Bioorganic & Medicinal Chemistry Letters 20 (2010) 48–51

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Solvent-free, microwave assisted synthesis of polyhalo heterocyclic ketene aminals as novel anti-cancer agents

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ARTICLE INFO

Article history:
Received 8 September 2009
Revised 6 November 2009
Accepted 11 November 2009
Available online 16 November 2009

Keywords:
Polyhalo heterocyclic ketene aminals
Solvent-free
Microwave assisted synthesis
C-Arylation

ABSTRACT

A series of polyhalo heterocyclic ketene aminals (polyhalo-HKAs) were synthesized under solvent-free conditions and evaluated in vitro against a panel of human tumor cell lines. Trifluoro-HKAs were the most cytotoxic compounds, followed by difluoro-HKAs and trichloro-HKAs. Trichloro-HKAs were more potent against the tumor cell lines Skov-3, Hep-2, K562, and A431 than difluoro-HKAs. An ethoxycarbonyl at the 2-position of the polyhalo HKAs gave the highest activity. Ethoxycarbonyl substituted **5o**, bearing three fluorine atoms on the isophthalonitrile ring, was found to be the most potent derivative with IC_{50} values lower than 3.7 μg/mL against five human tumor cell lines making it more active than cisplatin (DDP).

Heterocyclic ketene aminals (HKAs) have been frequently identified as pharmacophores and play important roles in drug discovery. As a type of versatile synthetic intermediates, HKAs have been utilized for the synthesis of a wide variety of heterocyclic and fused heterocyclic compounds,[1] including herbicides, pesticides,[2] anti-anxious agents,[3] antileishmanial agents,[4] antibacterial and anti-therapeutic drugs.[5] Overall, great progress on the synthesis of HKAs and their applications has been achieved.[6] Notably, HKAs can react with either alkyl halides,[7,8] activated acetylenes or electrophilic olefins[6,8] under neutral conditions to give exclusively the C-alkylated products. This is understandable because of the stronger nucleophilicity of the α-carbon in comparison with the nitrogen atom in HKAs, for example, **1a**, as shown in Scheme 1.

Polyhalo isophthalonitriles, especially polyfluoro isophthalonitriles, have been widely used as antibacterial and anti-inflammatory agents or synthetic materials in organic synthesis.[9]

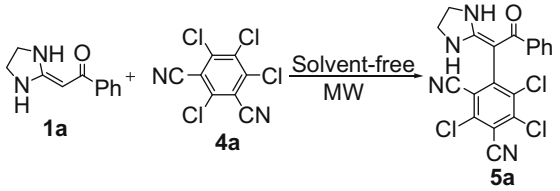
Consequently, fluorine-containing HKAs have attracted considerable attention in the field of pharmaceutical chemistry, because of the lipophilicity of fluorine and the improved activity profile originating from its superior metabolic stability.[10]

Furthermore, such hybrid molecules containing HKAs and polyfluoro isophthalonitriles possess biological activities, which may lead to the enhancement of the activity of either component alone and may result in novel biological applications. In addition, the halogens and the cyano group can be readily derived, providing many opportunities to construct molecule libraries which can be for screened for biological activity against a variety targets.

However, to the best of our knowledge, no C-arylation has been observed between HKAs and halobenzenes under neutral conditions. Only the anion of HKAs, which were coped with NaH, can react with 2,4-dinitrohalobenzenes to afford C-arylated products with very lower yields (26–44%) via a radical nucleophilic mechanism.[11] According to the literature, α-carbon substituted products form under neutral conditions, and N-substituted products form under basic conditions.[1,7] To obtain the C-arylation products with highly selective and good yields, neutral conditions are necessary.

An efficient method for the facile construction of HKAs molecular libraries through arylation with polyhalo isophthalonitriles under neutral and solvent-free conditions was developed. The compounds were evaluated in vitro against a panel of human tumor cell lines.

To examine the practicality of the projected synthetic route, a set of experiments were carried out using 2-(imidazolidin-2-yli-



Scheme 1. Reaction of HKAs **1a** with polyhalo isophthalonitrile **4a** in solvent-free conditions under microwave irradiation.

