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New trifluoromethyl quinolone derivatives: Synthesis and investigation of antimicrobial properties

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ABSTRACT

A series of quinolone derivatives, containing different heterocyclic amines were prepared. Synthesized compounds were evaluated for their in vitro antimicrobial activities against two Gram-positive bacteria, three Gram-negative bacteria as well as four fungi. All the derivatives showed good activity towards Gram-positive bacteria and less activity towards Gram-negative bacteria. They also showed moderate to comparable activity against *Aspergillus niger* and *Candida albicans* and low to moderate antifungal activity against *Aspergillus fumigatus* and *Aspergillus flavus*.

The increasing incidence of infection caused by the rapid development of bacterial resistance to most of the known antibiotics is a serious health problem.[1–3] Consequently, there is an urgent need for the development of novel types of antimicrobial agents targeting unique mechanisms and pathways. Bacteria and fungi generally develop drug resistance in three ways: producing metabolizing enzymes for the degradation of the drugs, modifying their targets to render the drugs ineffective, and expressing a high level of efflux proteins that 'pump' the drug out in order to lower its concentration.[2–7] As multidrug-resistant bacterial strains proliferate, the necessity for effective therapy has stimulated research into the design and synthesis of novel antimicrobial molecules.

Quinolone moiety is of great importance to chemists as well as biologists as it is found in a large variety of naturally occurring compounds possessing diverse biological activities. Quinoline derivatives have been used as antimalarial,[8] anti-inflammatory,[9] anticancer,[10] antibiotic,[11] antihypertensive,[12] anti HIV[13,14] and as tyrokinase PDGF-RTK inhibiting agents.[15] Additionally, some known fluoroquinolone antibiotics such as Ciprofloxacin, Levofloxacin, Gatifloxacin and Norfloxacin are well known drugs.

Thus, the presence of fluorine a highly electronegative centre, enhances lipophilicity, and can alter the physico-chemical properties of the molecule significantly (such as solubility or the log*P*) in a predictable way. This could result in increasing the stability, reducing the toxicity to eukaryotic cells, besides improving the antibacterial activity thereby improving overall the therapeutic efficiency. Also, substitution of hydrogen by a trifluoromethyl group could also result in increasing the therapeutic efficiency. In this case, the size is no doubt much larger (the volume of a trifluoromethyl group is close to that of an isopropyl group),[16] but it is the enhanced volume that contributes to the hydrophobicity, which is higher than in the case fluorine is present. The trifluoromethyl have been reported to possess biological activities being herbicides,[17] fungicides,[18] analgesic,[19] antipyretic,[20] and good inhibitors of platelet aggregation.[21]

Prompted by the varied biological activities of quinolone derivatives and understanding the importance of trifluoromethyl compounds, we envisaged the synthesis of potential antimicrobial agents,[22,23] containing two biodynamic moieties that is, trifluromethylquinolone and a heterocyclic amine, separated by a suitable alkyl/alkenyl spacer. All the synthesized compounds were screened for antibacterial and antifungal activity and also determined their log*P* and molar refractivity (MR).

6-Substituted-2-(trifluoromethyl)quinolin-4(1*H*)-ones (**3a–d**) were prepared[24] in 79–85% yield by cyclocondensation of substituted aniline with ethyl 4,4,4-trifluoro-3-oxobutanoate (**2**) in polyphosphoric acid at 150 °C for 2 h. (Scheme 1, Table 1).

Compound **3a–d**, on reaction with 2-(4-bromobutyl)isoindoline-1,3-dione (**4**) in presence of K_2CO_3 in DMF at 25 °C for 6 h gave a mixture of N- and O-substituted quinolines[25]. Both N- and O-substituted compounds were isolated by column chromatography. It was observed that the ratio of N- and O-substituted compounds depends on the substituents on the quinoline ring. In case of methoxy substituent, only N-substituted product was formed. (Scheme 2, Table 2).

