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# 2-Aryl benzazole derived new class of anti-tubercular compounds: Endowed to eradicate *mycobacterium tuberculosis* in replicating and non-replicating forms

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ABSTRACT

The high mortality rate and the increasing prevalence of *Mtb* resistance are the major concerns for the Tuberculosis (TB) treatment in this century. To counteract the prevalence of *Mtb* resistance, we have synthesized 2-aryl benzazole based dual targeted molecules. Compound **9m** and **9n** were found to be equally active against replicating and non-replicating form of *Mtb* ($MIC_{(MABA)}$ 1.98 and 1.66 μg/ml; $MIC_{(LORA)}$ 2.06 and 1.59 μg/ml respectively). They arrested the cell division (replicating *Mtb*) by inhibiting the GTPase activity of FtsZ with $IC_{50}$ values 45 and 64 μM respectively. They were also capable of kill *Mtb* in non-replicating form by inhibiting the biosynthesis of menaquinone which was substantiated by the MenG inhibition ($IC_{50}$ = 11.62 and 7.49 μM respectively) followed by the Vit-K2 rescue study and ATP production assay.

## 1. Introduction

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (*Mtb*) is the single disease which causes an estimate of 1.5 million deaths according to WHO Global Tuberculosis Report 2019 [1]. Despite the tremendous effort it is difficult to control, as evidenced from the comparative database of Global Tuberculosis Report 2018 [2] and 2019, where a decrease of only ~ 0.1 million mortality rate was observed. In Africa and Asia, new TB incidences were found between 100,000 to 2,500,000 [1]. TB treatment itself is challenging regarding its early and accurate diagnosis, administration of effective drug regimen and resistant screening. Moreover, the high tolerance of *Mtb* towards first line (e.g., Isoniazid, rifampicin, Pyrazinamide) [3–7] and second line antibiotics (e.g., Streptomycin, Ethionamide, Ofloxacin) [8–10] are the major concerns. Therefore, it is pertinent to revisit our drug designing strategy for broadening the antibiotic spectrum against *Mtb*.

The popular Direct Observation Therapy (DOT) fundamentally relies on the combination therapy [11]. The antibiotics used in a systematic monotherapy have a greater possibility for the high-level of endogenous resistance, which can be because of lower cell permeability or increased efflux or up-regulation of the target enzyme. Thus, for the TB patients anti-tuberculosis drugs are used in combination with others [12]. However, sometimes effectiveness of the combination therapy over systematic monotherapy was found to get compromised with nephrotoxicity and ototoxicity in several clinical studies [13]. The genetic reason for the occurrence of high level of endogenous resistance against a particular antibiotic is due to its single gene product target [14]. Alternatively, the probability of high level resistance is low for the drugs which interacts with multiple biological targets, *i.e.*, a product of multiple genes. Hence, for a single targeted drug there is high chance for single step mutation in the target enzyme or the target alteration [15]. Therefore, multi-targeted drugs have an added advantage over the single targeted drugs in prevention of target-based resistance development.

Selection of a target is important for new drug development. It needs to be pursued based on the significance of the target and unavailability of the same in normal mammalian cell to minimize the toxicity in host cell [16–21]. There are several promising targets for

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new drug development against *Mtb* [22–24], and there are several multi-targeting molecules reported in literature [25–27]. The designing of those molecules are primarily based upon the incorporation of biologically labile linkers [28] where two known drug molecules are connected with each other, however, the success of this designing relies on the abundance of the enzyme to cleave the linker. There is another method of designing, in which the molecule can target several enzymes in a particular metabolic pathway (series inhibition). However, it is quite rare to design molecules (without a linker) in such a way that they can interact simultaneously with two different targets.

Filamenting temperature-sensitive mutant Z (FtsZ) is functionally similar to tubulin protein, which is an important enzyme for the bacterial cell division. FtsZ monomers self–assembled during the bacterial cell division and form the Z-ring at the site of septum formation [29]. The whole process from assemble, organization and ring formation is regulated by the binding of GTP and its hydrolysis [30]. Several studies have identified FtsZ as a potential target for the inhibitor designing to eradicate *Mtb* in its replicating form [31–34]. On the other hand, to kill the pathogen in its non-replicating form it is important to stop their ATP synthesis pathway by inhibiting certain enzymes involved in this process. Menaquinone (MQ) is a lipid soluble electron carrier which plays an important role to harness the required energy from ATP in its non-replicating form. Therefore, inhibition of the MQ biosynthesis can be an effective measure to kill *Mtb* in its non-replicating form. The unavailability of the targets in eukaryotic cells makes them very much attractive for different drug development program.