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doi:10.1016/j.bmcl.2009.11.044

Table 1
Synthesis of **5a** in solvent-free under microwave irradiation

Entry	Power	*T* (°C)	Time (min)	Yield[a] (%)
1	MW/170 W	110	12	70
2	MW/170 W	120	12	88
3	MW/170 W	130	12	86
4	MW/200 W	110	12	70
5	MW/200 W	120	12	89
6	MW/200 W	130	12	84
7	MW/230 W	110	12	71
8	MW/230 W	120	12	87
9	MW/230 W	130	12	80

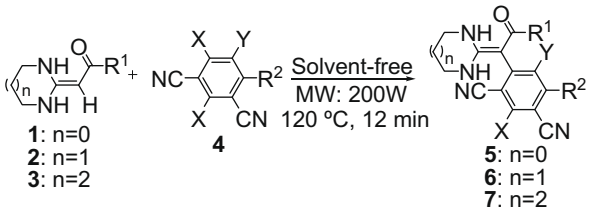
[a] Isolated yield based on HKAs **1a**.

dene)-1-phenyl-ethanone **1a** and 2,4,5,6-tetrachloroisophthalonitrile **4a** as model substrates under microwave irradiation (MW) in solvent-free conditions (Scheme 1). After screening different temperatures and determining the maximum power of microwave irradiation, we found that the optimum reaction conditions to form the product **5a** were 120 °C for 12 min with a maximum power of 200 W (Table 1, entry 5).

These results stimulated us to further explore the utility and scope of the present protocol by using various HKAs **1**–**3** with a range of halogenated isophthalonitriles **4**, as shown in Scheme 2. As a result, this methodology was found to be applicable to a diverse set of HKAs, with various substituents and rings (**1**–**3**), and polyhalogen isophthalonitriles (**4a**–**c**), producing the corresponding C-arylation products (Table 2).

Notably, the C-arylation products **5**–**7** were attained exclusively in most cases. This is ascribed to the stronger nucleophilicity of the α-carbon compared with that of the nitrogen atom,[1,6] and the electronic effect of the *ortho*- and *para*-cyano groups. The 2-site of the aryl ring in **4** was deactivated as a result of the steric effect of the two *ortho*-cyano groups, thus leading to nucleophilic attack specifically at the 4-position of the aromatic ring.[9a]

It is worth mentioning that the structure of the polyhalo isophthalonitriles **4** have obvious influence on the reaction. The reactivity of **4** varied with the electron-withdrawing properties of the groups (R′, X and Y) on the aromatic ring. The reactivity order of polyhalo isophthalonitrile under the typical conditions was found to be **4c** > **4b** > **4a** (Table 2, entries 1–3, 5–7, 8–10, 13–15, 18–20, 21–23). On the other hand, the substituents and members of the ring in HKAs only slightly influenced the reactivity (e.g., 1, 5, 8, 13, 16, 18, 21).



Scheme 2. Synthesis of polyhalo HKAs.

All new compounds were fully characterized using ^{19}F NMR, ^{1}H NMR, ^{13}C NMR and high resolution mass spectrometry.[12] The successful synthesis of the C-arylation products rather than the N-arylation products was proven by ^{1}H NMR. For example, compound **5b** has two active hydrogen atoms with a chemical shift of 6.65 (br, 1H, NH) and 9.97 (br, 1H, NH). However, the N-arylation product would have only had one active hydrogen atom. The two active hydrogen atoms have also been confirmed by D_2O exchange experiments. In addition, the C-arylation product **5o** was cyclized to form polyhalo isoquinolin-1(2*H*)-imine, whose structure was confirmed by X-ray analysis (CCDC 736001).[13] The regiospecificity of nucleophilic displacement at the 4-position of **4** by HKAs **1**–**3** was verified by physical and spectral properties. It was shown by ^{13}C NMR that the isophthalonitrile ring of **5**–**7** were unsymmetric with six aromatic resonances.

