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Microwave enhanced solid support synthesis of fluorine containing benzopyrano-triazolo-thiadiazepines as potent anti-fungal agents

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Abstract—A facile, dry media procedure has been developed for the synthesis of a series of a new class of fluorine containing 3-alkyl-7-chloro-11a,12-dihydro-11-phenyl-12-(substituted aryl)-11*H*-benzopyrano[4,3-*e*][1,2,4]-triazolo[3,4-*b*][1,3,4]-thiadiazepines (**4a**–**k**) under microwaves using basic alumina as solid support. The reaction time has been brought down from hours (60–65 h) to minutes (3–5 min) with improved yield as compared to conventional method, demonstrating the versatility of the process. The method reported herein is devoid of the hazards of solution-phase reactions. The synthesized compounds have been screened 'in vitro' for anti-fungal activity against *Rhizoctonia solani*, *Fusarium oxysporum* and *Collectotrichum capsici*. Most of the compounds have shown good activity against these pathogens.

1. Introduction

Synthetic organic reactions performed under non-traditional conditions are gaining popularity, primarily to circumvent growing environmental concerns.[1] Microwave irradiation is a powerful technique which is being increasingly used to accelerate thermal organic reactions.[2] Further, solvent-free approach that involves microwave (MW) exposure of neat reactants catalyzed by the surface of less expensive and recyclable mineral supports, such as alumina, silica gel, clay or 'doped' surfaces, is described which is applicable to a wide range of organic reactions.[3] In addition, the limitations of the microwave-assisted reactions in solvents, namely the development of high pressure and need for specialized sealed vessels, are circumvented via the solid support strategy, which enables organic reactions to occur rapidly at atmospheric pressures[4] and upscale the reactions on a preparative scale.[5]

Various 1,2,4-triazole derivatives are associated with diverse pharmacological activities, such as anti-microbial, bactericidal, anti-inflammatory anti-viral, anti-hypertensive, anthelmintic and analgesic effects.[6] The synthesis of compounds belonging to 1,5-benzothiazepine series constitutes an important area of research due to their use as known cardiovascular drugs acting as calcium channel blockers,[7] for example, Diltiazem and Clentiazem. Like 1,5-benzothiazepines other seven-membered ring heterocycle 'thiadiazepines' are also reported for their potent anti-microbial activity.[8] They also act as intermediates for preparations of substituted caprolactams useful for treatment of HIV disease[9] and excellent charge generating agents.[10] The synthesis of fused ring system triazolo-thiadiazepines/thiadiazines has been extensively studied by various workers[11] due to their wide spectrum of biocidal[12] and pharmacological activities.[13]

Further, benzopyran nucleus is found in many naturally occurring compounds like flavones, which are well-known natural plant pigments, and it is expected that the fusion of benzopyran moiety may render the resulting compounds more active. Flavanones[14] are important intermediates for the synthesis of biologically active flavones and isoflavones and are suggested in the diet as agents responsible for the prevention of coronary diseases[15] and prostate cancer[16] and act as anti-tumor promotors.[17] Further, chloro-flavanones have been extensively studied by chemists and pharmacologists due to a wide variety of bioactivity associated with them.[18] Such applications stress the interest in the preparation of new members of this class of compounds. In addition to it, incorporation of fluorine further enhances

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Table 1. Comparative study of the synthesis of **4a** (R = CH_3 and R′ = 2-F) under microwaves (MW) and conventionally (Δ)

Exp.	Medium	Mode of heating	Time (min/h)	Temp[a] (°C)	Yield (%)
1	Mont. KSF	MW	10 min	130	50
2	Acidic alumina	MW	10 min	136	58
3	Basic alumina	MW	3 min	145	82
4	Silica gel	MW	10 min	130	Traces
5	Neat	MW	25 min	100	Nil
6	Neat + εDMF	MW	20 min	140	38
7	Piperidine + toluene	Δ	60 h	Reflux	47
8	TFA + toluene	Δ	65 h	Reflux	40

