Development of Privileged Groebke-Blackburn-Type 4-(3-aminoimidazo [1,2-*a*]pyridin-2-yl)benzoic Acid Core into a Combinatorial Library on Solid Phase

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Abstract: A library of 4-(3-acyl- or carbamoylaminoimidazo[1,2-*a*]pyridin-2-yl)benzamides (**8**) was synthesized on solid phase. A suitably protected core acid (**1**) was synthesized in multigram quantity using previously published procedure and used as the acylating reagent for modifying a set of AMEBA resins. Subsequent liberation of the amino group (using a novel hydrazine procedure) and its acylation or carbamoylation provided, after cleavage, final products in higher chemical yields and purities compared to known protocols that include formation of the imidazo[1,2-*a*]pyridine core on solid support.

Keywords: Imidazo[1,2-*a*]pyridines, solid phase, combinatorial libraries, isocyanide-based multi-component reactions, privileged structures.

INTRODUCTION

The efficient synthesis of imidazo[1,2-*x*]azines *via* a reaction between a 2-aminoazine, an aldehyde and an isocyanide known as the Groebke-Blackburn multicomponent reaction (GB-MCR) [1], has triggered numerous efforts to develop combinatorial libraries based on this drug-like core [2]. This resulted in increased presence of the respective chemotypes in various screening collections and, hence, their extensive annotation *vs.* a number of biological targets. Analysis of the recent patent literature reveals (Fig. **1**) that imidazo[1,2-*a*]azines manifested themselves as modulators of sodium channels [3], ubiquitin ligase inhibitors [4], potential antidiabetic SGLT1 inhibitors [5], hystone deacetylase inhibitors [6], skeletal muscle myosin modulators [7], angiogenesis inhibitors [8], as well as ligands for G-protein coupled receptors (e. g., PAR2 [9]). Thus, imidazo[1,2-*a*]azine fragment can be regarded as a privileged structure for drug design [10]. This consideration has prompted us to include various Groebke-Blackburn-type templates in our combinatorial library synthesis program. Herein, we report on the synthesis of a library of imidazo[1,2-*a*]pyridines containing various carboxamide and urea appendages, on solid phase.

RESULTS AND DISCUSSION

Besides the use of ring-substituted 2-aminoazines, GR-MCR products can be diversified *i. via* the use of various aldehydes and isocyanides, or *ii*. by combining a diversity set of aldehydes with a single *convertible* isocyanide. In the latter case, the initially formed GB-MCR products are converted into primary amines that can be further modified at the amino group via, for example, acylation (carbamoylation) [11] or *N*-arylation [2]. Solid-phase protocols for production of imidazo[1,2-*a*]azine libraries *via* GB-MCR described to-date, included preparation of resin-supported aldehyde [11] or isonitrile [12] and exposing such modified resin to 2-aminoazine and the third reaction partner. Our initial attempts to produce large (>100 members) combinatorial arrays using GB-MCR with a resin-supported reagents resulted in low (<60%) product purities. Therefore, we decided to explore an alternative strategy by preparing a suitably functionalized imidazo[1,2-*a*]azine core in solution and then using this core as a scaffold for solid-phase development of the final set of compounds. We recently reported on the use of *tert*-butyl isocyanide as a convertible reagent in GB-MCR. It was shown that removal of the *tert*-butyl group from the initially formed *tert*-butylaminoimidazo [1,2-*a*]azines with TFA led to intermediate formation of trifluoroacetamides (and, hence, the need to hydrolyze them) [13]. We reasoned that the trifluoroacetyl-protected amino group of GB-MCR products resulting from such protocol could be useful as the amino group can be unmasked only after the imidazo[1,2-*a*]azine core is placed on solid support (e. g., *via* a carboxy function).