The newly synthesized polyhalo HKAs **5–7** were evaluated for in vitro anti-cancer activity against human cells according to procedures described in the literature.[14] The tumor cell line panel consisted of myeloid leukaemia (HL-60 and K562), epidermoid carcinoma (A431), ovarian carcinoma (Skov-3), and laryngeal carcinoma (Hep-2) cells. Cisplatin (DDP) was used as the reference drug. The results of the cytotoxicity studies are summarized in Table 3 and Scheme 3 (IC_{50} value, defined as the concentration corresponding to 50% growth inhibition).

As shown in Table 3, some of the compounds showed excellent activity against the antitumor cells. In fact **5n** and **5o** are up to 155

Table 2
Synthesis of various polyhalo HKAs using the solvent-free protocol

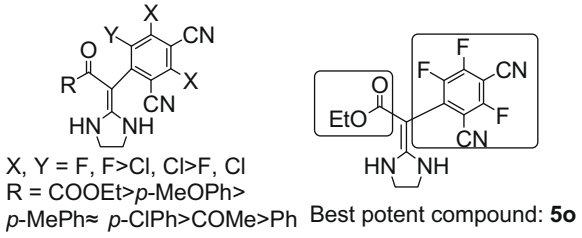
Entry	HKAs	Polyhalo-benzonitrile	Product	*n*	R^1	R^2	X	Y	Power/Temp	Time (min)	Yield[a] (%)
1	**1a**	**4a**	**5a**	0	Ph	Cl	Cl	Cl	200 W/120 °C	12	89
2	**1a**	**4b**	**5b**	0	Ph	F	F	Cl	200 W/120 °C	12	93
3	**1a**	**4c**	**5c**	0	Ph	F	F	F	200 W/120 °C	12	98
4	**1a**	**4d**	**5d**	0	Ph	PhNH	F	F	200 W/120 °C	12	84
5	**1b**	**4a**	**5e**	0	*p*-ClC_6H_4	Cl	Cl	Cl	200 W/120 °C	12	85
6	**1b**	**4b**	**5f**	0	*p*-ClC_6H_4	F	F	Cl	200 W/120 °C	12	91
7	**1b**	**4c**	**5g**	0	*p*-ClC_6H_4	F	F	F	200 W/120 °C	12	98
8	**1c**	**4a**	**5h**	0	*p*-MeC_6H_4	Cl	Cl	Cl	200 W/120 °C	12	83
9	**1c**	**4b**	**5i**	0	*p*-MeC_6H_4	F	F	Cl	200 W/120 °C	12	89
10	**1c**	**4c**	**5j**	0	*p*-MeC_6H_4	F	F	F	200 W/120 °C	12	92
11	**1d**	**4a**	**5k**	0	*p*-$MeOC_6H_4$	Cl	Cl	Cl	200 W/120 °C	12	81
12	**1d**	**4b**	**5l**	0	*p*-$MeOC_6H_4$	F	F	Cl	200 W/120 °C	12	86
13	**1e**	**4a**	**5m**	0	OEt	Cl	Cl	Cl	200 W/120 °C	12	93
14	**1e**	**4b**	**5n**	0	OEt	F	F	Cl	200 W/120 °C	12	93
15	**1e**	**4c**	**5o**	0	OEt	F	F	F	200 W/120 °C	12	95
16	**1f**	**4a**	**5p**	0	Me	Cl	Cl	Cl	200 W/120 °C	12	92
17	**1f**	**4b**	**5q**	0	Me	F	F	Cl	200 W/120 °C	12	94
18	**2**	**4a**	**6a**	1	*p*-FC_6H_4	Cl	Cl	Cl	200 W/120 °C	12	82
19	**2**	**4b**	**6b**	1	*p*-FC_6H_4	F	F	Cl	200 W/120 °C	12	87
20	**2**	**4c**	**6c**	1	*p*-FC_6H_4	F	F	F	200 W/120 °C	12	96
21	**3**	**4a**	**7a**	2	Ph	Cl	Cl	Cl	200 W/120 °C	12	86
22	**3**	**4b**	**7b**	2	Ph	F	F	Cl	200 W/120 °C	12	89
23	**3**	**4c**	**7c**	2	ph	F	F	F	200 W/120 °C	12	96

[a] Isolated yields based on HKAs.