[a] Final temperature is measured at the end of microwave irradiation by introducing a glass thermometer in the reaction mixture.

the biological activity by increasing solubility in lipoid material and fat deposits in the body.[19] Hence, prompted by these observations and in continuation of our earlier interest on the synthesis of biodynamic benzothiazepines[20] and other thia-aza heterocycles using a non-traditional approach,[21] an attempt has been made to fuse bioactive thiadiazepine nucleus with triazole and benzopyran ring in a single molecular framework under microwave irradiation by varying different parameters, that is, (i) using inorganic solid supports such as aluminas (acidic or basic), montmorillonite KSF and silica gel, (ii) using neat reaction and (iii) using a few drops of DMF as homogenizer and energy transfer media to check the most effective condition for the above synthesis (Table 1).

2. Results and discussion

From the results obtained as shown in Table 1, it is clear that basic alumina is the most adaptable support for synthesizing **4a**, since a comparatively higher yield was achieved in a shorter time. The usage of mineral support eliminates the necessity of any external basic and acidic catalysts as required under thermal conditions. The reaction has also been performed under neat conditions (without solvent, support or catalyst); however, no reaction occurred, which could be made successful by adding a few drops of DMF. But the product is formed in comparatively lower yield and purity. For the sake of comparison, the reaction was also carried out conventionally in acidic (TFA + toluene) and basic (piperidine + toluene) media. The results obtained from both the thermal conditions showed that the product was obtained in a lower field (40–47%) after prolonged heating (60–65 h). Other compounds (**4b–k**) listed in Table 2 are synthesized using basic alumina.

The mechanistic pathway of the reaction of 3-arylidene flavanones (**2**) with 4-amino-5-alkyl 3-mercaptotriazole (**1**) first involves the formation of intermediate 'Michael adduct' (**3**) via nucleophilic attack[22] of the sulfhydryl group on the β-carbon atom of the double bond of **2**, which is rendered electrophilic due to vinyl-carbonyl conjugation. It has been observed that when substituents are present in an α,β-unsaturated ketone, only the nucleophilic addition of the mercapto group to the β-carbon atom takes place, followed by condensation of the carbonyl group with the aromatic primary amine to give a seven-membered ring system[23,24,7a], leading to the formation of a new class of tetracyclic ring system (**4**).

The structure of all synthesized compounds was established on the basis of their spectroscopic data. IR spectra of **4a–k** showed a sharp absorption band at 1610–1595 cm^{-1} due to C=N stretching. The disappearance of absorption bands at 1680–1675 cm^{-1} (>C=O) and 3400–3300 cm^{-1} (–NH_2) rules out the possibility of the formation of the 'Michael' type adduct (**3**) contradicting the observation of Prasad and Naidu,[25] in the reactions of (**1**) with chalcones. In the ^{1}H NMR spectra of **4a–k**, along with aromatic and alkyl protons, three protons attached to the sp^3 hybridized carbons, that is, C-11H, C-11aH and C-12H were expected to show absorption in the upfield region of ^{1}H NMR spectra. In the spectra recorded at 90 MHz, these three protons showed very weak absorption signals, while in ^{1}H NMR spectra recorded at 300 MHz, the signals were observed as two doublets and a double doublet, each integrating

Table 2. Physical data of benzopyrano[4,3-*e*]-1,2,4-triazolo[3,4-*b*][1,3,4]-thadiazepines (**4a–k**)

Compound	R	R′	Time (min)	Yield (%)	Mp (°C)
4a	CH_3	2-F	3	82	112–114
4b	CH_3	4-OCF_3	4	80	130–132
4c	CH_3	2-Cl	4	76	160–162
4d	CH_3	H	3	81	106–108
4e	C_2H_5	4-F	3	79	125–127
4f	C_2H_5	2-Cl, 4-F	4	81	142–144
4g	C_2H_5	2-F	3	78	139–141
4h	C_2H_5	3,4-diF	5	75	135–137
4i	C_3H_7	2-F	4	76	118–120
4j	C_3H_7	4-OCF_3	3	72	147–149
4k	C_3H_7	2-Cl, 4-F	4	73	153–155