Based on our pervious findings we have seen that aliphatic chains with variable carbon numbers, especially prenyl groups play a significant role to kill the *Mtb* in non-replicating form and also improves the anti-tubercular activity [35,36]. It is most likely because of the recognition of isoprenyl group by the membrane bound MenG, which eventually converts demethylmenaquinone (having isoprenyl group) to menaquinone. In this report we have prepared three sets of hybrid molecules having benzimidazole, benzoxazole and benzothiazole moieties (active scaffold against FtsZ) with the attachment of various aliphatic chains (Fig. 1). All these heteroaryl systems were functionalized at their 2-position with substituted aromatic ring. Collectively, we had synthesized eighty four molecules in multiple steps. The synthesized molecules were tested against H37Rv, H37Ra strains in their replicating and non-replicating form. We also investigated the mechanism of action of the best active molecules.

## 2. Results and discussion

### 2.1. Synthesis of the target molecules

In this study we had prepared several benzazole derivatives comprising of three series *viz.*, benzimidazole, benzoxazole and benzothiazole. For the synthesis of the benzazole derivatives we first prepared the intermediates **7a-n** and **8a-n**. These intermediates **7a-n** and **8a-n** were prepared from 4-hydroxybenzaldehyde and 4-hydroxymethylbenzoate. To avoid *syn* dihydroxylation of the alkenyl chains (allyl, prenyl, geranyl and farnesyl) during $KMnO_4$ mediated oxidation of the aldehyde to carboxylic acid, we prepared **6a-d** through O-alkylation of 4-hydroxymethylbenzoate followed by the alkaline hydrolysis of methylbenzoate (Scheme 1).

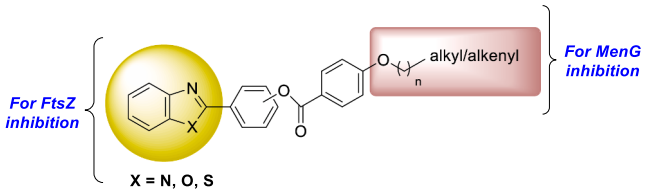



**Fig. 1.** General structure of the synthesized molecules: the heteroaromatic system is connected with the alkyl/alkenyl chain through a spacer.

The respective 2-arylbenzimidazole molecules (**9a-n**, **10a-n**) were prepared through oxidative cyclization of *o*-phenylenediamine with **7a-n** and **8a-n** in the presence of 20% p-TsOH [37] (Scheme 2).

However, for 2-arylbenzoxazole the above mentioned methodology did not work. Hence to synthesize the target molecules **14a-n**, we prepared their corresponding imine by treating 2-hydroxyaniline with 4-methoxybenzaldehyde in the presence of catalytic amount of acetic acid followed by the cyclization in the presence of DDQ to form the benzoxazole ring (**12**) [38]. Thereafter, the building blocks **3a-j** and **6a-d** were attached with the benzoxazole moiety by an ester linkage (Scheme 3). The failure of DDQ mediated oxidative cyclization of 3-methoxybenzaldehyde is presumed because of the + R effect of the –OH group. In an effort to overcome this problem we used 3-nitrobenzaldehyde and we obtained quantitative yield (**15**) during the cyclization. Thereafter, the nitro group was converted to hydroxyl through a series of reactions. The compounds (**18a-n)** were then finally prepared by using the building blocks **3a-j** and **6a-d** in the presence of EDC.HCl and DMAP with quantitative yield (Scheme 3).

