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Synthesis of novel substituted / unsubstituted- (2,8-bis-trifluoromethyl-quinolin-4-yloxy)-acetic acid: Derivatives of cephalosporin and their antibacterial activity

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Substituted/unsubstituted-(2,8-bis-trifluoromethyl-quinolin-4-yloxy)-acetic acid derivatives of cephalosporin have been synthesized by condensation of acid chlorides of substituted/unsubstituted - (2,8-bis-trifluoromethyl-quinolin-4-yloxy)-acetic acid with various silylated (6*R*,7*R*)-7-amino-3-substituted cephalosporanic acids. The products have been tested for their antibacterial activity.

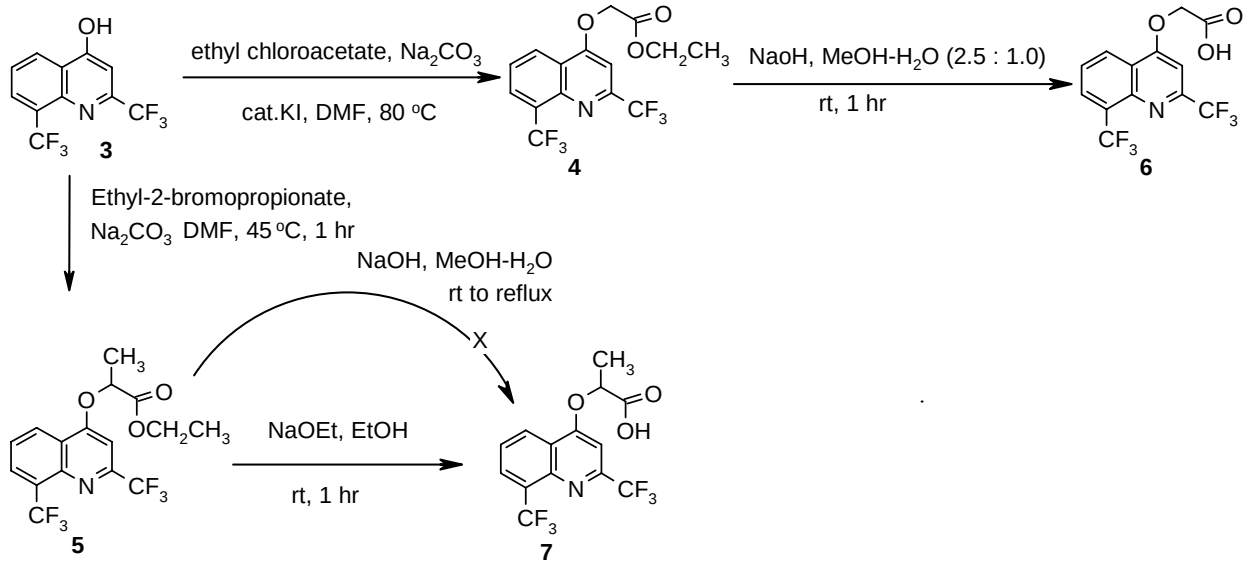
Keywords: Quinolinoxy acetic acids, cephalosporins, substituted cephalosporanic acids, hexamethyldisilazane, chlorotrimethylsilane, silylation, antibacterial activity