A multigram quantity of the core 4-[3-(trifluoroacetyl-amino)imidazo[1,2-*a*]pyridin-2-yl]benzoic acid (**1**) has been prepared as described earlier (Scheme **1**) [13]. A set of secondary amine resins **3**{1-14} (prepared *via* reductive amination [14] of the AMEBA resin [15] with primary amines **2**{1-14} depicted in Fig. **2**) was acylated with **1** using DIC/HOBt method [16]. Removal of trifluoroacetyl group from **4** with aqueous KOH methanol [13], however, was found problematic and resulted only in partial conversions, as monitored by LCMS analysis of the material cleaved off the solid support. This was unsurprising as the resin was unlikely to properly swell in aqueous methanol. We found however, that trifluoroacetyl group is cleanly removed from **4** using hydrazine hydrate in DMF [17]. The primary amino

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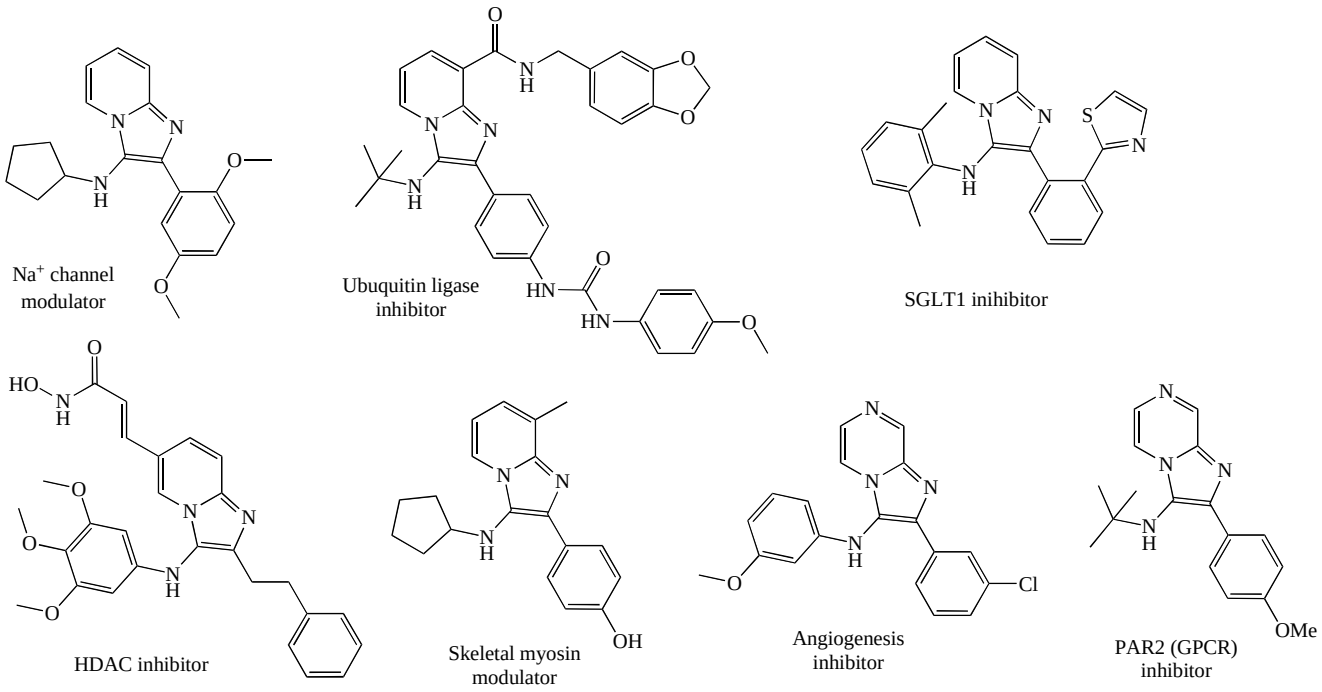
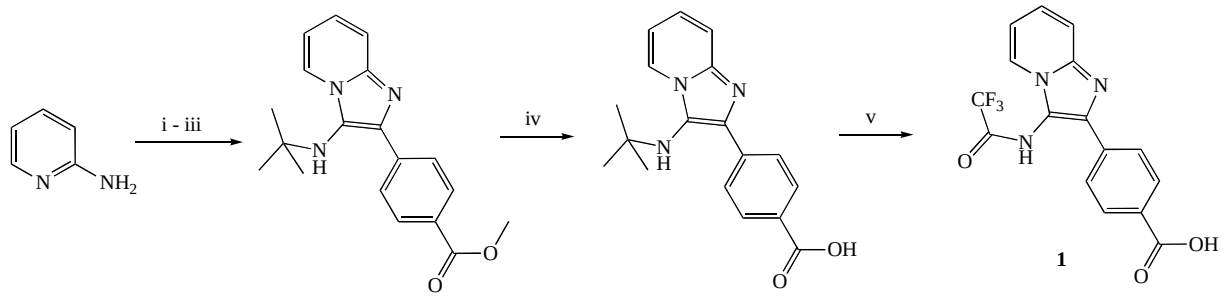