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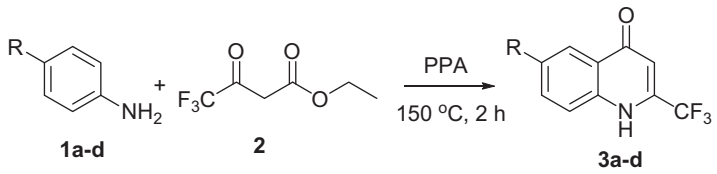
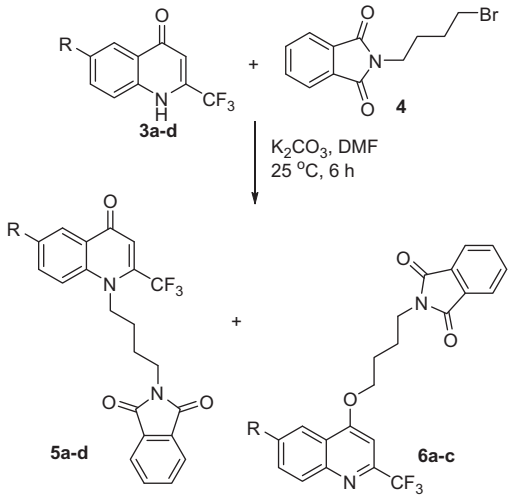


Scheme 1. Synthesis of 2-(trifluoromethyl)quinolin-4(1*H*)-ones.

Table 1
Synthesis of trifluoromethylquinolones

R	Product **3**	Yield (%)	Mp (°C)	Lit. mp (°C)
H	**3a**	85	208–210	206–208[24]
F	**3b**	82	249–251	250–251[24]
CH_3	**3c**	84	252–253	251–253[24]
OCH_3	**3d**	79	152–154	–



Scheme 2. Reaction of 2-(trifluoromethyl)quinolin-4(1*H*)-ones (**3a**–**d**) with 2-(4-bromobutyl)isoindoline-1,3-dione (**4**).

6-Fluoro-2-(trifluoromethyl)quinolin-4(1*H*)-one (**3b**) was reacted with excess of 1,4-dibromobutane (**7**) in presence of K_2CO_3 in DMF at 25 °C for 4 h to obtain crude 1-(4-bromobutyl)-6-fluoro-2-(trifluoromethyl)quinolin-4(1*H*)-one (**8**) which was purified by column chromatography. Similarly (*E*)-1-(4-bromobut-2-en-1-yl)-6-fluoro-2-(trifluoromethyl)quinolin-4(1*H*)-one (**11**) was prepared from 6-fluoro-2-(trifluoromethyl)quinolin-4(1*H*)-one (**3b**) and (*E*)-1,4-dibromobut-2-ene (**10**). Compounds **8** and **11**, when reacted separately with different heterocyclic secondary amines gave corresponding desire products in good yields[26]. (Scheme 3, Table 3)

All the newly synthesized compounds **5a–d**, **6a–c**, **9a–d** and **12a–d** were screened for their in vitro antimicrobial activities to determine zone of inhibition at 100 μg/mL against two Gram-positive bacteria (*Staphylococcus aureus* MTCC 096 and *Bacillus subtilis* MTCC 441), three Gram-negative bacteria (*Escherichia coli* MTCC 443, *Salmonella typhi* MTCC 733, and *Klebsiella pneumoniae* MTCC 432) as well as four fungi (*Aspergillus niger* MTCC 282, *Aspergillus fumigatus* MTCC 343, *Aspergillus flavus* MTCC 277, and *Candida albicans* MTCC 227) using Cup plate method[27,28] where inoculated Muller–Hilton agar for bacteria and Sabouraud dextrose agar for fungi was separately poured onto the sterilized petri dishes (25–30 mL: each petri dish). The poured material was allowed to set (30 min.) and thereafter the 'CUPS' (08 mm diameter) was made by punching into the agar surface with a sterile cork borer and scooping out the punched part of the agar. Into these cups, the test compound solution (0.1 mL) was added with the help of a micro pipette. The plates were incubated at 37 °C for 14 h for bacteria and 30 h for fungi and the results were noted. The test solution was prepared using DMSO as solvent. Minimum Inhibitory Concentration (MIC) of all the compounds were also studied by serial dilution method.[29] Clinically antimicrobial drugs Ciprofloxacin and Miconazole were used as the positive control and DMSO was used for blank.