IPC: Int.Cl.[8]C07D

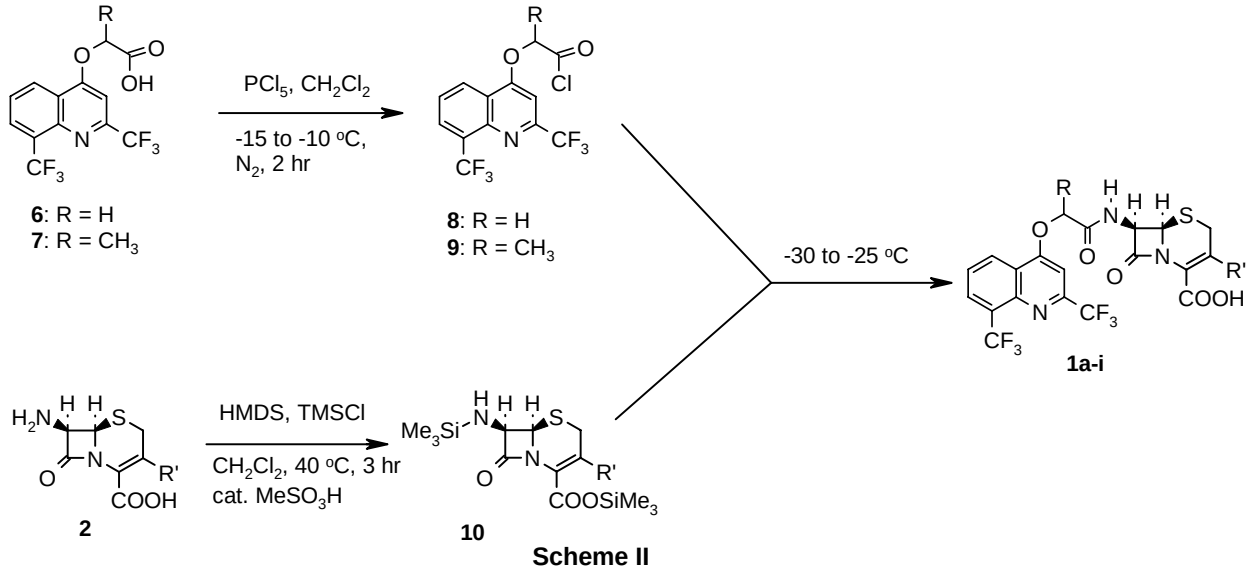
Most of the clinically useful β-lactam cephalosporin antibiotics possess the structurally modified side chains that enhance the activity of the drug. Large number of such analogs has been in use till date. But, in recent years, bacterial resistance to these antibiotics is found to be increasing at an alarming rate due to the resistance of bacteria to these drugs. As a result, successful treatment of bacterial infection is threatened. In order to overcome this problem, there is an ever-growing need to synthesize new antibiotics with increased activity. As a result, we focus our attention to use a pharmacologically active pharmacophore which till date has not been reported. 2,8-Bis-trifluoromethyl-quinolin-4-yloxy moiety, an active component of mefloquine[1] is chosen as a suitable pharmacore that can be anchored on to the 7-amino group of cephem nuclei. These nuclei are (i) (6*R*, 7*R*)-7-aminocephalosporanic acid **2** (7-ACA, R'=-CH_2OAc) used for the synthesis of marketed cephalosporins e.g. cefotaxime[2], cephacetrile[3], cephaloglycin[4], cephalothin[5] and cephapirin sodium[6]. (ii) (6*R*, 7*R*)-7-aminodesacetylcephalosporanic acid **2** (7-ADCA, R'=-CH_3)-intermediate of marketed drugs cefadroxil[7], ceftamet[8], cephalexin[9] and cephradine[10], (iii) (6*R*, 7*R*)-7-amino-3-chlorocephalosporanic acid **2** (7-ACCA, R'= -Cl)—crucial intermediate used for the commercial product cefaclor[11], (iv) (6*R*, 7*R*)-7-amino-3- (furan-2-carbonylsulfanylmethyl) cephalosporanic acid **2** [7-ATFCA, R'= -CH_2SCO(2-furoyl)]—key intermediate for the commercial antibiotic ceftiofur[12] and (v) (6*R*, 7*R*)-7-amino-3-methoxymethylcephalosporanic acid **2** (7-AMCA, R'= -CH_2OCH_3)—used for the commercial production of cefpodoxime proxetil[13]. As these nuclei have got broad applications, it is planned to design the synthesis in such a way that, this would allow to give variation at C-3 and C-7 positions for the biological studies.

Results and Discussion

2,8-Bis-trifluoromethyl-quinolin-4-ol (ref. 14) **3** was alkylated with α-haloesters/Na_2CO_3 to give esters **4** and **5** which were hydrolysed to the corresponding acids **6** and **7**. For the hydrolysis of ester functionality in compound **5**, we have initially used NaOH/MeOH. Surprisingly, this method did not work. However, when the hydrolysis was carried out using NaOEt/EtOH, the acid **7** was obtained very easily (**Scheme I**).



Scheme I



Scheme II

Table I—Antibacterial activity of compounds **1a-i**

Microorganisms	Compds											
	A	B	C	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	**1h**	**1i**
S.aureus ATCC29213	0.25	1	1	0.25	2.00	0.50	0.125	0.25	0.25	0.125	1.00	0.25
S. aureus ATCC25923	0.50	1	1	0.125	1.00	0.25	<0.03	0.25	0.25	0.125	0.50	0.25
S.epidermidis 1222	0.50	1	1	0.125	1.00	0.25	<0.03	0.25	0.25	0.25	0.50	0.25
MRSE(4)	0.50	1	2	2.00	>16.0	-	2.00	0.25	0.25	1.00	2.00	0.125
S.saprophy-ticus 15305	0.125	1	1	0.25	1.00	0.25	0.06	0.25	0.25	0.25	0.25	0.50
S.*epidermidis* 155	8->16	1	>16	0.06	1.00	0.125	<0.03	0.25	0.25	0.125	1.00	1.00
MRSA (B)	8->16	1	8->16	0.50	2.00	1.00	2.00	2.00	0.25	0.125	0.25	1.00