Fig. (1). Selected biologically active Groebke-Blackburn-type imidazo[1,2-*a*]azines [3-9].



Scheme 1. Large-scale synthesis of the library core reagent **1** [13].

Reagents and conditions. (i) 1 eq. 4-OHCC$_6$H$_4$COOMe, MeCN, reflux, 2 h; (ii) TMSCl (1 eq.), MeCN-DCM, rt, 30 min; (iii) *t*-BuNC (i – iii, 76%); (iv) aq. KOH (1 eq.), rt, 4 h (93%); (v) TFA, reflux, 3 h (88%).

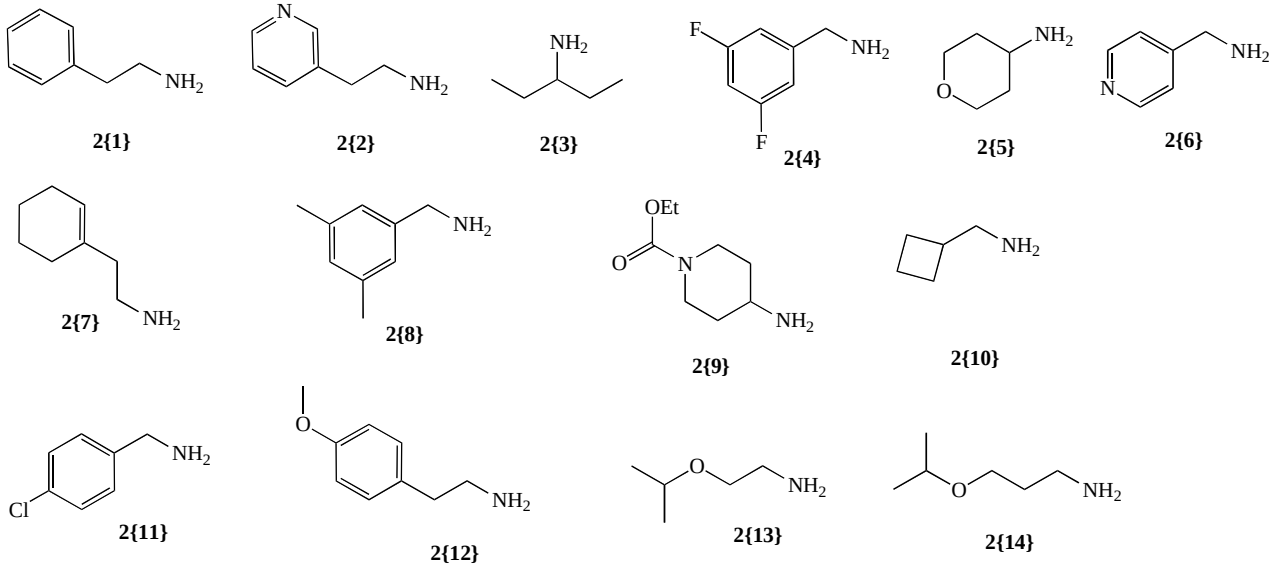


Fig. (2). Diversity reagents **2**{1-14}.

