1418, 1391, 1354, 1300, 1210, 1141, 1103, 1072, 1024, 995, 975, 900, 882, 847, 803, 778, 727, 715, 695, 682, 653, 642, 618 cm^{-1}. Anal. calcd for $C_{15}H_{12}BrF_3N_4O_2$: C 43.19, H 2.90, N 13.43; found C 43.22, H 2.85, N 13.35.

Compound 4f ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.00 (t, J=7.6 Hz, 3H, CH_3), 4.00 (q, J=6.8 Hz, 2H, CH_2), 6.46 (s, 1H, CH), 6.80 (s, 1H, CH), 7.24 (d, J=7.6 Hz, 2H, ArH), 7.59 (d, J=7.6 Hz, 2H, ArH), 12.54 (br, 1H, NH); IR (KBr) v: 3222, 3110, 2985, 2817, 1721, 1660, 1601, 1561, 1472, 1428, 1417, 1389, 1354, 1301, 1212, 1137, 1099, 1070, 1021, 991, 894, 867, 854, 803, 762, 721, 716, 703, 682, 649, 642 cm^{-1}. Anal. calcd for $C_{15}H_{12}BrF_3N_4O_2$: C 43.19, H 2.90, N 13.43; found C 43.21, H 2.91, N 13.41.

Compound 4g ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.00 (t, J=7.6 Hz, 3H, CH_3), 4.00 (q, J=6.8 Hz, 2H, CH_2), 6.49 (s, 1H, CH), 7.09—7.21 (m, 3H, ArH+CH), 7.40—7.46 (m, 1H, ArH), 7.82 (s, 1H, ArH), 11.69 (br, 1H, NH); IR (KBr) v: 3107, 2987, 2876, 2809, 2361, 1719, 1612, 1559, 1507, 1489, 1453, 1420, 1393, 1370, 1354, 1338, 1305, 1266, 1229, 1201, 1162, 1117, 1097, 994, 872, 785, 756, 725, 691, 652 cm^{-1}. Anal. calcd for $C_{15}H_{12}F_4N_4O_2$: C 50.57, H 3.39, N 15.73; found C 50.55, H 3.37, N 15.75.

Compound 4h ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.00 (t, J=7.6 Hz, 3H, CH_3), 4.00 (q, J=6.8 Hz, 2H, CH_2), 6.71 (s, 1H, CH), 6.90 (s, 1H, CH), 7.73 (d, J=8.4 Hz, 2H, ArH), 8.24 (d, J=8.0 Hz, 2H, ArH), 12.72 (s, 1H, NH); IR (KBr) v: 3221, 3101, 3069, 2987, 2876, 2816, 1717, 1614, 1558, 1539, 1477, 1447, 1418, 1353, 1305, 1269, 1163, 1101, 1015, 991, 926, 876, 813, 786, 736, 728, 709, 684, 650 cm^{-1}. Anal. calcd for $C_{15}H_{12}F_3N_5O_4$: C 47.00, H 3.16, N 18.27; found C 47.04, H 3.21, N 18.22.

Compound 4i ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.00 (t, J=7.6 Hz, 3H, CH_3), 4.00 (q, J=6.8 Hz, 2H, CH_2), 6.68 (s, 1H, CH), 7.18—7.23 (m, 2H, ArH), 7.36—7.43 (m, 2H, ArH), 7.80 (s, 1H, CH), 11.55 (br, 1H, NH); IR (KBr) v: 3109, 2983, 2869, 2803, 1733, 1601, 1552, 1507, 1490, 1418, 1380, 1352, 1338, 1305, 1245, 1210, 1201, 1158, 1040, 997, 944, 928, 879, 823, 800, 779, 726, 707, 655, 636 cm^{-1}. Anal. calcd for $C_{15}H_{12}F_4N_4O_2$: C 50.57, H 3.39, N 15.73; found C 50.53, H 3.42, N 15.68.

Compound 4j ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.00 (t, J=7.2 Hz, 3H, CH_3), 4.00 (q, J=6.8 Hz, 2H,

CH_2), 6.02 (s, 2H, CH_2), 6.37 (s, 1H, CH), 6.74 (d, J=8.0 Hz, 1H, ArH), 6.79 (s, 1H, ArH), 6.88 (d, J=8.0 Hz, 1H, ArH), 7.79 (s, 1H, ArH), 11.55 (br, 1H, NH); IR (KBr) *v*: 3217, 3107, 2985, 2903, 2360, 1867, 1717, 1607, 1547, 1510, 1490, 1418, 1380, 1352, 1338, 1245, 1230, 1196, 1158, 1040, 997, 944, 928, 879, 823, 800, 779, 726, 707, 655, 636 cm^{-1}. Anal. calcd for $C_{16}H_{13}F_3N_4O_4$: C 50.27, H 3.43, N 14.66; found 50.31, H 3.40, N 14.71.