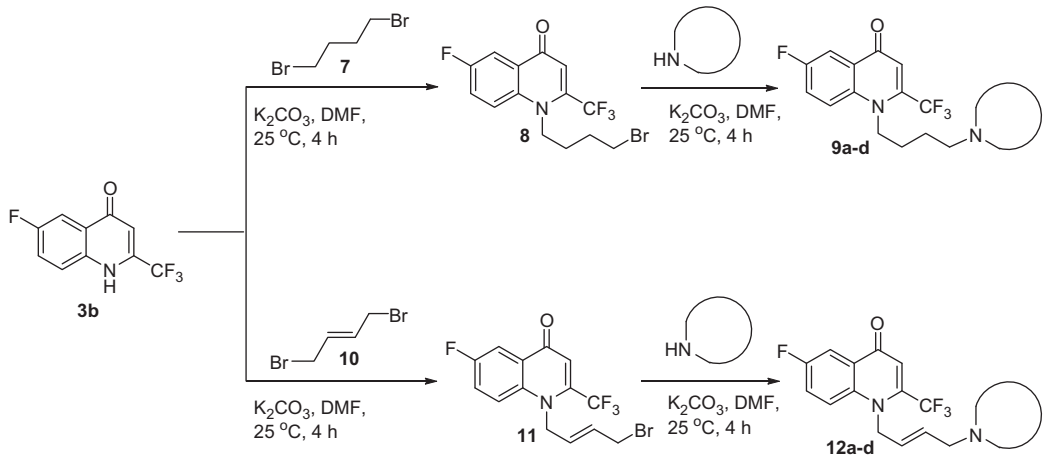
Table 2
Synthesis of N- and O-substituted trifluoromethylquinolines

R	Product **5**		Product **6**	
	Yield (%)	Mp (°C)	Yield (%)	Mp (°C)
H	72	100–101	14	92–94
F	81	125–127	10	98–99
CH_3	74	106–108	22	84–86
OCH_3	92	104–105	0	–

On comparison, the antimicrobial activity of the above synthesized compounds, it was found that the tested compounds are more effective against the Gram-positive bacteria. It looks that the strong lipophilic character of the molecule plays an essential role in producing antimicrobial effect. This property is seen as an important parameter related to membrane permeation in biological system. Many processes of drug disposition depend on the capability to cross membranes and hence there is a high correlation with measures of lipophilicity. Hydrophobic drugs with high partition coefficients are preferentially distributed to hydrophobic compartments such as lipid bilayers of cells while hydrophilic drugs (low partition coefficients) preferentially are found in hydrophilic compartments such as blood serum. Hydrophobicity/lipophilicity plays a major role in determining where drugs are distributed within the body after adsorption and as a consequence, how rapidly they are metabolized and excreted. In this context the presence of the hydrophobic moiety would be important for such activity. Moreover, many of the proteins involved in drug disposition have hydrophobic binding sites thereby further adding to the importance of lipophilicity.[30]

The lipophilicity of the compounds, expressed as log*P*, explains the main predictor for the activity. The octanol/water partition coefficient *C*log*P* being a measure of hydrophobicity/lipophilicity was calculated using ChemDraw Ultra 13.0 software integrated with Cambridgesoft Software (Cambridgesoft Corporation).[31] The results obtained are given in Table 4. The calculated values of log*P* for 2-(4-((6-substituted-2-(trifluoromethyl)quinolin-4-yl)oxy)butyl) isoindoline-1,3-diones **6a–c** were higher than that of 2-(4-(6-substituted-4-oxo-2-(trifluoromethyl)quinolin-1(4*H*)-yl)butyl)isoindoline-1,3-diones **5a–d**. The lipophilic power of compounds has increased with increasing log*P*. The antimicrobial activity observed of O-substituted compounds **6a–c** are slightly higher than that of N-substituted compounds **5a–d**.

The molar refractivity (MR), which represents size and polarizability of a molecule describing steric effects, was also calculated (using ChemDraw Ultra 13.0 software) to explain the activity behavior of the synthesized compounds. From Tables 5 and 6, it



Scheme 3. Synthesis of compounds **9a–d** and **12a–d**.