A = Ciprofloxacin, B = Linezolid, C = Cefotaxime

Table II—The characterization data of compounds **1a-i**

Compd	Yield (%)	Spectroscopic data – ^{1}H NMR and ^{13}C NMR (DMSO-d_6, 200 MHz, δ)
1a	40	^{1}H NMR: δ 2.03 (3H, s, CH_3), 3.40-3.73 (2H, ABq, J_{AB}=18.1 Hz, β-lactam SCH_2), 4.7, 5.0 (2H, ABq, J_{AB}=12.9 Hz, CH_2), 5.1 (1H, d, J=4.8 Hz, β-lactam C_6H), 5.2 (2H, s, OCH_2), 5.7-5.8 (1H, dd, J_1=4.96 Hz, J_2=4.87 Hz, β-lactam C_7H), 7.4 (1H, s, Ar-C_3H), 7.88 (1H, t, J_1=7.7 Hz, J_2=7.9Hz, Ar-C_6H), 8.3 (1H, d, J=7.2 Hz, Ar-C_5H), 8.6 (1H, d, J=8.3 Hz, Ar-C_7H), 9.4 (1H, d, J=8.1 Hz, NH). ^{13}C NMR: δ 20.5, 25.6, 57.2, 58.9, 62.7, 67.3, 99.3, 121.8, 123.6, 123.8, 125.9, 126.4, 127.1, 127.4, 130.2, 143.6, 148.1, 148.8, 162.8, 163.9, 167.2, 170.2. MS (ESI) m/z $[M+H]^+$ 594.2. Anal. Calcd For $C_{23}H_{17}F_6N_3O_7$ S: C, 46.58; H, 2.89; N, 7.08. Found: C, 46.77; H, 2.78; N, 7.30%.
1b	42	^{1}H NMR: δ 2.0 (3H, s, CH_3), 3.3-3.6 (2H, ABq, J_{AB}= 18.1 Hz, SCH_2), 5.1 (1H, d, J=4.6 Hz, β-lactam C_6H), 5.2 (2H, s, OCH_2), 5.6-5.7 (1H, dd, J_1=4.63 Hz, J_2=4.61 Hz, β-lactam C_7H), 7.5 (1H, s, Ar-C_3H), 7.86 (1H, t, J_1=7.8 Hz, J_2=7.9 Hz, Ar-C_6H), 8.3 (1H, d, J=7.2Hz, Ar-C_5H), 8.6 (1H, d, J=8.2 Hz, Ar-C_7H), 9.3 (1H, d, J=8.0 Hz, NH). ^{13}C NMR: δ 19.6, 20.9, 57.2, 59.0, 67.6, 99.4, 122.0, 123.1, 125.6, 126.2, 126.6, 126.8, 130.3, 130.9, 143.9, 148.3, 149.0, 163.1, 163.7, 163.8, 167.4. MS (ESI) m/z $[M+H]^+$ 536.2. Anal. Calcd For $C_{21}H_{15}F_6N_3O_5$ S: C, 47.14; H, 2.82; N, 7.85. Found: C, 47.32; H, 3.08; N, 7.98%.
1c	77	^{1}H NMR: δ 3.5-3.9 (2H, ABq, J_{AB}=18.0 Hz, β-lactam SCH_2), 5.11 (2H, s, OCH_2), 5.16 (1H, d, J=4.8 Hz, β-lactam C_6H), 5.68-5.75 (1H, dd, J_1=4.88 Hz, J_2=4.85Hz, β-lactam C_7H), 7.3 (1H, s, Ar-C_3H), 7.74-7.82 (1H, t, J_1=7.84 Hz, J_2=7.88 Hz, Ar-C_6H), 8.2 (1H, d, J=7.19 Hz, Ar-C_5H), 8.5 (1H, d, J=8.33 Hz, Ar-C_7H), 9.38 (1H, d, J=8.08 Hz, NH). ^{13}C NMR: δ 30.0, 57.0, 58.8, 59.7, 67.4, 99.2, 118.3, 120.9, 121.8, 123.8, 125.4, 125.9, 126.5, 127.1, 127.3, 130.2, 143.6, 161.6, 162.8, 163.3, 167.2. MS (ESI) m/z $[M+H]^+$ 556.7. Anal. Calcd For $C_{20}H_{12}ClF_6N_3O_5$ S: C, 43.2; H, 2.2; N, 7.56. Found: C, 43.42; H, 2.44; N, 7.18%.