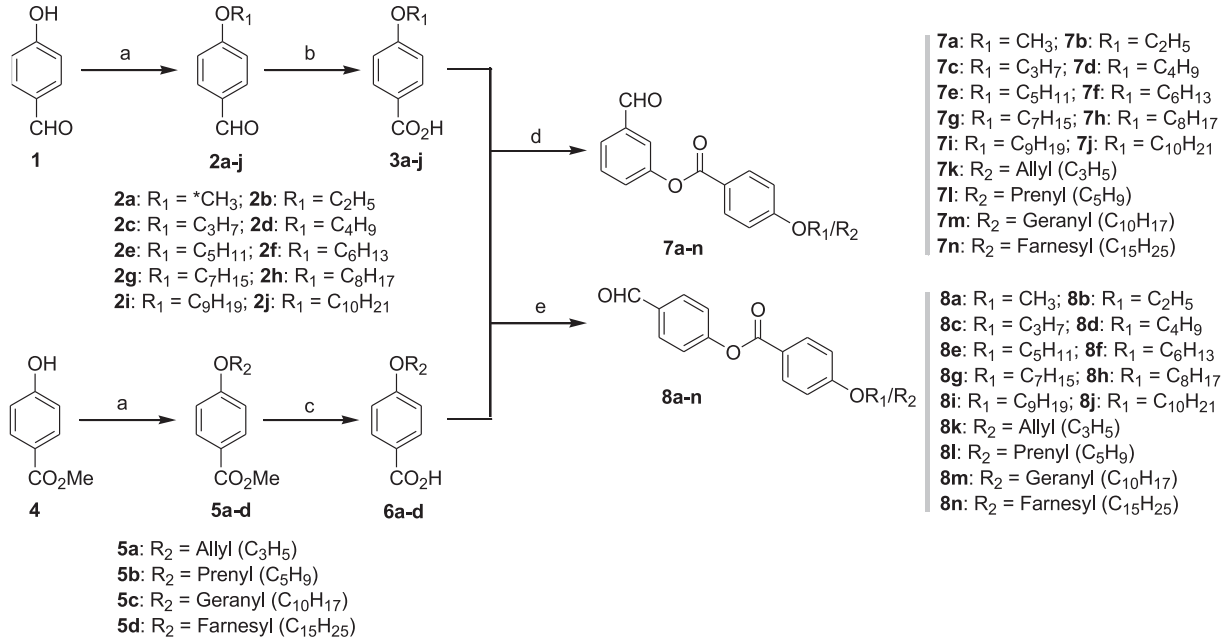
Similar to benzoimidazole, the 2-arylbenzothiazole molecules were prepared by DDQ mediated oxidative cyclization between 2-aminothiophenol and corresponding aldehydes (**19a-n** and **20a-g**). Like the *meta* isomers, we prepared the *para* isomers with higher alkyl and alkenyl chains (**23a-g**) by three steps (Scheme 4) [39,40].

### 2.2. Determination of antitubercular activity and cytotoxicity

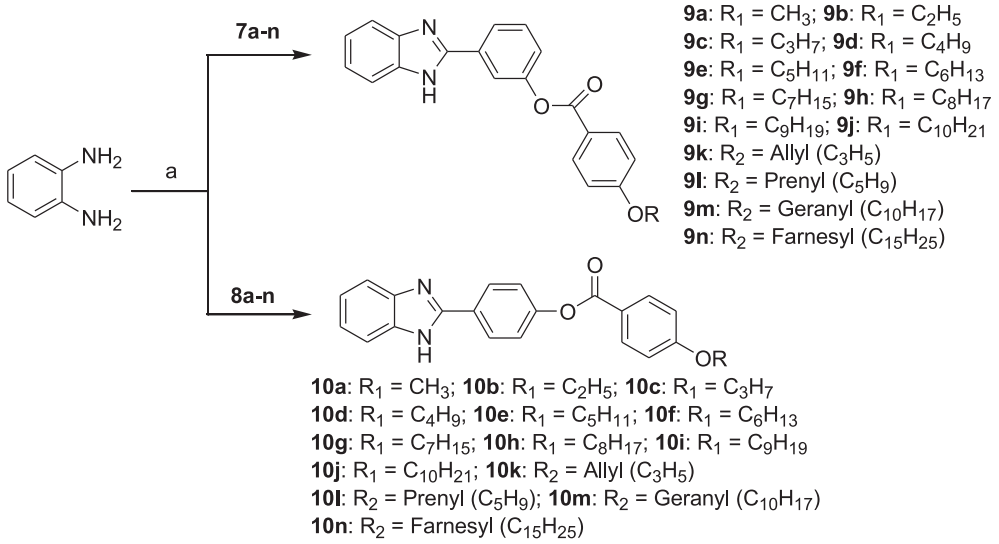
The synthesized compounds were tested for their anti-tubercular activity against *Mtb* strains H37Ra (non pathogenic) and H37Rv (pathogenic). Minimum inhibitory concentration (MIC) values were determined by two different methods, Microplate Alamar Blue assay (MABA) [41] and Low-Oxygen-Recovery Assay (LORA) [42]. Mammalian PBMC cell was used to determine their cytoxicity and the corresponding $IC_{50}$ values were calculated from their dose response curve [43]. The anti-tubercular activity and cytotoxicity value of the synthesized molecules are given in Table 1.