Table 3
Synthesis of compounds **9a–d** and **12a–d**

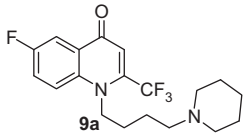
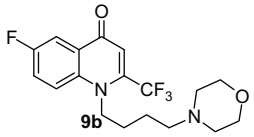
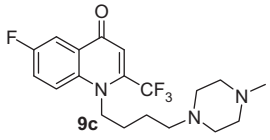
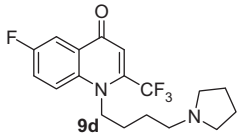
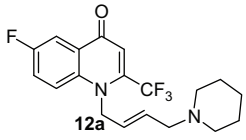
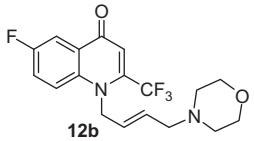
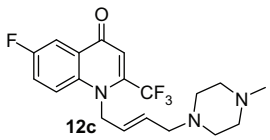
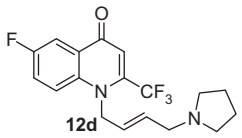
Compound	Yield (%)	Mp (°C)
 **9a**	94	40–42
 **9b**	92	84–85
 **9c**	91	42–43
 **9d**	86	71–73
 **12a**	70	69–71
 **12b**	65	93–95
 **12c**	68	68–69
 **12d**	62	73–75

Table 4
Calculated log*P* and molar refractivity (MR) of compounds **5a–d**, **6a–c**, **9a–d** and **12a–d**

Compound	log*P*	MR
5a	3.35	107.47
5b	3.51	107.87
5c	3.84	113.37
5d	3.23	114.72
6a	4.64	103.37
6b	4.80	103.78
6c	5.13	109.27
9a	3.50	96.44
9b	2.37	93.57
9c	2.52	100.71
9d	3.08	91.85
12a	3.21	96.47
12b	2.08	93.59
12c	2.23	100.73
12d	2.79	91.87
Ciprofloxacin	1.32	89.39
Miconazole	5.09	102.57

can be inferred that the higher value of molar refractivity favors the activity ratio.

The values of the MIC against microorganisms tested are reported in Tables 5 and 6. The investigations showed significant inhibitory effects, with the majority of the compounds having MIC values 6.25–50 μg/mL. The antibacterial data indicated that all the synthesized compounds showed significant antibacterial activity against all the Gram-positive strains. Among them compounds **6a–c**, **5c**, **9c**, **9d** and **12c** were found to be more potent. As shown in Table 5, none of the compounds have inhibitory effect against *E. coli*. Less activity was noted against *S. typhi* and *K. pneumonia*. According to the investigations, compounds containing phthalimide and *N*-methyl piperazine have shown enhanced activity.

The antifungal activity of synthesized quinolone derivatives in vitro are summarized in Table 6. All the compounds showed good to comparable activity against *A. niger* and *C. albicans*. Some compounds were endowed with a medium activity against *A. fumigatus*. For *A. flavus*, the tested compounds showed low to moderate antifungal activity.

In conclusion, several quinolones derivatives were synthesized in good yields. The pharmacological study was undertaken to evaluate the effects of substituents on the antibacterial and antifungal activities. All the synthesized compounds exhibited good antibacterial activity towards Gram-positive bacteria and some of the

Table 5
Antibacterial activity data of **5a–d**, **6a–c**, **9a–d** and **12a–d**.

Compound	MIC in μg/mL and zone of inhibition[a] (in mm)				
	S. aureus	*B. subtilis*	*E. coli*	*S. typhi*	*K. pneumonia*
5a	12.5 (13–16)	12.5 (12–14)	50 (<10)	25 (<10)	12.5 (13–16)
5b	6.25 (15–18)	12.5 (13–16)	50 (<10)	12.5 (13–16)	12.5 (13–16)
5c	6.25 (15–18)	6.25 (15–20)	25 (<10)	12.5 (13–16)	12.5 (13–16)
5d	6.25 (16–18)	12.5 (13–16)	50 (<10)	25 (<10)	6.25 (16–20)
6a	6.25 (16–19)	6.25 (16–18)	50 (<10)	25 (<10)	12.5 (12–15
6b	6.25 (15–18)	6.25 (15–17)	25 (<10)	12.5 (12–15)	12.5 (12–15)
6c	6.25 (15–20)	6.25 (15–18)	50 (<10)	12.5 (12–15)	6.25 (15–19)
9a	12.5 (12–15)	25 (<10)	50 (<10)	50 (<10)	12.5 (12–15)
9b	6.25 (15–18)	12.5 (13–15)	50 (<10)	25 (<10)	25 (<10)
9c	6.25 (15–19)	6.25 (15–18)	50 (<10)	50 (<10)	25 (<10
9d	6.25 (14–20)	6.25 (15–18)	50 (<10)	12.5 (12–14)	12.5 (13–16)
12a	12.5 (13–15)	12.5 (12–14)	50 (<10)	25 (<10)	12.5 (12–15)
12b	12.5 (12–14)	6.25 (14–18)	25 (<10)	50 (<10)	25 (<10
12c	6.25 (15–18)	6.25 (14–18)	50 (<10)	12.5 (12–14)	12.5 (12–15)
12d	6.25 (15–20)	12.5 (12–16)	50 (<10)	25 (<10)	12.5 (12–16)
Ciprofloxacin	6.25 (17–22)	6.25 (18–21)	6.25 (18–22)	12.5 (14–16)	6.25 (18–20)