1d	48	^{1}H NMR: δ 3.2-3.7 (2H, ABq, J_{AB}=18.0 Hz, β-lactam SCH_2), 3.8-4.2 (2H, ABq, J_{AB}=13.3 Hz, CH_2), 5.0 (1H, d, J=4.7 Hz, β-lactam C_6H), 5.1 (2H, s, OCH_2), 5.6-5.7 (1H, dd, J_1=4.88 Hz, J_2=4.85 Hz, β-lactam C_7H), 6.7 (1H, m, furyl-H), 7.3 (1H, m, furyl-H), 7.4 (1H, m, furyl-H), 7.8 (1H, t, J_1=7.83 Hz, J_2=7.86 Hz, Ar-C_6H), 8.0 (1H, s, Ar-C_3H), 8.2 (1H, d, J=7.1 Hz, Ar-C_5H), 8.5 (1H, d, J=8.4Hz, Ar-C_7H), 9.3 (1H, J=8.1 Hz, NH). MS (ESI) m/z $[M+H]^+$ Calcd For $C_{26}H_{17}F_6N_3O_7S_2$: 661.0. Found 662.0.
1e	60	^{1}H NMR: δ 1.6 (3H, d, J=6.3 Hz, CH_3), 2.0 (3H, s, CH_3) 3.4-3.6 (2H, ABq, J_{AB}=18.0 Hz, β-lactam SCH_2) 4.6-5.0 (2H, ABq, J_{AB}=12.8 Hz, CH_2), 5.1 (1H, d, J=4.7 Hz, β-lactam C_6H), 5.4 (1H, q, OCH), 5.61-5.67 (1H, dd, J_1=4.82 Hz, J_2=4.87 Hz, β-lactam C_7H), 7.3 (1H, s, Ar-C_3H), 7.84-7.92 (1H, t, J_1=7.78 Hz, J_2=7.91 Hz, Ar-C_6H), 8.3 (1H, d, J=7.1 Hz, Ar-C_5H), 8.6 (1H, d, J=8.3 Hz, Ar-C_7H), 9.5 (1H, d, J=7.67 Hz, NH). MS (ESI) m/z $[M+H]^+$ Calcd For $C_{24}H_{19}F_6N_3O_7S$: 607. Found 607.9.
1f	81	^{1}H NMR: δ 1.6 (3H, d, J=5.7 Hz, CH_3), 2.0(3H, s, CH_3), 3.38(2H, br, s, SCH_2 and H_2O in DMSO-d_6), 5.0(1H, d, J=4.75 Hz, β-lactam C_6H), 5.4(2H, m, β-lactam C_7H and OCH), 7.36(1H, s, Ar-C_3H), 7.88(1H, t, J_1=7.8 Hz, J_2=7.88 Hz, Ar-C_6H), 8.3(1H, d, J=6.6 Hz, Ar-C_5H) 8.6(1H, d, J=8.4 Hz, Ar-C_7H), 9.4(1H, d, J=7.7 Hz, NH, diastereomeric mixture). MS (ESI) m/z $[M+H]^+$ Calcd For $C_{22}H_{17}F_6N_3O_5S$: 549.0; Found 550.0.
1g	54	^{1}H NMR: δ 1.6 (3H, d, J=6.0 Hz, CH_3), 3.18-3.33 (1H, ABq, J_{AB}=10.8 Hz, β-lactam SCH_2, diastereomeric mixture), 3.55-3.69 (1H, ABq, J_{AB}=9.4 Hz, β-lactam SCH_2, diastereomeric mixture), 3.78-3.90 (1H, ABq, J_{AB}=9.1 Hz, CH_2, diastereomeric mixture, 1:1) 4.14-4.24 (1H, ABq, J_{AB}=9.1 Hz, CH_2, diastereomeric mixture, 1:1) 