Table 3
Cytotoxic activities of polyhalo HKAs in vitro[a] (IC_{50}, μg/mL[b])

No.	Compound	HL60	HepG-2	Skov-3	A431	K562
1	**5a**	9.1	10.2	9.9	2.3	8.5
2	**5b**	4.7	32.6	32.6	87.1	20.8
3	**5c**	0.2	9.1	30.3	5.5	19.6
4	**5d**	0.3	102	0.2	5.3	5.6
5	**5e**	0.5	5.2	1.6	1.5	0.8
6	**5f**	0.3	47.5	8.6	1.8	1.6
7	**5g**	0.3	12.5	3.8	3.2	1.8
8	**5h**	15.7	15.8	9.2	4.1	1.4
9	**5i**	0.03	49.1	6.7	1.7	41.9
10	**5j**	0.04	29.2	2.0	0.5	0.9
11	**5k**	2.3	10.8	6.4	0.5	0.08
12	**5l**	0.05	9.8	1.1	0.7	22.6
13	**5m**	0.4	0.2	4.1	0.2	0.5
14	**5n**	0.02	2.5	4.9	3.9	0.09
15	**5o**	0.02	0.7	3.3	3.7	0.03
16	**5p**	3.7	5.8	14.1	1.5	0.1
17	**5q**	0.3	1.3	1.5	2.9	4.4
18	**6a**	2.1	31.8	10.4	1.1	0.2
19	**6b**	0.6	45.1	8.2	0.9	1.8
20	**6c**	0.04	11.0	0.5	1.8	2.5
21	**7a**	0.2	14.5	2.7	1.0	0.1
22	**7b**	0.1	27.8	4.6	1.5	2.1
23	**7c**	0.1	24.9	4.2	1.9	0.3
24	Cisplatin (DDP)	3.1	8.2	10.7	2.3	8.5

[a] Cytotoxicity as IC_{50} for each cell line, is the concentration of compound which reduced by 50% the optical density of treated cells with respect to untreated cells using the MTT assay.
[b] Data represent the mean values of three independent determinations.



Scheme 3. Structure–activity relationship of polyhalo HKAs.

times more active than cisplatin against HL60 cells. Compound **5o** is almost 300 times more active against K562 cells than cisplatin.

The data indicates that five-membered heterocyclic ketene aminals **5a–5c** with a benzoyl substituent at the 2-position of the HKAs ring have lower activity towards all tumor cell lines (Table 3, entries 1–3). However, five-membered heterocyclic ketene aminals **5e**–**q** (except **5h**) with substituted benzoyl, acetyl, and ethoxycarbonyl substituents at position-2 of the HKAs ring exhibited excellent cytotoxic activities (entries 5–7, 9–17). Among them, compound **5o**, bearing ethoxycarbonyl substituents, was the most active (entry 15). Compared with all polyhalo-substituted derivatives **5**–**7**, 2,4,5-trifluoro substituted HKAs (trifluoro-HKAs) had better activity than the 2,4-difluoro-5-chloro substituted HKAs (difluoro-HKAs) and 2,4,5-trichloro substituted HKAs (trichloro-HKAs), such as **5c**, **5g**, **5j**, **5o**, **6c,** and **7c**. Trichloro-HKAs were more potent against the tumor cell lines Skov-3, Hep-2, K562, and A431 than difluoro-HKAs, for example **5a**, **5e**, **5h**, **5m**, **6a** and **7a**. Difluoro-HKAs had higher activities against HL60 than trichloro-HKAs, such as **5b**, **5f**, **5i**, **5l**, **5n**, **5q**, **6b**, and **7b**. Trifluoro-HKAs had excellent activities against HL60 and K562. Difluoro-HKAs were active against HL60 while trifluoro-HKAs were active against K562 cells. Most of these compounds were more active against HL60, Skov-3, K562, and A431 cells than DDP. However these compounds had only moderate activities against HepG-2 cells. Compound **5o** was found to be the most potent against the 5 human tumor cell lines and is 100 times more active than cisplatin (DDP) in some cell lines (Table 3, entry 15). These results suggested that substitution of the 2-position with an electron withdrawing group played a vital role in the modulation of the cytotoxic activities (Scheme 3).