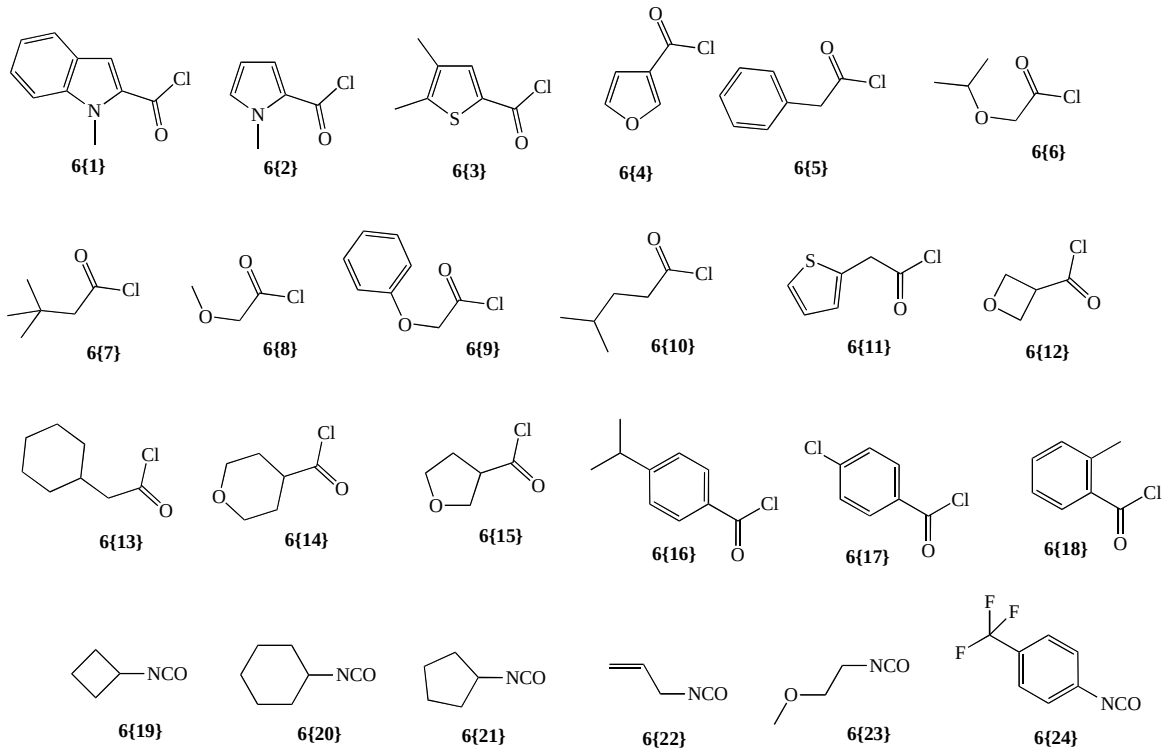
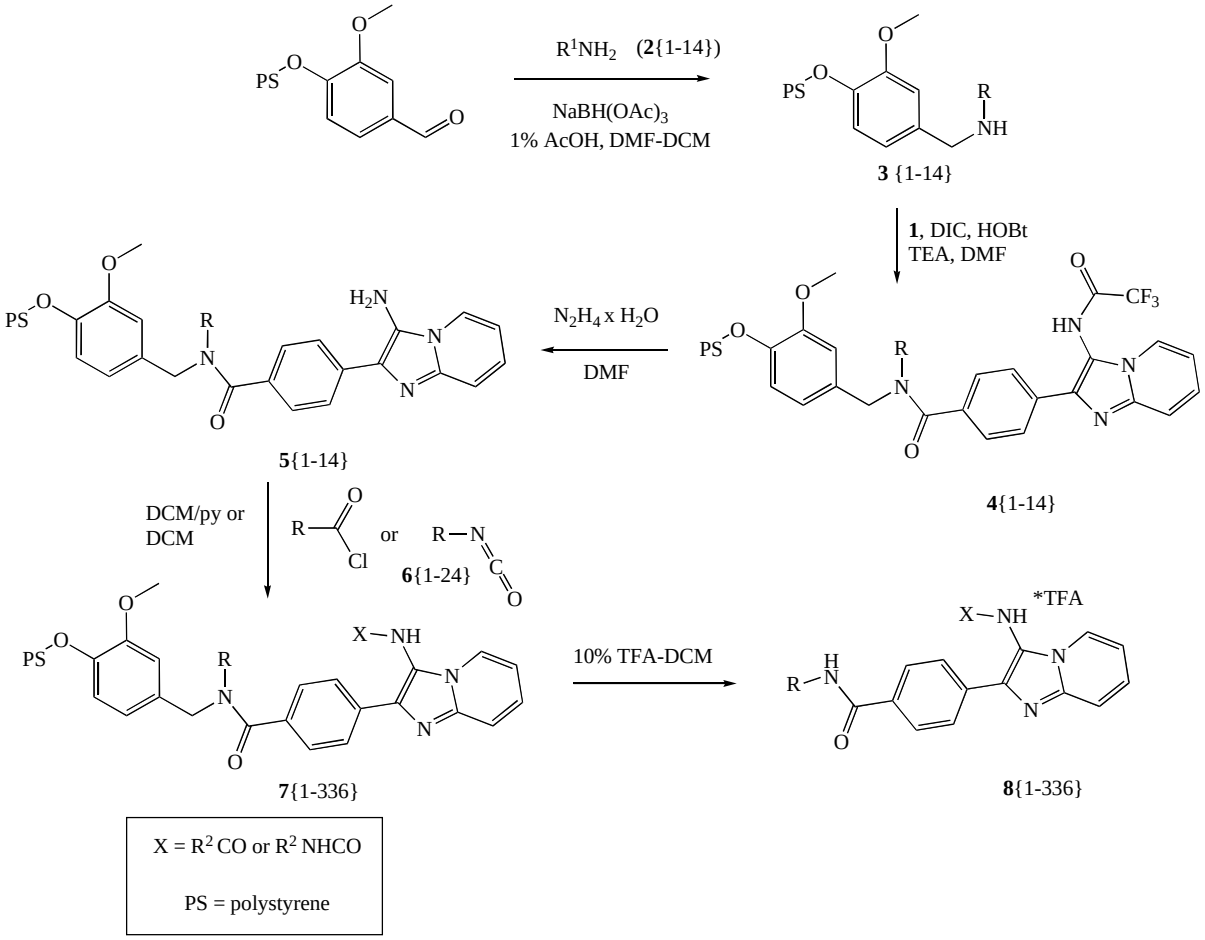