5.0 (1H, d, J=4.5 Hz, β-lactam C_6H), 5.3 (1H, q, OCH), 5.50-5.68 (1H, dd, J_1=4.9 Hz, J_2=4.85 Hz, β-lactam C_7H, diastereomeric mixture, 1:0.8), 6.68 (1H, m, furyl-H), 7.22-7.35 (2H, m, furyl-H), 7.73-7.81 (1H, t, J_1=7.9 Hz, J_2=7.82 Hz, Ar-C_6H), 7.96 (1H, s, Ar-C_3H), 8.2 (1H, d, J=7.24 Hz, Ar-C_5H), 8.5 (1H, d, J=8.28 Hz, Ar-C_7H), 9.3 ($^2/_5$ H, d, J=7.62 Hz, NH, diastereomeric mixture), 9.4 ($^3/_5$ H, d, J=7.65 Hz, NH, diastereomeric mixture). ^{13}C NMR: δ 18.5, 27.1, 29.8, 57.6, 59.6, 74.3, 99.3, 113.3, 117.4, 122.2, 126.08, 126.68, 127.44, 127.71, 130.54, 144.06, 148.57, 149.8, 162.4, 163.3, 163.9, 170.54, 170.67, 179.3. MS (ESI) m/z $[M+H]^+$ 676.5. Anal. Calcd For $C_{27}H_{19}F_6N_3O_7S_2$: C, 48.04; H, 2.83; N, 6.22. Found: C, 48.28; H, 3.05; N, 6.03.
1h	64	^{1}H NMR: δ 3.12 (3H, s, OCH_3), 3.33-3.57 (2H, ABq, J_{AB}=18.0 Hz, β-lactam SCH_2), 4.1 (2H, s, CH_2), 5.0 (1H, d, J=4.76 Hz, β-lactam C_6H), 5.1 (2H, s, OCH_2), 5.62-5.68 (1H, dd, J_1=4.83 Hz, J_2=4.4 Hz β-lactam C_7H), 7.4 (1H, s, Ar-C_3H), 7.76-7.85 (1H, t, J_1=7.85 Hz, J_2=7.86 Hz, Ar-C_6H), 8.2 (1H, d, J=7.15 Hz, Ar-C_5H), 8.5 (1H, d, J=8.31 Hz, Ar-C_7H), 9.3 (1H, d, J=8.08 Hz, NH). MS (ESI) m/z $[M+H]^+$ 566.3. Anal. Cacld For $C_{22}H_{17}F_6N_3O_6S$: C, 46.77; H, 3.03; N, 7.44. Found: C, 46.56; H, 3.23; N, 7.65%.
1i	28	^{1}H NMR: δ 1.58 (3H, d, J = 6.3 Hz, CH_3), 3.1 (3H, s, OCH_3), 3.29-3.55 (2H, ABq, J_{AB}=18.1 Hz, SCH_2), 4.1 (2H, s, OCH_2), 5.0 (1H, d, J = 4.62 Hz, β-lactam C_6H), 5.3 (1H, q, -OCH-), 5.49-5.56 (1H, dd, J_1=4.63 Hz, J_2= 4.96 Hz, β-lactam C_7H), 7.3 (1H, s, Ar-C_3H), 7.75-7.83 (1H, t, J_1=7.96 Hz, J_2=7.84 Hz, Ar-C_6H), 8.2(1H, d, J = 7.19 Hz, Ar-C_5H), 8.5 (1H, d, J=8.24 Hz, Ar-C_7H), 9.4 (1H, d, J = 7.74 H_z, NH, diastereomeric mixture). ^{13}C NMR: δ 18.2, 25.2, 57.38, 59.28, 69.83, 74.0, 99.0, 118.2, 121.9, 123.7, 125.5, 125.9, 126.5, 127.1, 127.3, 130.2, 143.7, 148.1, 148.8, 162.1, 163.0, 163.6, 170.2. MS (ESI) m/z $[m+H]^+$ Cacld For $C_{23}H_{19}F_6N_3O_6S$: 579; Found 580.0.