In conclusion, a number of novel polyhalo HKAs derivatives were prepared and proven to have remarkably potent antitumor activities. The substitution of the 2-position of HKAs with an electron withdrawing group (COOEt) such as **5n** and **5o**, which contained two fluorine atoms or three fluorine atoms on the ring of isophthalonitrile proved to be most favorable. Compounds **5n** and **5o** are the most promising leads for further structural modifications guided by the valuable information provided from the detailed SARs described here.

Acknowledgments

The authors wish to acknowledge the financial support of grants from NSFCs (Nos. 30860342, 20762013).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.11.044.

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12. *General procedure*: A dry mortar was charged with HKAs **1**–**3** (1 mmol) and polyhalo isophthalonitrile **4** (1.1 mmol). The mixture was mixed at room temperature by vigorously grinding with a pestle for a few minutes (ca. 1–2 min). The mixture was placed in a microwave tube and irradiated in a microwave reactor (Discover), with control of power and temperature by infrared detection, at 120 °C for 12 min (maximum power 200 W). After completion, the reaction mixture was purified by column chromatography (petrol/ethyl acetate = 1:3, v/v) on silica-gel to give the desired products **5**–**7**. *Compound* **5a**: yellow solid, mp 263–265 °C. IR (KBr): 3425, 3248, 2236, 1598,