Fig. (3). Diversity reagents **6**{1-24}.



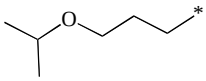
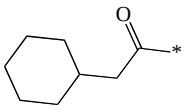
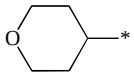
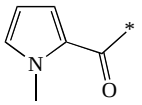
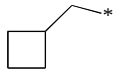
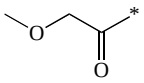
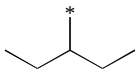
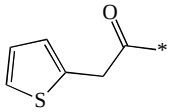
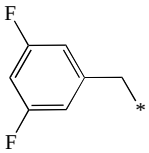
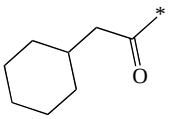
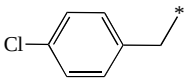
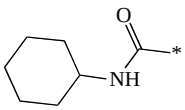
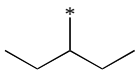
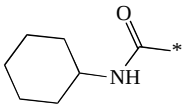
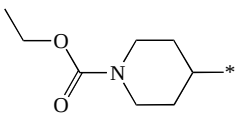
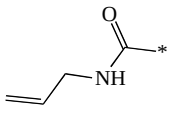
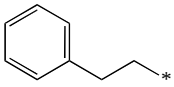
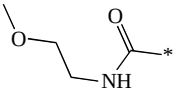
Scheme 2. Library synthesis.