For 2-Aryl benzimidazole derivatives (**9a-9n**; *para*-derivatives), we observed a decent increase of anti-tubercular activity with the elongation of alkyl chain length and for **9f** with 6-carbon aliphatic chain it reaches to the optimum value of 6.03 μg/ml (MIC against replicating) and 31.46 μg/ml (MIC against non-replicating) against H37Rv, and for H37Ra these values were 6.25 and 25.00 μg/ml respectively. The 5 fold increase of its activity against non-replicating *Mtb* prompted us to incorporated alkenyl group in place of alkyl chain. Compounds **9k-9n** with alkenyl chain showed almost limiting activity (MIC 2.49–1.66 μg/ml) against replicating *Mtb*, however, there activity against the non-replicating *Mtb* was found to increased by 20 times (for **9n**) compared to **9f**. With the increase of alkenyl chain length and number of double bonds, activity remains almost the same against replicating *Mtb* but improved against non-replicating *Mtb* for both R37Rv and R37Ra strains. These observations clearly demonstrated the importance of alkenyl chain, typically prenyl group for diminishing *Mtb* in its non-replicating form. Similarly, for the *meta*-isomers of the same (**10a-10n**), we did not observe any increment in their activity with the increase of alkyl chain length. The best activity was observed for **10a** with methyl group but it was inactive against non-replicating *Mtb* (for H37Rv and H37Ra). However, compound **10h** with 8-carbon chain, showed almost comparable or better activity in both replicating and non-replicating *Mtb*. In the event of **10k-10n** with alkenyl chain, we observe improvement of their activity against replicating *Mtb* but unlike the *para*-isomers they were comparatively less active against non-replicating *Mtb*. This experimental data indicated that perhaps the conformation of the meta-analogues was not preferred by the target responsible for the killing of non-replicating *Mtb*.

Molecules belonging to 2-Aryl benzoxazole series did not show appreciable activity against *Mtb* either in replicating or non-replicating




**Scheme 1.** Reagents and conditions: (a) $R_1Cl/R_2Cl$, $K_2CO_3$ in DMF, 80 °C, 8–12 h; (b) $KMnO_4$, $NaH_2PO_4$ in CAN-$H_2O$ (1:1), rt, 3 h; (c) NaOH in dioxane-$H_2O$ (1:1), reflux, 15 h; (d) *m*-hydroxybenzaldehyde, DCC, DMAP in DMF, rt, 3–8 h; (e) *p*-hydroxybenzaldehyde, DCC, DMAP in DMF, rt, 3–8 h. *Starting material *p*-methoxybenzaldehyde.