1538, 1320, 649 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 3.51 (s, 2H, CH_2), 3.74 (s, 2H, CH_2), 7.03–7.25 (m, 6H, PhH, NH), 9.66 (br, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 42.2, 44.2, 88.1, 113.2, 113.7, 114.3, 118.8, 127.2, 128.0, 129.3, 137.1, 138.2, 140.4, 142.4, 149.8, 163.2, 184.7; HRMS (TOF ES$^+$): *m/z* calcd for $C_{19}H_{11}Cl_3N_4NaO^+$ [(M+Na)$^+$], 438.9891; found, 438.9898. *Compound* **5b**: yellow solid, mp >300 °C. IR (KBr): 3208, 3144, 2244, 1588, 1536, 1319, 1091, 666 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6) δ 3.66 (s, 2H, CH_2), 3.92 (s, 2H, CH_2), 6.65 (br, 1H, NH) 7.19–7.25 (m, 5H, PhH), 9.97 (br, 1 H, NH). ^{13}C NMR (125 MHz, acetone-d_6) δ 43.7, 45.3, 87.2, 93.2, 105.9, 108.7, 112.3, 123.4, 128.7, 128.8, 130.3, 143.5, 152.2, 161.3, 163.0 (d, J = 92.5 Hz), 165.0, 187.2. ^{19}F NMR (470 MHz, acetone-d_6) δ −94.8 (s, 1F), −101.4 (s, 1F). HRMS (TOF ES$^+$): *m/z* calcd for $C_{19}H_{11}ClF_2N_4NaO^+$ [(M+Na)$^+$], 407.0482; found, 407.0484. 9i **5c**: yellow solid, mp 178 °C. IR (KBr): 3392, 3239, 2244, 1592, 1538, 1319, 1043, 666 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6) δ 3.71 (s, 2H, CH_2), 3.93 (s, 2H, CH_2), 6.72 (br, 1H, NH), 7.20–7.30 (m, 5H, PhH), 10.04 (br, 1 H, NH). ^{13}C NMR (125 MHz, acetone-d_6) δ 43.6, 45.4, 82.0, 92.8, 104.1, 108.6, 112.1, 128.9, 130.3, 141.7, 143.3, 146.0, 148.0, 154.9 (d, J = 247.5 Hz), 161.3 (d, J = 246.3 Hz), 165.3, 187.8. ^{19}F NMR (470 MHz, acetone-d_6) δ −104.7 (d, J = 9.3 Hz, 1F), −120.2 (d, J = 23.4 Hz, 1F), −134.1 (m, 1F). HRMS (TOF ES$^+$): *m/z* calcd for $C_{19}H_{12}F_3N_4O$ [M$^+$], 369.0958; found, 369.0967. *Compound* **5d**: yellow solid, mp 158–160 °C. IR (KBr): 3381, 3054, 2230, 1592, 1527, 1317, 1042, 700 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 3.51 (s, 2H, CH_2), 3.70–3.74 (m, 2H, CH_2), 6.69–7.08 (m, 5H, PhH) 7.12–7.14 (m, 1H, NH) 7.21–7.34 (m, 5H, PhH), 9.37 (br, 1H, NH), 9.71 (br, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 42.3, 44.2, 89.3 (d, J = 15.0 Hz), 94.7 (d, J = 12.5 Hz), 111.1, 113.1, 117.1, 121.1, 124.4, 127.3, 128.0, 129.1, 129.2, 135.4 (d, J = 20.0 Hz), 139.7 (d, J = 13.8 Hz), 140.2, 142.7, 148.1 (d, J = 258.8 Hz), 162.5 (d, J = 258.8 Hz), 163.7, 185.5. HRMS (TOF ES$^+$): *m/z* calcd for $C_{25}H_{18}F_2N_5O$ [M$^+$], 442.1474; found, 442.1480. *Compound* **5e**: yellow solid, mp 256–258 °C. IR (KBr): 3426, 3234, 2356, 1598, 1539, 1320, 628 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 3.51 (s, 2H, CH_2), 3.73–3.74 (m, 2H, CH_2), 7.05–7.28 (m, 5H, ArH, NH) 9.64 (br, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 42.2, 44.2, 88.0, 113.2, 114.1, 114.3, 118.6, 128.2, 129.2, 133.8, 136.9, 138.5, 140.7, 141.0, 149.2, 163.2, 183.1. HRMS (TOF ES$^+$): *m/z* calcd for $C_{19}H_{10}Cl_4N_4NaO^+$ [(M+Na)$^+$], 472.9501; found, 472.9511. *Compound* **5f**: yellow solid, mp 210–211 °C. IR (KBr): 3414, 3250, 2365, 2245, 1587, 1538, 1323, 642 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 3.57 (s, 2H, CH_2), 3.71 (s, 2H, CH_2), 7.08–7.27 (m, 5H, ArH, NH) 9.67 (br, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 42.2, 44.0, 