for one proton. Two doublets at δ 3.40–3.52 (J = 1.2–1.5 Hz) and δ 3.98–4.03 (J = 12.1–12.5 Hz) assigned to C-11H and C-12H, because these protons are attached to sp^3 carbons which are attached to electronegative oxygen and sulfur atom, respectively. A double doublet at δ 3.15–3.19 (J = 12.1–12.5 Hz, J_2 = 1.2–1.5 Hz) assigned to C-11aH. This pattern of proton absorption is in conformity with the observation made by Levai[26] for benzopyrano-benzothiazepines (see Scheme 1).

^{13}C NMR spectra of synthesized compounds showed three characteristic absorption signals in the region δ 76.55–76.78, 47.83–48.12 and 60.22–60.62 assigned to three sp^3 carbons C-11, C-11a and C-12, respectively, along with other signals.[27] The presence of fluorine attached to phenyl ring has been confirmed by ^{19}F NMR. The formation of final product (**4a**) was further confirmed on the basis of mass spectrum, which showed a molecular ion peak (M^+) at 476 and 478 (M^++2) due to chlorine isotopic peak.

The synthesized compounds were screened for anti-fungal activity against three pathogenic fungi, namely *Rhizoctonia solani*, causing root rot of okra, *Fusarium oxysporum*, causing wilt of mustard and *Colletotrichum capsici*, causing leaf spot and fruit rot of chilli; most of the compounds show good activity against these pathogens. In the pot trial experiment it was found that **4b** and **4j** having an OCF_3 group showed maximum germination (75–80%) indicating that it is most effective in controlling the growth of pathogen. 'Baynate' and 'Thiram' recommended as standard fungicide as seed dressers to control this disease are also having –N–C–S linkage, similar to the synthesized compounds, which is responsible for their anti-fungal activity.

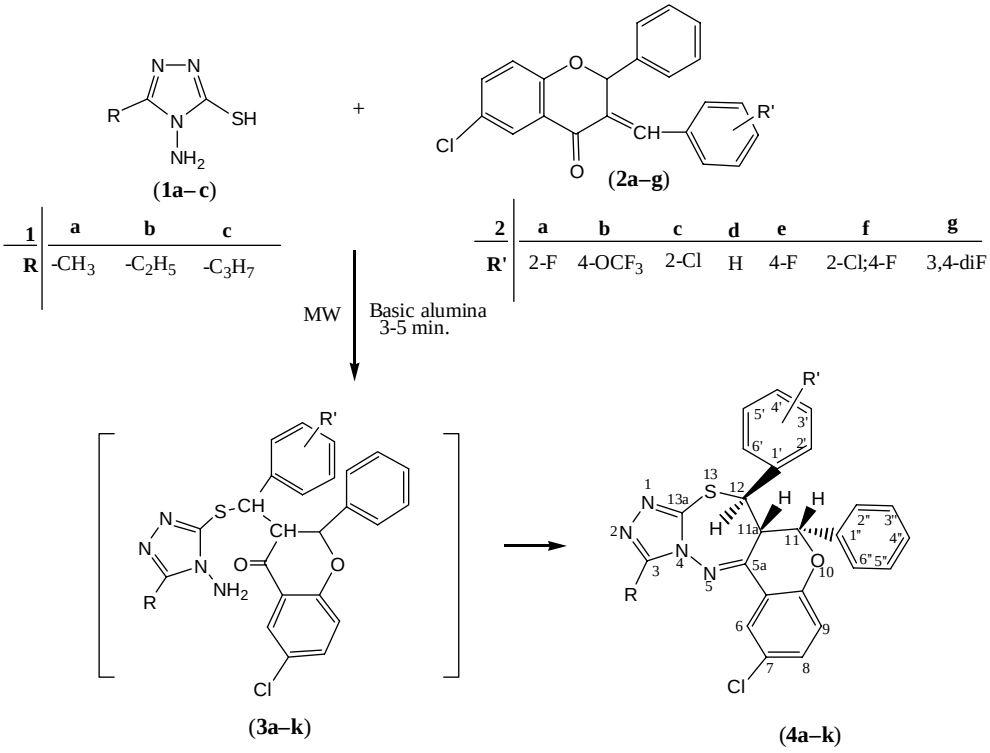
3. Evaluation of anti-fungal activity by two methods