The acids **6** and **7** were coupled with amine **2**. The coupling reaction was carried out by activating the carboxylic acid to the acid chlorides **8** and **9** and treated with silylated amine **10** to obtain the amide **1a-i** (**Scheme II**, **Table I**).

For the synthesis of compounds **1h** and **1i**, the silylation of amine **2** (R'=CH_2OCH_3) was carried out using 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 1.2 mole) and chlorotrimethylsilane (TMSCl, 0.03 mole) to give the silylated product **10** (R'= -CH_2OCH_3). However, for compounds **2** [R'= -CH_2OAC, -CH_3, -Cl, -CH_2SCO-(2-furyl)], silylation was carried out using HMDS (0.8 mole) and TMSCl (0.8 mole). This modification was made because it was suspected that if excess amount of TMSCl was used in case of compound **2** (R'=-CH_2OCH_3), the methyl ether would be cleaved.

Antibacterial activity

The MIC was determined by using standard agar dilution methods as described by National Committee for Clinical Laboratory Standards (NCCLS). Briefly, Mueller-Hinton (MH) Agar plates with different concentrations of drug ranging from 0.03 µg/mL to 16 µg/mL were prepared and inoculated with 1×10^6 organisms (0.5 Macfarland diluted 1:10 times) using multi-point inoculator. Plates were incubated at 37°C overnight and observed for inhibition of the growth. The minimum concentration where no visible growth occurred was taken as MIC.

The standard bacterial strains were procured from American Type Culture Collection (ATCC), Rockville, USA. The patient isolates were procured from Poona Hospital. The patient isolates were identified upto species level using biochemical tests. All the strains were sub cultured from fresh glycerol stocks stored at -70ºC, 48 hr before the experiment and sub cultured on soyabean casein digest agar (SCDA), 24 hr before the actual experiment.

The antibacterial activity was compared with the known drugs ciprofloxacin (A), linezolid (B), cefotaxime (C). The MIC of the compounds was studied against common gram-positive pathogens (**Table II**). All the compounds exhibited remarkable *in vitro* activity against *S.aureus* ATCC29213, *S.aureus* ATCC25923, *S.epidermidis* 12228, MRSE *(*4), *S.saprophyticus* 15305, *S.epidermidis* 155 and MRSA (B). The MIC of compound **1a** ranged from 0.06 to 0.25 for susceptible strains and 0.50-2.50 for methicillin-resistant strains. Compounds **1b** exhibited slightly higher MIC whereas an exceptional lower MIC values were obtained with compound **1d** which ranged from <0.03 to 0.125 for susceptible isolates and 2.00 µg/mL for resistant strains. The MIC values showed that all the molecules synthesized have antibacterial activity against *S.aureus*, which is the cause of 8-21% mortality in hospitals environment. Activity against *S.aureus* suggests that these molecules should also exhibit activity against other gram-positive infectents. The compounds exhibited no activity against gram-negative organisms and thus are specific in nature.

Experimental Section

Melting points are recorded on Electrothermal 9300 and Electrothermal 2000 and are uncorrected. The ^{1}H NMR spectra were run on a Brucker DRX 2000 instrument using TMS as an internal standard. Infrared spectra were recorded on a FTIR Shimadzu 8201 spectrometer. Mass spectra were run on a Perkin-Elmer PE Sciex API 3000 mass spectrometer using API mode. Raw materials used were commercially available.

(2,8-Bis-trifluoromethyl-quinolin-4-yloxy)-acetic acid ethyl ester 4. To a DMF (200 mL) solution of 2,8-Bis-trifluoromethyl-quinolin-4-ol **3** (50.0 g, 0.1779 mole), was added ethyl chloroacetate (32.7 g, 0.2668 mole), sodium carbonate (30.2 g, 0.2849 mole) and catalytic amount of potassium iodide. The mixture was stirred at 80 ºC for 2 hr. After 2 hr, the reaction was completed as monitored by TLC (1: 4, ethyl acetate:hexane). The reaction mixture was brought to room temperature, poured into water (500 mL) and extracted with ethyl acetate (3 × 200 mL). The organic layer was washed with water (2 × 100 mL) followed by brine (50 mL) and dried over anhydrous Na_2SO_4. The ethyl acetate was removed under *vacuo* to obtain a solid which was stirred with hexane (150 mL) and filtered to furnish (2,8-bis-trifluoromethyl-quinolin-4-yloxy)-acetic acid ethyl ester **4** as off-white solid (58.2 g, yield 89%). m.p 106 °C; ^{1}H NMR ($CDCl_3$, 200 MHz, δ) 1.23-1.30 (3H, t, CH_3), 4.21-4.32 (2H, q, CH_2), 4.87 (2H, s, OCH_2), 6.93 (1H, s, Ar-C_3H), 7.58-7.66 (1H, t, J_1 = 7.89 H_z, J_2=7.86 H_z, Ar-C_6H), 8.1 (1H, d, J = 7.24 H_z, Ar-C_5H), 8.48 (1H, d, J = 8.45 H_z, Ar-C_7H); MS (ESI) m/z $[M+H]^+$ 368.1; Anal. Calcd For $C_{15}H_{11}F_6NO_3$: C, 49.07; H, 3.02; N, 3.81. Found: C, 49.20; H, 3.19; N, 3.95.