85.8, 92.1 (t, J = 20.0 Hz), 104.1 (d, J = 13.8 Hz), 108.3, 111.7, 121.9 (d, J = 10.0 Hz), 128.2, 129.4, 134.0, 140.9, 150.3, 160.7 (d, J = 191.3 Hz), 162.8 (d, J = 143.8 Hz), 163.2, 183.3. HRMS (TOF ES$^+$): *m/z* calcd for $C_{19}H_{10}Cl_2F_2N_4NaO^+$ [(M+Na)$^+$], 441.0092; found, 441.0098. *Compound* **5g**: yellow solid, mp 180–181 °C. IR (KBr): 3397, 3242, 2245, 1594, 1538, 1321, 647 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 3.65 (s, 4H, CH_2), 7.12–7.27 (m, 5H, ArH, NH) 9.67 (br, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 43.3, 45.4, 80.7, 91.6 (t, J = 18.8 Hz), 102.5 (d, J = 11.3 Hz), 108.2, 111.6, 128.2, 129.6, 134.1, 139.8 (d, J = 17.5 Hz), 140.6, 145.5 (d, J = 248.8 Hz), 153.5 (dd, J = 270.0, 15.0 Hz), 160.1 (d, J = 263.8 Hz), 163.4, 184.5. HRMS (TOF ES$^+$): *m/z* calcd for $C_{19}H_{11}ClF_3N_4O$ [M$^+$], 403.0568; found, 403.0568. *Compound* **5m**: yellow solid, mp 199–200 °C. IR (KBr): 3371, 2982, 2889, 2239, 1657, 1101 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 1.06 (t, J = 6.35 Hz, 3H, CH_3), 3.45–3.47 (m, 2H, NCH_2), 3.61–3.65 (m, 2H, NCH_2), 3.96 (m, 2H, OCH_2), 6.93 (br, 1H, NH), 8.12 (br, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 15.0, 42.6, 44.0, 58.3, 73.0, 113.3, 113.3, 114.5, 118.6, 136.9, 138.0, 140.1, 148.6, 162.3, 165.5. HRMS (TOF ES$^-$): *m/z* calcd for $C_{15}H_{10}Cl_3N_4O_2^-$ [M−H$^+$], 382.9875; found, 382.9877. *Compound* **5n**: yellow solid, mp 186–187 °C. IR (KBr): 3352, 2986, 2892, 2245, 1648, 1097 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 1.09–1.10 (m, 3H, CH_3), 3.46–3.48 (m, 2H, NCH_2), 3.62–3.65 (m, 2H, NCH_2), 3.97 (m, 2H, OCH_2), 6.97 (br, 1H, NH), 8.19 (br, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 14.9, 42.6, 44.0, 58.4, 71.1, 91.1 (t, J = 17.5 Hz), 103.9, 108.5, 120.0, 121.6 (d, J = 12.5 Hz), 149.7, 160.7 (d, J = 262.5 Hz), 162.3 (d, J = 262.5 Hz), 162.4, 165.5. ^{19}F NMR (470 MHz, DMSO-d_6) δ −95.7 (s, 1F), −102.5 (s, 1F). HRMS (TOF ES$^-$): *m/z* calcd for $C_{15}H_{10}ClF_2N_4O_2^-$ [M−H$^+$], 351.0466; found, 351.0470. *Compound* **5o**: yellow solid, mp 169–170 °C. IR (KBr): 3347, 2984, 2894, 2245, 1648, 1100 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 1.10–1.13 (m, 3H, CH_3), 3.54–3.61 (m, 4H, NCH_2), 4.00–4.02 (m, 2H, OCH_2), 7.19 (br, 1H, NH), 8.32 (br, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 14.7, 43.0, 43.9, 58.6, 66.6, 90.3 (t, J = 18.8 Hz), 102.2 (d, J = 11.3 Hz), 108.4, 111.9, 139.0 (d, J = 13.8 Hz), 145.4 (d, J = 240 Hz), 153.4 (dd, J = 271.3, 18.8 Hz), 159.9 (d, J = 262.5 Hz), 162.7, 165.6. ^{19}F NMR (470 MHz, DMSO-d_6) δ −106.1 (d, J = 9.3 Hz, 1F), −121.2 (d, J = 14.0 Hz, 1F), −134.1 (m, 1F). HRMS (TOF ES$^+$): *m/z* calcd for $C_{15}H_{11}F_3N_4NaO_2^+$ [(M+Na)$^+$], 359.0726; found, 359.0724. *Compound* **6a**: yellow solid, mp 233–234 °C. IR (KBr): 3444, 3246, 1709, 1600, 1518, 1359, 597 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 1.87 (s, 2H, CH_2) 3.20–3.44 (m, 4H, CH_2), 6.67 (br, 1H, NH), 7.00–7.01 (m, 4H, ArH), 11.43 (br, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 21.3,39.8, 39.8, 91.9, 114.6, 115.4, 115.7, 116.2 (d, J = 