3.1. Poison plate technique[28]

The compounds synthesized were dissolved in acetone and compounds were prepared in 1000 and 500 ppm concentrations. Potato-dextrose-agar medium was prepared in flasks and sterilized. To this medium, a requisite quantity of solution was added and then the medium was poured into petri plates in three replications. A culture of test fungus was grown on PDA for 6–7 days. Small disc (4 mm) of the fungus culture was cut with a sterile corkborer and transferred asceptically, upside-down in centre of petri dishes containing the medium and fungicides. Plates were incubated at 25 ± 1 °C for 6 days. Colony diameter was measured and data were statistically analysed (Table 3).

3.2. Pot trial method[29]

White seeded sorghun grains were soaked in water for about 12 h, 160 g of the soaked kernels was placed in 500 ml flasks and 20 ml of water was added to each. The material was autoclaved twice on successive days before inoculation. After sterilization, fungus bits were inoculated in each flask and flasks were kept for 10 days at 25–27 °C. One hundred seeds of okra were taken for one treatment of each compound. Inoculum was added at 2 g/kg of soil, 3 days prior to sowing. Sowing was



Scheme 1.

Table 3. Effect of concentrations of different chemicals on the mean radial growth (cms) of different fungi in vitro

Compound	*Rhizoctonia solani*		*Fusarium oxysporum*		*Colletotrichum capsici*	
	1000 ppm	500 ppm	1000 ppm	500 ppm	1000 ppm	500 ppm
4a	1.15[a]	1.92[a]	2.02[b]	2.82	1.98[b]	2.91
4b	2.11[b]	2.22[b]	1.62[b]	1.98[a]	1.52[b]	1.95[a]
4c	3.98	4.30	4.05	4.32	3.82	4.20
4d	3.60	4.86	4.95	5.12	4.13	4.82
4e	3.43	4.20	3.80	4.05	1.08[a]	2.70[b]
4f	6.42	7.83	2.92	3.69	3.25	3.68
4g	2.32[b]	4.38	1.98[b]	2.02[b]	2.26[b]	4.50
4h	3.28	3.69	4.23	4.98	3.42	4.00
4i	3.08	4.25	1.47[a]	2.62[b]	2.83	3.28
4j	1.80[b]	2.25[b]	3.05	3.68	2.03[b]	2.17[b]
4k	3.60	5.02	2.52	2.67	3.76	4.17
Check	9.00	9.00	8.17	8.17	7.33	7.33
CD%	0.74	1.22	0.77	1.14	1.08	1.25

[a] Min value.
[b] At par with min. values.

done after 3 days and germination data were recorded after 7, 15 and 25 days of sowing. Suitable checks were maintained and the data were statistically analysed (Table 4).

4. Experimental

Melting points were determined in open glass capillary and were uncorrected. IR spectra were recorded on a Perkin-Elmer (Model 577) in KBr pellets. ^{1}H NMR was recorded on Jeol Model FX 90Q and Bruker DRX-300 using $CDCl_3$ as solvent at 89.55 and 300.15 MHz. ^{13}C NMR spectra were recorded on Bruker DRX-300 and ^{19}F NMR on FX 90Q using $CDCl_3$ at 75.47 and 84.25 MHz, respectively. TMS was used as internal reference for ^{1}H NMR and ^{13}C NMR and hexafluorobenzene as external reference for ^{19}F NMR. Mass spectrum of representative compound was recorded on Kratos 50 mass spectrometer at 70 eV. Purity of all compounds was checked by TLC using silica gel 'G' coated glass plates and benzene/ethyl acetate (8:2) as eluent. The microwave-assisted reactions were carried out in a multimode MW oven (Panasonic-NN-781JF) equipped with inverter technology (generating fixed frequency throughout the required time) for realistic control of the microwave operating at 1000 W generating 2450 MHz frequency. Montmorillonite KSF and aluminas were Aldrich products and used as received. 4-Amino-5-alkyl-3-mercaptotriazoles[30] and 6-chloroflavanone[31] and 6-chloro-3-(substituted-arylidene)-flavanones[32] have been prepared by literature method.