group was now available for further modification. Fourteen resin-supported GB-MCR-type amines **5** were reacted with a set of acyl chlorides and isocyanates **6**{1-24} Fig. (**3**). Following the cleavage with 10% TFA in DCM and evaporation of the volatiles, the 336 product mixtures **8** were analyzed by LCMS [18]. To our delight, the desired product was detected in all cases: 152 compounds were at least 80% pure and were not purified further (the rest of compounds were purified by reverse-phase HPLC). Chemical yields of these products were in the range 25-68% relative to the amount of **3** used per one final compound, based on calculated resin loading (Scheme **2**). Selected examples of the compounds **8** and their chemical yields are presented in Table **1** [19].

CONCLUSION

In conclusion, we have demonstrated that formation of imidazo[1,2-*a*]pyridine core *via* GB-MCR prior to solid-phase expansion of the library provided advantages to alternative protocols where GB-MCR is carried out with a solid phase supported reagents. The synthesized imidazo [1.2-*a*]pyridine-based bis-amides and amide ureas **8** represent novel compounds that are now part of biological annotation program in our laboratories. Additionally, these findings can potentially be extended to other imidazo[1,2-*x*]azines and –azoles prepared by GB-MCR. Currently we are investigating the scope of the presented combinatorial approach. The results of our efforts will be reported in due course.

Table 1. Selected Compounds 8 Prepared in this Work

Compound	R^1	X	MW	LC MS m/z (M+1)	Yield, %
8a			476.6	477	49
8b			443.5	444	38
8c			378.4	379	64
8d			446.6	447	67
8e			502.6	503	77
8f			502.0	503	45
8g			447.6	448	54
8h			490.6	491	63
8i			457.5	458	61

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[14] *General procedure for reductive amination on AMEBA resin:* 4-(4-formyl-3-methoxyphenoxy)butyryl aminomethyl resin (AMEBA resin, 5.0 g, 8.35 mmol, 1.67 mmol/g) was dispersed in anhydrous THF (50 mL) and an amine R^1NH_2 (**2**) (41.7 mmol) was added. The resulting suspension was shaken at room temperature for 2 h. Sodium triacetoxyborohydride (5.3 g, 25.0 mmol) and acetic acid (2.4 ml, 41.7 mmol) were added and the resulting mixture was shaken for an additional 16 h at room temperature. The resin was separated by filtration, washed twice with THF, MeOH, DCM, and MeOH and air-dried.

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[16] *General procedure for acylation of alkylamino AMEBA resin:* To a solution of the core acid **1** (15 mmol) in DMF (30 mL) were added diisopropylcarbodiimide (DIC, 15 mmol) and 1-hydroxybenzotriazole (HOBt, 15 mmol) and the resulting mixture was stirred for 30 min. Then an aminoalkyl resin **3** (10 mmol) was added and the mixture was thoroughly shaken for 12 h at room temperature. The resin was separated by filtration, washed twice with DMF, methanol, dichloromethane, and methanol, and air-dried. (*Note:* we established that the 50% molar excess of the acid **1** was required to achieve maximum degree of resin acylation. However, the acid **1** can easily be recovered from the filtrate solution). To cap any non-acylated secondary amine centers on the resin thus obtained, it was shaken with an excess of 10% solution of acetic anhydride in DCM for 3 hours, filtered off, washed twice with DCM, methanol, DCM and methanol, and air-dried.