21.3 Hz), 121.0, 130.7 (d, J = 6.3 Hz), 139.1, 139.7, 140.7, 142.0, 150.8, 158.9, 163.5 (d, J = 243.8 Hz), 183.3. HRMS (TOF ES$^+$): *m/z* calcd for $C_{20}H_{12}Cl_3FN_4NaO^+$ [(M+Na)$^+$], 470.9953; found, 470.9963. *Compound* **6b**: yellow solid, mp 228–230 °C. IR (KBr): 3399, 3264, 2245, 1729, 1605, 1517, 1354, 601 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 1.87–1.88 (m, 2H, CH_2) 3.32–3.38 (m, 5H, CH_2, NH), 6.97–7.19 (m, 4H, PArH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 21.1, 38.4, 38.4, 88.2, 104.9, 108.3, 111.7, 114.8 (d, J = 21.3 Hz), 122.6, 129.6, 139.1, 150.6, 157.5, 159.9, 161.3 (d, J = 31.3 Hz), 163.2, 162.8 (d, J = 191.3 Hz), 182.1. HRMS (TOF ES$^+$): *m/z* calcd for $C_{20}H_{12}ClF_3N_4NaO^+$ [(M+Na)$^+$], 439.0544; found, 439.0551. *Compound* **6c**: yellow solid, mp 195–196 °C. IR (KBr): 3414, 3268, 2245, 1706, 1599, 1518, 1313, 601 cm^{-1}. ^1H NMR (500 MHz, Acetone-d_6) δ 1.98–2.07 (m, 3H, CH_2, NH), 3.45 (s, 4H, CH_2), 6.92–7.20 (m, 5H, ArH, NH). ^{13}C NMR (125 MHz, Acetone-d_6) δ 21.1, 39.7, 39.7, 84.1, 93.1 (d, J = 17.5 Hz), 104.9 (d, J = 12.5 Hz), 108.5, 112.2, 115.7 (d, J = 21.3 Hz), 130.8 (d, J = 6.3 Hz), 140.2, 141.1 (d, J = 17.5 Hz), 147.6 (d, J = 241.3 Hz), 155.0 (dd, J = 267.5, 17.5 Hz), 159.3, 161.5 (d, J = 265.0 Hz), 163.8 (d, J = 245.0 Hz), 185.1. HRMS (TOF ES$^+$): *m/z* calcd for $C_{20}H_{12}F_4N_4NaO^+$ [(M+Na)$^+$], 423.0839; found, 423.0840. *Compound* **7a**: yellow solid, mp 220–223 °C. IR (KBr): 3383, 3255, 2237, 1614, 1357, 649 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 1.31–1.74 (m, 4H, CH_2) 3.12–3.48 (m, 4H, CH_2), 6.37 (br, 1H, NH), 6.96–7.64 (m, 5H, PhH), 11.27 (br, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 27.3, 27.4, 44.7, 45.3, 93.2, 113.2, 113.4, 114.4, 119.3, 126.9, 127.9, 128.9, 137.3, 138.3, 140.3, 142.7, 150.3, 166.5, 185.5. HRMS (TOF ES$^+$): *m/z* calcd for $C_{21}H_{15}Cl_3N_4NaO^+$ [(M+Na)$^+$], 467.0204; found, 467.0213. *Compound* **7b**: yellow solid, mp 207–210 °C. IR (KBr): 3384, 3269, 2243, 1614, 1350, 703 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 1.34–1.71 (m, 4H, CH_2), 3.14–3.46 (m, 4H, CH_2), 6.39 (br, 1H, NH), 7.01–7.46 (m, 5H, PhH), 11.21 (br, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 27.3, 27.3, 44.8, 45.3, 91.1–91.5 (m), 104.6, 108.2, 111.8, 122.3, 127.2, 127.9, 129.1, 142.6, 151.6, 159.8, 161.7 (d, J = 50.0 Hz), 163.6, 166.7, 185.8. HRMS (TOF ES$^+$): *m/z* calcd for $C_{21}H_{15}ClF_2N_4NaO^+$ [(M+Na)$^+$], 435.0795; found, 435.0806. *Compound* **7c**: yellow solid, mp 178–179 °C. IR (KBr): 3384, 3254, 2242, 1602, 1352, 630 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 1.53 (s, 4H, CH_2) 3.00–3.36 (m, 4H, CH_2), 7.32–7.90 (m, 6H, PhH, NH). ^{13} C NMR (125 MHz, DMSO-d_6) δ 27.1, 27.1, 45.1, 45.1, 89.1, 108.7, 112.0, 128.0, 128.6, 128.9, 129.5, 131.0, 142.1, 143.0 (m), 145.2 (m), 152.8 (d, J = 257.5 Hz), 160.6 (d, J = 260.0 Hz), 167.2, 187.5. HRMS (TOF ES$^+$): *m/z* calcd for $C_{21}H_{15}F_3N_4NaO^+$ [(M+Na)$^+$], 419.1090; found, 419.1098.

13. The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
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