Table 6
Antifungal activity data of **5a–d**, **6a–c**, **9a–d** and **12a–d**

Compound	MIC in μg/mL and zone of inhibition[a] (in mm)			
	A. niger	*A. fumigatus*	*A. flavus*	*C. albicans*
5a	12.5 (13–16)	25 (<10)	25 (<10)	6.25 (17–20)
5b	6.25 (17–20)	12.5 (12–14)	25 (<10)	6.25 (17–20)
5c	12.5 (12–14)	25 (<10)	12.5 (12–14)	6.25 (15–17)
5d	12.5 (12–15)	25 (<10)	25 (<10)	6.25 (15–20)
6a	6.25 (17–20)	12.5 (12–14)	25 (<10)	6.25 (17–20)
6b	6.25 (17–20)	12.5 (12–14)	12.5 (12–14)	6.25 (15–18)
6c	6.25 (17–20)	12.5 (12–14)	50 (<10)	6.25 (15–17)
9a	12.5 (12–14)	25 (<10)	12.5 (12–14)	6.25 (15–19)
9b	12.5 (13–15)	25 (<10)	25 (<10)	6.25 (15–17)
9c	6.25 (14–18)	12.5 (12–14)	25 (<10)	12.5 (12–14)
9d	12.5 (12–15)	12.5 (12–15)	12.5 (12–14)	6.25 (16–20)
12a	6.25 (17–20)	25 (<10)	25 (<10)	12.5 (12–14)
12b	6.25 (17–20)	25 (<10)	25 (<10)	6.25 (15–19)
12c	12.5 (12–14)	12.5 (12–14)	12.5 (12–14)	6.25 (15–20)
12d	12.5 (12–15)	12.5 (12–14)	12.5 (12–14)	6.25 (15–18)
Miconazole	6.25 (17–22)	12.5 (14–17)	6.25 (17–20)	6.25 (17–22)

synthesized compounds showed good to moderate antifungal activity. These compounds however did not show any promising activity towards Gram-negative bacteria. In conclusion, antimicrobial activity of the synthesized compounds increases with increasing logP and molar refractivity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.03.120.