Table 4. Evaluation of benzopyrano[4,3-*e*]1,2,4-triazolo[3,4-*b*][1,3,4]-thiadiazepines (**4a–k**) as seed dressers against *Rhizoctonia solani* causing root rot of okra (in pot trial)

Compound	Percent germination	Plant stand 25 DAS
4a	41.00	59.00
4b	75.00	60.00
4c	57.00	41.00
4d	48.00	33.00
4e	45.00	57.00
4f	68.00	60.00
4g	59.00	38.00
4h	39.00	20.00
4i	40.00	29.00
4j	80.00	62.00
4k	62.00	50.00
Baynate (0.2%)	98.00	64.00
Thiram(0.3%)	79.00	68.00
Check with inoculum	10.00	6.00
Check without inoculum	90.00	81.00

DAS, days after sowing.

4.1. Synthesis of benzopyran-1,2,4-triazolo[34-*b*][1,3,4]-thiadiazepine (4a)

This was prepared in two different ways: (i) conventional synthesis and (ii) microwave mediated synthesis.

4.1.1. Conventional synthesis. An equimolar mixture of 4-amino-5-methyl-3-mercaptotriazole (**1a**) and 6-chloro-3-(2-fluorobenzylidene) flavanone (**2a**) (0.01 mol) was solubilized in dry toluene (30 ml). Trifluoroacetic acid (8 drops) as acidic catalyst, or piperidine (10 drops) as a basic catalyst, was then added to the reaction mixture and refluxed with azeotropical removal of water formed for an appropriate time (60–65 h) until the reactants disappeared as followed by TLC. The excess of solvent was removed under reduced pressure and the residue left was recrystallized from dry methanol to give the respective product **4a**.

4.1.2. Microwave-assisted synthesis using different inorganic solid supports. An equimolar mixture of **1a** and **2a** (0.01 mol) was adsorbed on solid support (5 g) (mont. KSF/aluminas/silica gel) with the help of methanol. The adsorbed material was dried, placed in an alumina bath[33] inside the microwave oven and then irradiated until the completion of reaction (TLC). The mixture was cooled and product was extracted into methanol and the excess solvent was evaporated on a roto-evaporator to give compound, which was recrystallized from methanol and identified as **4a**.

From the comparative results (Table 1), it can be concluded that basic alumina under MW irradiation is the simplest and most effective support for the synthesis of **4a**. Hence, other compounds **4b–k** were similarly prepared by this method.

Compound 4a. ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H, CH_3), 3.15 (dd, 1H, H-11a, J_1 = 12.1 Hz, J_2 = 1.3 Hz), 3.41 (d, 1H, H-11, J = 1.3 Hz), 3.98 (d, 1H, H-12, J = 12.1 Hz), 6.92–8.05 (m, 12H, Ar-H). ^{13}C NMR ($CDCl_3$), δ 20.5 (CH_3), 47.83 (C-11a), 60.62 (C-12), 76.55 (C-11), 164.81 (C-5a), 161.30 (C-3), 160.02 (C-13a), 159.61(C-2′), 157.21–118.26 (other aromatic carbons). ^{19}F NMR ($CDCl_3$) δ −118.02 (s, F-2′C). Anal. Calcd for $C_{25}H_{18}ClFN_4OS$: C, 62.96; N, 11.75; S, 6.72. Found: C, 62.78; N, 11.71; S, 6.70.