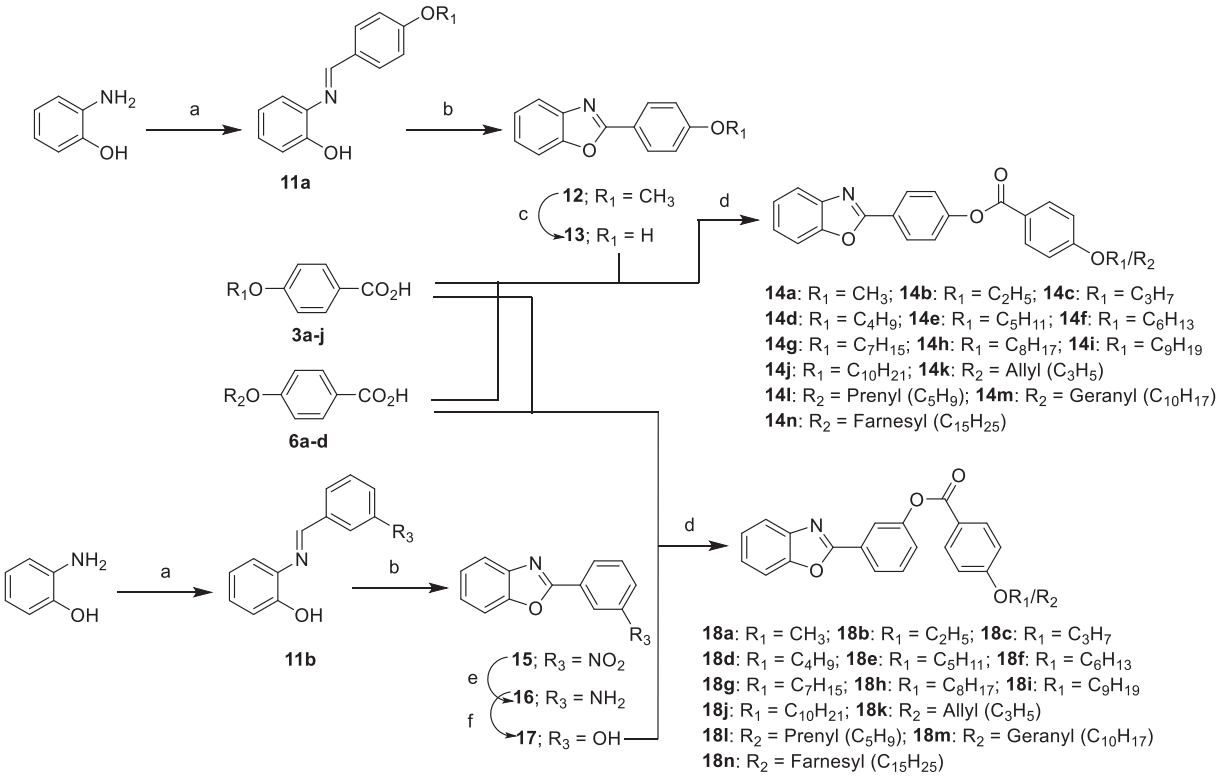

**Scheme 2.** Reagents and conditions: (a) p-TsOH in DMF, 80 °C, 3–6 h.

form. Only for compounds **14j** and **14l** we observed MIC value ~50 μg/ml against replicating or non-replicating *Mtb* for both H37Rv and H37Ra. However, for compounds **14m** and **14n**, we observed improved anti-tubercular activity, attributed to geranyl and farnesyl group respectively. Most importantly, we observed better activity for these molecules against the non-replicating *Mtb* compared to replicating, which was similar to the molecules of 2-Aryl benzimidazole series. For the *meta*-isomers the profile was almost the same with higher MIC values compared to their *para*-isomers.

In case of the 2-Aryl benzothiazole derivatives (**19a**-**19n**, **20a**-**20g** and **23a**-**23g**), we observed anti-tubercular activity of 30.12 μg/ml for **19h** (with 8-carbon chain) against replicating *Mtb*. On the other hand, compound **19i** with of 9-carbon alkyl chain was found to be the most active against the non-replicating *Mtb*. For the molecules with geranyl (**19m**) and farnesyl (**19n**) chains the MIC values were found within the range of 56–32 μg/ml against replicating and 40–28 μg/ml against non-replicating *Mtb*. On the contrary, for the *meta*-isomers we found that the activity decreased with the increase of the alkyl chain length against replicating *Mtb* and the best activity was recorded for **20a** with methyl chain. Again, an improved anti-tubercular activity was found (< 50 μg/ml) for the alkenyl chain. However, compounds **23e**, **23f** and **23g** with prenyl, geranyl and farnesyl groups respectively showed no significant difference in their activity towards replicating and non-replicating *Mtb*. From the comparative activity of the synthesized molecules it was concluded that the conformation (*meta* or *para*) and presence of the heteroatom in the heteroaromatic ring has a significant role in their activity against replicating and non-replicating forms of *Mtb*.