2-(2,8-Bis-trifluoromethyl-quinolin-4-yloxy)-propionic acid ethyl ester 5. To a DMF (150 mL)

solution of 2,8-bis-trifluoromethyl-quinolin-4-ol **3** (50.0 g, 0.1779 mole), was added powdered sodium carbonate (30.2 g, 0.2846 mole) and ethyl-2-bromopropionate (48.3 g, 0.2668 mole). The reaction mixture was stirred at 45 °C for 1 hr. After 1 hr, the reaction was completed as monitored by TLC (1: 4, ethyl acetate:hexane). The reaction mixture was cooled to ambient temperature, poured into water (500 mL) and extracted with ethyl acetate (3 × 250 mL). The ethyl acetate layer was washed with water (3 × 100 mL) followed by brine (100 mL) and dried over anhydrous Na_2SO_4. The ethyl acetate was removed under *vacuo* to obtain a solid which was stirred with heptane (100 mL) and then filtered to obtain 2-(2,8-bis-trifluoromethyl-quinolin-4-yloxy)-propionic acid ethyl ester **5** as yellowish solid (50.1 g, yield 74%). m.p 96.5 - 97.4 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz, δ) 1.17-1.24 (3H, t, CH_3), 1.76 (3H, d, J = 6.7 Hz, CH_3), 4.19-4.24 (2H, q, OCH_2), 5.01 (1H, q, CH), 6.9 (1H, s, Ar-C_3H), 7.57-7.65 (1H, t, J_1 = 7.90 Hz, J_2 = 7.83 Hz, Ar-C_6H), 8.08 (1H, d, J = 7.23 Hz, Ar-C_5H), 8.48 (1H, d, J = 8.43 H_z, Ar-C_7H); MS (ESI) m/z $[M+H]^+$ 382.0; Anal. Calcd for $C_{16}H_{13}F_6NO_3$: C, 50.41; H, 3.44; N, 3.67. Found: C, 50.62; H, 3.61; N, 3.52.

(2,8-Bis-trifluoromethyl-quinolin-4-yloxy)-acetic acid 6. To the suspension of (2,8-bis-trifluoromethyl-quinolin-4-yloxy)-acetic acid ethyl ester **4** (50.0 g, 0.1362 mole) in a mixture of methanol (125 mL) and water (50 mL), was added NaOH (7.1 g, 0.1775 mole) resulting in a clear solution in 20 min. The reaction mixture was stirred at room temperature for 1 hr. After 1 hr, the reaction was completed as monitored by TLC (1:4, ethyl acetate:hexane). The reaction mixture was diluted with water (500 mL) and then was adjusted to *p*H 2.0 with concentrated hydrochloric acid (20 mL). The precipitate was collected by filtration and dried to afford (2,8-bis-trifluoromethyl-quinolin-4-yloxy)-acetic acid **6** as colourless solid (45.0 g, yield 97%). m.p. 191 °C; ^{1}H NMR (DMSO-d_6, 200 MHz, δ) 5.17 (2H, s, OCH_2), 7.53 (1H, s, Ar-C_3H), 7.76-7.84 (1H, t, J_1 = 7.89 Hz, J_2 = 7.84 Hz, Ar-C_6H), 8.26 (1H, d, J = 7.18 Hz, Ar-C_5H), 8.48 (1H, d, J = 8.35 Hz, Ar-C_7H); MS (ESI) m/z $[M+H]^+$ 339.1; Anal. Calcd for $C_{13}H_7F_6NO_3$: C, 46.04; H, 2.08; N, 4.19. Found: C, 46.21; H, 2.2; N, 4.34.

2-(2,8-Bis-trifluoromethyl-quinolin-4-yloxy)-propionic acid 7. To a suspension of 2-(2,8-bis-trifluoromethyl-quinolin-4-yloxy)-propionic acid ethyl ester **5** (40.0 g, 0.1049 mole) in absolute ethanol (120 mL) was added sodium ethoxide (9.6 g, 0.1411 mole). The reaction mixture was stirred at room temperature for 1 hr, the reaction was completed as monitored by TLC (1: 4, ethyl acetate:hexane). The reaction mixture was diluted with water (500 mL) and then acidified to *p*H 2.0 with conc. HCl (20 mL) at 5 ºC. The aqueous phase was extracted with ethyl acetate (2 × 300 mL) which was washed with water (2×100 mL) followed by brine (100 mL) and finally dried with anhydrous Na_2SO_4. The ethyl acetate was removed under *vacuo* to furnish 2-(2,8-bis-trifluoromethyl-quinolin-4-yloxy)-propionic acid **7** as off-white solid (38.6 g, yield 93%). m.p 173 – 74 ºC; ^{1}H NMR (DMSO-d_6, 200 MHz, δ) 1.63 (3H, d, J=6.7 Hz, CH_3), 5.52 (1H, q, CH), 7.41 (1H, s, Ar-C_3H), 7.74-7.82 (1H, t, J_1 = 7.88 Hz, J_2 = 7.87 Hz, Ar-C_6H), 8.25 (1H, d, J = 7.17 Hz, Ar-C_5H), 8.48 (1H, d, J = 8.35 Hz, Ar-C_7H); MS (ESI) m/z $[M+H]^+$ 354.0; Anal. Calcd for $C_{14}H_9F_6NO_3$: C, 47.61; H, 2.57; N, 3.97. Found: C, 47.55; H, 2.69; N, 4.18.