[17] *General procedure for removal of trifluoroacetyl group:* the acylated and acetyl-capped resin **4** was suspended in an excess of a mixture of hydrazine hydrate and DMF (1:4) and the resulting mixture was shaken at 80 °C for 72 hours. The resin **4** was separated by filtration, washed twice with DMF, methanol, DCM, and methanol, and air-dried to give the resin **5**. The full amino group deprotection was achieved as evidenced by LCMS analysis of TFA cleavage product off a small amount of **5**.

[18] *General procedure for acylation/carbamoylation of **5** and TFA cleavage of the final compounds:* A 0.5 mmol aliquote of the resin **5** was dispersed in a solution of the respective acyl chloride or isocyanate **6** (3 mmol) and pyridine (3 mmol) in DCM (20 mL). The resulting mixture was shaken at room temperature for 18 hours. The resin **7** was separated by filtration, washed twice with DMF, methanol, DCM, and methanol, and air-dried. It was then dispersed in 10% solution of TFA in DCM (3 mL) and shaken at room temperature for 2 hours. The resin was filtered off, washed with a small amount of methanol. The combined filtrate and washings were evaporated to dryness to provide crude compound **8**.

[19] Characterization data for representative compounds: **8a** – off-white solid, mp = 184 °C (MeOH, decomp.); ^{1}H NMR (300 MHz, d_6-DMSO) δ 10.6 (s, 1H), 8.55 (t, *J* = 5.3 Hz, 1H), 8.29 (d, *J* = 6.4 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 2H), 7.98 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.70 (t, *J* = 7.3 Hz, 1H), 7.30 (t, *J* = 6.9 Hz, 1H), 3.53 (m, 1H), 3.43 (t, *J* = 5.6 Hz, 2H), 3.35 (dd, *J* = 5.6, 12.5 Hz, 2H), 2.46 (d, *J* = 7.0 Hz, 2H), 1.70-1.85 (m, 8H), 0.99 – 1.30 (m, 5H), 1.08 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 172.9, 165.5, 158.5 (q, $J_{C\text{-}F}$ = 36.0 Hz, $CF_3\underline{C}OO^-$), 139.8, 134.8, 132.2, 131.9, 130.1, 127.6, 126.8, 124.9, 117.3, 115.8 (q, $J_{C\text{-}F}$ = 294.0 Hz, $\underline{C}F_3COO^-$), 115.0, 114.6, 70.6, 65.2, 42.9, 37.0, 34.5, 32.6, 29.8, 25.8, 25.6, 22.1; HRMS (EI) calcd for $C_{28}H_{36}N_4O_3$ (M^+) 476.6241, found 476.6239. **8d** - beige solid, mp = 176-178 °C (MeOH); ^{1}H NMR (300 MHz, d_6- DMSO) δ 10.8 (s, 1H), 8.34 (d, *J* = 7.5 Hz, 1H), 8.14 (d, *J* = 9.6 Hz, 1H), 7.83 (d, *J* = 9.6 Hz, 1H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.44 (d, *J* = 5.3 Hz, 1H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 3.9 Hz, 1H), 7.05 (dd, *J* = 3.9, 5.9 Hz, 1H), 4.16 (s, 2H), 3.82 (m, 1H), 1.53 (m, 4H), 0.88 (t, *J* = 7.7 Hz, 6H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 170.4, 165.5, 158.2 (q, $J_{C\text{-}F}$ = 36.1 Hz, $CF_3\underline{C}OO^-$), 140.1, 136.0, 135.0, 132.8, 132.1, 129.3, 127.7, 127.0, 126.8, 126.5, 125.3, 124.6, 116.7, 115.8 (q, $J_{C\text{-}F}$ = 294.2 Hz, $\underline{C}F_3COO^-$), 114.9, 114.5, 52.2, 36.3, 26.8, 10.5; HRMS (EI) calcd for $C_{25}H_{26}N_4O_2S$ (M^+) 446.5756, found 446.5761.