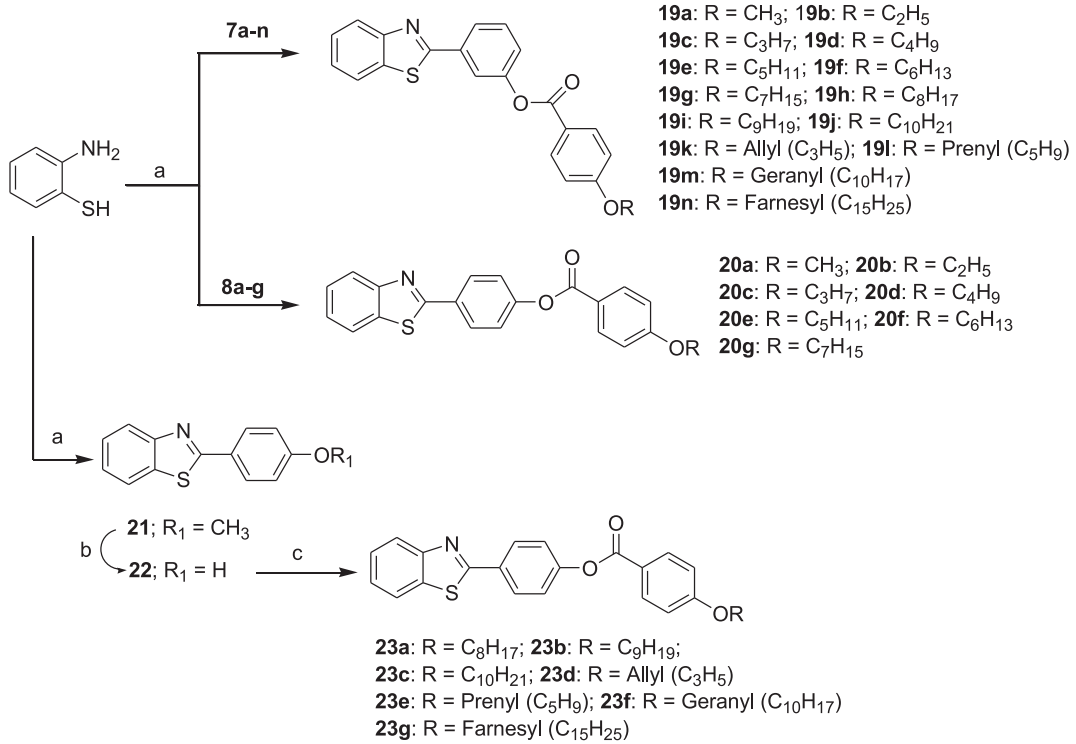
### 2.3. Effect of the active molecules on cell morphology

The effect of the synthesized derivatives on the cell division of *Mtb* (H37Ra), was evaluated by comparing the morphology of untreated




**Scheme 3.** Reagents and conditions: (a) *p*-Methoxybenzaldehyde or *m*-nitrobenzaldehyde, MeOH, AcOH (cat.), rt, 3 h; (b) DDQ in DCM, rt, 2 h; (c) HBr in AcOH, 80 °C, overnight; (d) EDC.HCl, DMAP in THF, rt, 4–5 h; (e) $NiCl_2{\cdot}6H_2O$, $NaBH_4$ in MeOH, rt, 1 h; (f) i. $NaNO_2$, HCl, 5 °C; ii. Heating at 80 °C for 6 h.

bacilli with treated bacilli under fluorescence microscope. Fluorescein diacetate (FDA) was used as the fluorophore. Best three molecules were selected with MIC < 4 μg/ml against the replicating *Mtb*. The elongation in the morphology of the treated bacilli compared to the control bacilli attributes to the inhibition of bacterial cell division by the compounds **9k**, **9l** and **9m** (Fig. 2). The elongation in the bacterial morphology occurs due to decrease of cross linking of the peptidoglycan region of the cell wall so that the surface area of the cell increased [44]. In the presence of compound **9k** we observed maximum elongation (> 10 μm) compared to **9l** and **9m** (≥5 μm) and it was




**Scheme 4.** Reagents and conditions: (a) CAN, $H_2O_2$, grinding, 3–10 min; (b) HBr in AcOH, 80 °C, 6 h; (c) EDC.HCl, DMAP in THF, rt, 3–5 h.