Compound 4k ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.00 (t, J=7.6 Hz, 3H, CH_3), 4.00 (q, J=6.8 Hz, 2H, CH_2), 6.83 (s, 1H, CH), 7.37—7.47 (m, 4H, ArH), 7.78 (s, 1H, ArH), 11.62 (br, 1H, NH); IR (KBr) *v*: 3110, 2987, 2872, 2801, 2361, 1985, 1938, 1721, 1602, 1542, 1509, 1485, 1453, 1420, 1389, 1352, 1338, 1294, 1266, 1219, 1201, 1187, 1094, 1008, 993, 886, 864, 821, 762, 725, 701, 678, 644 cm^{-1}. Anal. calcd for $C_{15}H_{12}ClF_3N_4O_2$: C 48.34, H 3.25, Cl 9.51, N 15.03; found C 48.35, H 3.24, Cl 9.50, N 15.10.

Compound 4l ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.00 (t, J=7.6 Hz, 3H, CH_3), 4.00 (q, J=6.8 Hz, 2H, CH_2), 6.50 (s, 1H, CH), 7.21—7.23 (m, 1H, ArH), 7.38—7.42 (m, 3H, ArH), 7.83 (s, 1H, ArH), 11.72 (br, 1H, NH); IR (KBr) *v*: 3220, 3107, 2983, 2875, 1723, 1616, 1562, 1501, 1477, 1419, 138, 1365, 1354, 1342, 1299, 1256, 1232, 1201, 1166, 1098, 1015, 993, 972, 890, 874, 801, 775, 713, 690, 651 cm^{-1}. Anal. calcd for $C_{15}H_{12}ClF_3N_4O_2$: C 48.34, H 3.25, Cl 9.51, N 15.03; found C 48.37, H 3.21, Cl 9.48, N 15.07.

Compound 4m ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.00 (t, J=7.6 Hz, 3H, CH_3), 3.97—4.01 (m, 2H, CH_2), 7.25 (s, 1H, CH), 7.83 (d, J=8.4 Hz, 1H, CH), 7.90 (s, 1H, ArH), 8.52 (dd, J_1=8.4, 2.4 Hz, 1H, ArH), 8.74 (d, J=2.0 Hz, 1H, ArH), 12.17 (br, 1H, NH); IR (KBr) *v*: 3205, 3099, 2987, 2871, 1702, 1611, 1530, 1510, 1475, 1413, 1392, 1357, 1334, 1310, 1256, 1228, 1201, 1184, 1094, 994, 870, 837, 821, 797, 779, 743, 734, 725, 705, 653, 636 cm^{-1}. Anal. calcd for $C_{15}H_{11}F_3N_6O_6$: C 42.07, H 2.59, N 19.62; found C 42.09, H 2.61, N 19.59.

Compound 4n ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.66 (s, 1H, CH), 7.40 (d, J=8.0 Hz, 2H, ArH), 7.50 (t, J=8.0 Hz, 2H, ArH), 7.66 (s, 1H, CH), 7.82 (d, J=7.0 Hz, 3H, ArH), 8.15 (d, J=8.0 Hz, 2H, ArH), 11.57 (br, 1H, NH); IR (KBr) *v*: 3108, 3041, 2985, 2867, 2807, 1652, 1559, 1524, 1450, 1428, 1414, 1351, 1319, 1277, 1208, 1147, 1074, 1002, 992, 859, 837, 812, 764, 739, 727, 694, 627, 597 cm^{-1}. Anal. calcd for $C_{19}H_{12}F_3N_5O_3$: C 54.95, H 2.91, N 16.86; found C 54.93, H 2.31, N 16.88.

Compound 4o ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.41 (s, 1H, CH), 7.05 (d, J=8.0 Hz, 2H, ArH), 7.27 (m, 3H, ArH), 7.46 (t, J=8.0 Hz, 2H, ArH), 7.64 (s, 1H, CH), 7.78 (t, J=8.0 Hz, 3H, ArH), 11.42 (s, 1H, NH); IR (KBr) *v*: 3103, 2978, 2863, 2803, 1650, 1602, 1561, 1490, 1449, 1419, 1350, 1320, 1309, 1281, 1243, 1203, 1178, 1146, 1121, 1074, 1015, 1003, 992, 920, 884, 820, 803, 753, 726, 699, 686, 623 cm^{-1}. Anal. calcd for $C_{19}H_{13}F_3N_4O$: C 61.62, H 3.54, N 15.13; found C 61.59, H 3.55, N 15.17.