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25. *Preparation of 2-(4-(4-oxo-2-(trifluoromethyl)quinolin-1(4H)-yl)butyl) isoindoline-1,3-dione (**5a**) and 2-(4-((2-(trifluoromethyl)quinolin-4-yl)oxy) butyl)isoindoline-1,3-dione (**6a**), representative procedure:* A mixture of 2-trifluoromethyl-4-quinolinone **3a** (0.20 g, 0.93 mmol), *N*-(4-bromobutyl) phthalimide (0.26 g, 0.93 mmol) and anhydrous K_2CO_3 (0.19 g, 1.34 mmol) in 5 mL DMF was stirred in a round bottom flask for 6–8 h at room temperature. The reaction mixture showed two spots on TLC and hence was subjected to column chromatography. The column was packed in petroleum ether and eluted with petroleum ether:ethylacetate mixture. Both the compounds were isolated and identified as compounds **5a** and **6a**. Compound **5a:** Colorless solid. Yield: 0.17 g (72%), mp 100–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.8 Hz, 1H), 7.82 (m,2H), 7.76 (d, J = 7.6 Hz, 1H), 7.71–7.61 (m, 2H), 7.59 (d, J = 7.6 Hz, 1H), 7.01 (s, 1H), 4.30 (t, J = 5.4 Hz, 2H), 3.84 (t, J = 6.2 Hz, 2H), 2.03 (br s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 162.9, 149.1, 148.0, 134.0, 131.9, 130.9, 129.5, 127.5, 123.2, 122.9, 121.6, 102.1, 96.6, 68.2, 37.4, 29.7, 26.2, 25.2. Anal. Calcd for $C_{22}H_{17}F_3N_2O_3$: C, 63.77; H, 4.13; N, 6.76. Found: C, 63.88; H, 4.06; N, 6.45. Compound **6a**: Colorless solid, Yield: 0.03 g (14%), mp 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.0 Hz, 1H), 7.88–7.85 (d, J = 8.4 Hz, 1H), 7.84–8.81 (m, 2H), 7.72–7.70 (m, 2H), 7.69–7.65 (m, 1H), 7.46 (m, 1H), 7.20 (s, 1H), 4.54 (t, J = 5.6 Hz, 2H), 3.72 (t, J = 6.6 Hz, 2H), 1.90 (br s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 166.8, 147.5, 137.1, 136.8, 134.0, 133.9, 132.0, 130.2, 128.0, 125.2, 124.0, 123.2, 121.7, 119.7, 111.7, 111.6, 65.7, 36.9, 29.7, 26.2, 25.3. Anal. Calcd for $C_{22}H_{17}F_3N_2O_3$: C, 63.77; H, 4.13; N, 6.76. Found: C, 64.01; H, 4.50; N, 6.87.
26. Preparation of 6-fluoro-1-(4-(piperidin-1-yl)butyl)-2-(trifluoromethyl) quinolin-4(1*H*)-one **(9a)** and (*E*)-6-Fluoro-1-(4-(piperidin-1-yl)but-2-en-1-yl)-

2-(trifluoromethyl)quinolin-4(1*H*)-one **(12a)**, representative procedure: Piperidine (0.06 g, 0.66 mmol) was dissolved in DMF (5 mL) along with anhydrous potassium carbonate (0.14 g, 0.99 mmol) The bromo compound (**8** and **11**) (0.66 mmol) was added to the solution, and the mixture was stirred at room temperature for 4 h. After completion of the reaction, the mixture was poured in ice cold water. The precipitate was washed with water and dried under vacuum to get the desired product **9a** and **12a** in good yield. Compound **9a**: Colorless solid. Yield: 0.19 g (94%), mp 40–42 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16–8.11 (m, 1H), 7.85–7.81 (m, 1H), 7.57–7.53 (m, 1H), 7.04 (s, 1H), 4.29 (t, J = 6.3 Hz, 2H), 2.44–2.41 (m, 4H), 2.02 (m, 2H), 1.82–1.77 (m, 2H), 1.63–1.61 (m, 4H), 1.55–1.44 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 162.8, 159.4, 145.1, 132.3, 126.9, 122.7, 121.2, 120.9, 119.6, 105.8, 97.0, 69.2, 58.9, 54.6, 26.9, 24.4, 23.5. Anal. Calcd for $C_{19}H_{22}F_4N_2O$: C, 61.61; H, 5.99; N, 7.56. Found: C, 62.02; H, 5.76; N, 7.93. Compound **12a**: Colorless solid. Yield: 0.14 g (70%), mp 69–71 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15–8.12 (m, 1H), 7.87–7.84 (m, 1H), 7.55 (m, 1H), 7.10 (s, 1H), 6.00–5.89 (m, 2H), 4.97–4.86 (br s, 2H), 3.05 (br s, 2H), 2.72 (br s, 4H), 2.39 (br s, 4H), 1.59 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 162.2, 159.3, 148.3, 145.0, 133.1, 132.0, 125.6, 123.1, 122.7, 121.2, 106.1, 105.8, 97.5, 69.1, 60.8, 54.4, 25.7, 24.1. Anal. Calcd for $C_{19}H_{20}F_4N_2O$: C, 61.95; H, 5.47; N, 7.60. Found: C, 62.23; H, 5.55; N, 7.22.

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