General procedure for the preparation of compounds 1a-g. **3-Acetoxymethyl-7- [2-(2,8-bis-trifluoromethyl-quinolin-4-yloxy)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 1a**. To a suspension of (6*R*, 7*R*)-7-aminocephalosporanic acids **2** (R' = -CH_2OCOCH_3) (5.0 g, 0.0184 mole) in dry dichloromethane (50 mL) was added 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (3.1 mL, 0.0147 mole) followed by chloro-trimethylsilane (TMSCl) (1.864 me, 0.0147mole). The mixture was refluxed for 3 hr and then cooled to room temperature. The catalytic amount of methane-sulphonic acid was added and stirred for 15 min.

In a separate round bottom flask, (2,8-bis-trifluoromethyl-quinolin-4-yloxy)-acetic acid **6** (6.33 g, 0.0193 mole) was taken in dry dichloromethane (50 mL) and cooled to –15 to –10 ºC. Phosphorous pentachloride (4.2 g, 0.0202 mole) was added under N_2 atmosphere and stirred at –15 to –10 ºC for 2 hr. The reaction mixture was brought to 0-5 ºC and N_2 was bubbled for 1.0 hr. To this acid chloride **8** (R=H) was added the above silylated reaction mass at -30 to –25 ºC in 20 min. and then stirred for 2 hr at -25 to –20ºC. The reaction mixture was then poured into cold water with slow stirring during which the product precipitated out which was collected by filtration. The solid was dissolved in ethyl acetate (150 mL), washed with brine (40 mL) and dried with anhydrous Na_2SO_4. The ethyl acetate was removed under *vacuo* to obtain crude product (10.5 g, 96%), which was purified by crystallisation with ethyl

actate-haxane (1:1.5) to furnish compound **1a** as off-white solid (4.3 g, yield 40%).

General procedure for preparing compounds 1h-i. **7-[2-(2,8-Bis-trifluoromethyl-quinolin-4-yloxy)-propionylamino]-3-methoxymethyl-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 1i**. To a suspension of (6*R*,7*R*)-7-amino-3-methoxymethyl-cephalosporanic acid **2** (7-AMCA, R' = CH_2OCH_3) (3.5 g, 0.0143 mole) in dry dichloromethane (50 mL) was added 1,1,1,3,3,3-hexamethyldisilazane (HDMS) (3.6 mL, 0.0172 mole) followed by catalytic amount of chlorotrimethylsilane (TMSCl) (55 µL, 0.43 mmole). The mixture was refluxed for 3 hr and then cooled to room temperature. In another round bottom flask, 2-(2,8-bis-trifluoromethyl-quinolin-4-yloxy)-propionic acid **7**, (R = CH_3) (5.36 g, 0.0152 mole) was taken in dry dichloromethane (50 mL) and cooled to -15 to –10 ºC. Phosphorous pentachloride (3.2 g, 0.0153 mole) was added under N_2 and then stirred at -15 to –10 ºC for 2 hr. The reaction was further stirred at 0-5 ºC for 1.5 hr with bubbling N_2 and then cooled to –20 ºC. To this acid chloride **7** (R = CH_3) the above silylated reaction mass was added maintaining the temperature at -25 to –20 ºC in 20 min and then stirred for 2 hr. The reaction mixture was poured into cold water with slow stirring during which the product precipitated out which was dissolved in ethyl acetate (150 mL), washed with brine and dried with anhydrous sodium sulphate. The ethyl acetate was removed under *vacuo* to obtain crude product (8.0 g, yield 96.3%) which was purified by crystallisation with ethyl acetate-hexane (75 mL, 1:1.5) to obtain compound **1i** as yellow solid (2.3 g, yield 28%).

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