Compound 4b. ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3H, CH_3), 3.16 (dd, 1H, H-11a, J_1 = 12.4 Hz, J_2 = 1.3 Hz), 3.43 (d, 1H, H-11, J = 1.3 Hz), 4.01 (d, 1H, H-12, J = 12.4 Hz) 6.90–8.08 (m, 12H, Ar-H). ^{19}F NMR ($CDCl_3$) δ −76.28 (s, –OCF_3). Anal. Calcd for $C_{26}H_{18}ClF_3N_4O_2S$: C, 57.51; N, 10.32; S, 5.91. Found: C, 57.34; N, 10.29; S, 5.89.

Compound 4c. ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H, CH_3), 3.16 (dd, 1H, H-11a, J_1 = 12.2 Hz, J_2 = 1.4 Hz), 3.41 (d, 1H, H-11, J = 1.2 Hz), 3.99 (d, 1H, H-12, J = 12.2 Hz), 6.91–8.03 (m, 12H, Ar-H). Anal. Calcd for $C_{25}H_{18}Cl_2N_4OS$: C, 60.86; N, 11.36; S, 6.50. Found: C, 60.68; N, 11.34; S, 6.48.

Compound 4d. ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3H, CH_3), 3.14 (dd, 1H, H-11a, J_1 = 12.1 Hz, J_2 = 1.3 Hz), 3.40 (d, 1H, H-11, J = 1.3 Hz), 4.01 (d, 1H, H-12, J = 12.1 Hz), 6.90–8.06 (m, 13H, Ar-H). Anal. Calcd for $C_{25}H_{19}ClN_4OS$: C, 65.42; N, 12.21; S, 6.99. Found: C, 65.22; N, 12.17; S, 6.97.

Compound 4e. ^{1}H NMR ($CDCl_3$) δ 1.46 (t, 3H, –CH_2–CH_3), 2.69 (q, 2H, –CH_2–CH_3), 3.17 (dd, 1H, H-11a, J_1 = 12.4 Hz, J_2 = 1.4 Hz), 3.48 (d, 1H, H-11, J = 1.4 Hz), 4.02 (d, 1H, H-12, J = 12.4 Hz), 6.95–8.06 (m, 12H, Ar-H). ^{13}C NMR ($CDCl_3$) δ 16.2 (–CH_2–CH_3), 17.1 (–CH_2–CH_3), 47.92 (C-11a), 60.58 (C-12), 76.58 (C-11), 164.89 (C-5a), 162.01 (C-3), 160.69 (C-13a), 158.61 (C-4′), 157.91–119.28. Anal. Calcd for $C_{26}H_{20}ClFN_4OS$: C, 63.60; N, 11.41; S, 6.53. Found: C, 63.40; N, 11.44; S, 6.55.

Compound 4f. ^{1}H NMR ($CDCl_3$) δ 1.50 (t, 3H, –CH_2–CH_3), 2.71 (q, 2H, –CH_2–CH_3), 3.18 (dd, 1H, H-11a, J_1 = 12.5 Hz, J_2 = 1.4 Hz), 3.50 (d, 1H, H-11, J_1 = 1.4 Hz), 4.03 (d, 1H, H-12, J = 12.5 Hz), 6.99–8.10 (m, 11H, Ar-H). ^{19}F NMR ($CDCl_3$) δ –119.21 (s, F-4′C). Anal. Calcd for $C_{26}H_{19}Cl_2FN_4OS$: C, 59.43; N, 10.66; S, 6.10. Found: C, 59.26; N, 10.63, S, 6.08.

Compound 4g. ^{1}H NMR ($CDCl_3$) δ 1.47 (t, 3H, –CH_2–CH_3), 2.68 (q, 2H, –CH_2–CH_3), 3.16 (dd, 1H, H-11a, J_1 = 12.3 Hz, J_2 = 1.2 Hz), 3.51 (d, 1H, H-11, J = 1.2 Hz), 3.99 (d, 1H, H-12, J = 12.3 Hz), 6.97–8.05 (m, 12H, Ar-H). ^{19}F NMR ($CDCl_3$) δ –118.99 (s, F-2′C). Anal. Calcd for $C_{26}H_{20}ClFN_4S$: C, 63.60; N, 11.41; S, 6.53. Found: C, 63.42; N, 11.44; S, 6.51.