Compound 4p ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 5.96 (d, J=7.2 Hz, 2H, OCH_2O), 6.33 (s, 1H, CH), 6.53 (dd, J_1=6.4, 1.6 Hz, 1H, ArH), 6.65 (d, J=1.6 Hz, 1H, ArH), 6.75 (d, J=8.0 Hz, 1H, ArH), 7.47 (t, J=8.0 Hz, 2H, ArH), 7.63 (t, J=7.2 Hz, 1H, ArH), 7.77 (s, 1H, CH), 7.80 (d, J=8.0 Hz, 2H, ArH), 11.45 (br, 1H, NH); IR (KBr) *v*: 3105, 3038, 2979, 2869, 2789, 1651, 1604, 1561, 1504, 1449, 1417, 1385, 1349, 1319, 1281, 1247, 1204, 1181, 1102, 1041, 931, 805, 791, 753, 726, 701, 687, 638 cm^{-1}. Anal. calcd for $C_{20}H_{13}F_3N_4O_3$: C 57.98, H 3.16, N 13.52; found C 57.94, H 3.20, N 13.55.

Compound 4q ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.48 (s, 1H, CH), 7.11 (d, J=8.0 Hz, 1H, ArH), 7.24 (t, J=8.0 Hz, 1H, ArH), 7.30 (s, 1H, CH), 7.44—7.50 (m, 3H, ArH), 7.66 (t, J=7.2 Hz, 1H, ArH), 7.80 (t, J=3.6 Hz, 3H, ArH), 11.42 (br, 1H, NH); IR (KBr) *v*: 3110, 3053, 2989, 2870, 2812, 2350, 1667, 1614, 1559, 1470, 1451, 1438, 1420, 1355, 1316, 1296, 1268, 1247, 1202, 1179, 1137, 1108, 1070, 1027, 997, 923, 867, 788, 738, 725, 691, 669, 645, 625, 599 cm^{-1}. Anal. calcd for $C_{19}H_{12}BrF_3N_4O$: C 50.80, H 2.69, N 12.47; found C 50.77, H 2.71, N 12.50.

Compound 4r ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.46 (s, 1H, CH), 7.07—7.16 (m, 4H, ArH), 7.48 (t, J=7.6 Hz, 2H, ArH), 7.65 (t, J=7.6 Hz, 1H, ArH), 7.76 (s, 1H, CH), 7.78 (s, 2H, ArH), 11.47 (br, 1H, NH); IR (KBr) *v*: 3045, 2986, 2870, 2811, 1672, 1605, 1560, 1511, 1450, 1421, 1353, 1315, 1305, 1272, 1247, 1226, 1207, 1189, 1177, 1144, 1112, 1000, 914, 856, 809, 793, 749, 725, 688, 637, 615 cm^{-1}. Anal. calcd for $C_{19}H_{12}F_4N_4O$: C 58.77, H 3.11, N, 14.43; found C 58.74, H 3.13, N 14.40.

Compound 4s ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.48 (s, 1H, CH), 6.92—6.97 (m, 2H, ArH), 7.07—7.11 (m, 1H, ArH), 7.29—7.34 (m, 1H, ArH), 7.48 (t, J=8.0 Hz, 2H, ArH), 7.62—7.68 (m, 1H, Ar), 7.78 (d, J=1.2 Hz, 1H, CH), 7.80 (s, 2H, ArH), 11.49 (br, 1H, NH); IR (KBr) *v*: 3224, 3104, 3044, 2985, 2793, 2348, 1653, 1614, 1561, 1488, 1452, 1420, 1356, 1279, 1230, 1184, 1150, 1121, 1075, 1030, 995, 947, 925, 905, 858, 814, 789, 761, 745, 726, 690, 649, 638, 627, 597 cm^{-1}. Anal. calcd for $C_{19}H_{12}F_4N_4O$: C 58.77, H 3.11, N 14.43; found C 58.75, H 3.10, N 14.44.

Crystallographic data

The single-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was was performed using a Rigaku Saturn diffractometer. Crystal data for **4k**: $C_{15}H_{12}ClF_3N_4O_2$, crystal dimension 0.26 nm×0.22 nm×0.20 mm, monoclinic, space group $P121/n1$, a=9.8927(12) Å, b=6.8055(6), c=24.403(3) Å, β=92.166 (6)°, V=1621.6(3) $Å^3$, M_r=372.74, Z=4, D_c=1.527 g/cm^3, λ=0.71070 Å, μ(Mo Kα) = 0.285 mm^{-1}, $F(000)$ = 760, S = 1.081, R_1=0.0467, wR_2=0.1208.

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