Compound 4h. ^{1}H NMR ($CDCl_3$) δ 1.51 (t, 3H, –CH_2–CH_3), 2.72 (q, 2H, –CH_2–CH_3), 3.19 (dd, 1H, H-11a, J_1 = 12.5 Hz, J_2 = 1.5 Hz), 3.52 (d, 1H, H-11, J = 1.5 Hz), 4.03 (d, 1H, H-12, J = 12.5 Hz), 6.98–8.10 (m, 11H, Ar-H). ^{19}F NMR ($CDCl_3$) δ −118.92 (s, F-4′C), −119.28 (s, F-3′C). Anal. Calcd for $C_{26}H_{19}ClF_2N_4OS$: C, 61.35; N, 11.01; S, 6.30. Found: C, 61.17; N, 10.98; S, 6.32.

Compound 4i. ^{1}H NMR ($CDCl_3$) δ 0.99 (t, 3H, –CH_2–CH_2–CH_3), 1.69 (m, 2H, –CH_2–CH_2–CH_3), 2.76 (t, 2H, –CH_2–CH_2–CH_3), 3.17 (dd, 1H, H-11a, J_1 = 12.3 Hz, J_2 = 1.4 Hz), 3.49 (d, 1H, H-11, J = 1.4 Hz) 4.02 (d, 1H, H-12, J = 12.3 Hz), 6.95–8.05 (m, 12H, Ar-H), ^{13}C NMR ($CDCl_3$) δ 13.8 (–CH_2–CH_2–CH_3), 25.41 (–CH_2–CH_2–CH_3), 26.12 (–CH_2–CH_2CH_3), 48.12 (C-11a), 60.62 (C-12), 76.78 (C-11), 165.10 (C-5a), 162.05 (C-3), 160.48 (C-13a), 159.78 (C-2′), 158.26–119.58 (other aromatic carbons). ^{19}F NMR ($CDCl_3$) δ −119.02 (s, F-2′C). Anal. Calcd for $C_{27}H_{22}ClFN_4OS$: C, 64.21; N, 11.09; S, 6.35. Found: C, 64.40; N, 11.06; S, 6.33.

Compound 4j. ^{1}H NMR ($CDCl_3$) δ 1.01 (t, 3H, –CH_2–CH_2–CH_3), 1.72 (m, 2H, –CH_2–CH_2–CH_3), 2.80 (t, 2H, CH_2–CH_2–CH_3), 3.18 (dd, 1H, H-11a, J_1 = 12.4 Hz, J_2 = 1.3 Hz), 3.47 (d, 1H, H-11, J = 1.3 Hz), 4.01 (d, 1H, H-12, J = 12.4 Hz), 6.96–8.09 (m, 12H, Ar-H). ^{19}F NMR ($CDCl_3$) δ −77.86 (s, –OCF_3). Anal. Cacld for $C_{28}H_{12}ClF_3N_4O_2S$: C, 58.90; N, 9.81; S, 5.62. Found: C, 59.07; N, 9.78; S, 5.60.

Compound 4k. ^{1}H NMR ($CDCl_3$) δ 1.03 (t, 3H, –CH_2–CH_2–CH_3), 1.71 (m, 2H, –CH_2–CH_2–CH_3), 2.78 (t, 2H, CH_2–CH_2–CH_3), 3.17 (dd, 1H, H-11a, J_1 = 12.5 Hz, J_2 = 1.4 Hz), 3.49 (d, 1H, H-11, J = 1.4 Hz), 4.02 (d, 1H, H-12, J = 12.5 Hz), 6.97–8.04 (m, 11H, Ar-H). ^{19}F NMR ($CDCl_3$) δ −118.62 (s, F-4′C), Anal. Calcd for $C_{27}H_{21}Cl_2FN_4OS$: C, 60.11; N, 10.39: S, 5.94. Found: C, 59.95; N, 10.37; S, 5.92.

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