**Table 1**
The anti-tubercular activity and cytotoxicity values of the synthesized molecules.

| Comp. | MIC (μg/ml) | | | | Cytotoxicity $IC_{50}$ (μg/ml) |
|---|---|---|---|---|---|
| | H37Rv | | H37Ra | | |
| | MABA** | LORA*** | MABA** | LORA*** | |
| **9a** | 24.39 | 80.24 | 25.00 | 100.00 | 131.52 |
| **9b** | 19.70 | 68.31 | 25.00 | 50.00 | 149.31 |
| **9c** | 21.18 | 72.51 | 25.00 | 50.00 | 160.89 |
| **9d** | 17.52 | 41.94 | 12.50 | 50.00 | 170.18 |
| **9e** | 9.47 | 30.64 | 12.50 | 50.00 | 147.17 |
| **9f** | 6.03 | 31.46 | 6.25 | 25.00 | 158.32 |
| **9g** | > 100 | nd* | 100.00 | nd* | 180.49 |
| **9h** | > 100 | nd* | 100.00 | nd* | 197.83 |
| **9i** | > 100 | nd* | > 100 | nd* | 183.57 |
| **9j** | > 100 | nd* | > 100 | nd* | 163.91 |
| **9k** | 2.49 | 24.36 | 3.13 | 25.00 | 157.11 |
| **9l** | 2.16 | 6.47 | 3.13 | 6.25 | 103.42 |
| **9m** | 1.98 | 2.06 | 3.13 | 3.13 | 179.30 |
| **9n** | 1.66 | 1.59 | 6.25 | 1.56 | 162.97 |
| **10a** | 23.85 | > 100 | 25.00 | 50.00 | 153.08 |
| **10b** | 41.87 | 70.07 | 50.00 | 100.00 | 171.01 |
| **10c** | > 100 | nd* | 50.00 | 100.00 | 108.34 |
| **10d** | > 100 | nd* | > 100 | nd* | 121.98 |
| **10e** | > 100 | nd* | > 100 | nd* | 142.37 |
| **10f** | > 100 | nd* | > 100 | nd* | 150.06 |
| **10g** | 82.78 | 78.24 | 100.00 | nd* | 167.81 |
| **10h** | 41.61 | 31.04 | 50.00 | 25.00 | 183.49 |
| **10i** | > 100 | nd* | > 100 | nd* | 156.03 |
| **10j** | > 100 | nd* | > 100 | nd* | 191.54 |
| **10k** | > 100 | nd* | > 100 | nd* | 161.06 |
| **10l** | 11.74 | 20.00 | 12.50 | 25.00 | 142.11 |
| **10m** | 7.22 | 12.91 | 6.25 | 12.50 | 169.31 |
| **10n** | 6.08 | 13.25 | 6.25 | 12.50 | 158.09 |
| **14a** | 63.18 | 91.46 | 50.00 | 100.00 | 162.39 |
| **14b** | 80.32 | > 100 | 100.00 | > 100 | 157.55 |
| **14c** | > 100 | nd* | > 100 | nd* | 168.81 |
| **14d** | > 100 | nd* | > 100 | nd* | 141.43 |
| **14e** | > 100 | nd* | > 100 | nd* | 159.35 |
| **14f** | > 100 | nd* | > 100 | nd* | 168.38 |
| **14g** | > 100 | nd* | > 100 | nd* | 157.02 |
| **14h** | > 100 | nd* | > 100 | nd* | 160.52 |
| **14i** | > 100 | nd* | 50.00 | nd* | 182.39 |
| **14j** | 49.52 | 52.04 | 50.00 | 50.00 | 136.41 |
| **14k** | 55.36 | 39.08 | 50.00 | 50.00 | 148.32 |
| **14l** | > 100 | nd* | > 100 | nd* | 165.11 |
| **14m** | 11.61 | 8.72 | 12.50 | 12.50 | 178.21 |
| **14n** | 9.65 | 5.43 | 12.50 | 6.25 | 161.54 |
| **18a** | 83.08 | > 100 | 100.00 | > 100 | 159.08 |
| **18b** | 39.06 | 72.58 | 50.00 | 100.00 | 121.39 |
| **18c** | > 100 | nd* | > 100 | nd* | 159.45 |
| **18d** | > 100 | nd* | > 100 | nd* | 182.05 |
| **18e** | > 100 | nd* | > 100 | nd* | 171.56 |
| **18f** | > 100 | nd* | > 100 | nd* | 168.39 |
| **18g** | > 100 | nd* | > 100 | nd* | 151.15 |
| **18h** | > 100 | nd* | > 100 | nd* | 168.30 |
| **18i** | > 100 | nd* | > 100 | nd* | 189.13 |
| **18j** | > 100 | nd* | > 100 | nd* | 172.58 |
| **18k** | 85.09 | 65.81 | 100.00 | 50.00 | 176.31 |
| **18l** | 50.08 | 41.27 | 25.00 | 50.00 | 172.45 |
| **18m** | 34.52 | 21.38 | 25.00 | 25.00 | 168.91 |
| **18n** | 65.11 | 18.45 | 25.00 | 12.50 | 159.37 |
| **19a** | 43.37 | 30.81 | 50.00 | 25.00 | 134.02 |
| **19b** | 60.20 | 80.31 | 50.00 | 100.00 | 153.15 |
| **19c** | 71.31 | 68.42 | 50.00 | 50.00 | 128.62 |
| **19d** | 88.59 | 79.09 | 100.00 | > 100 | 157.52 |
| **19e** | > 100 | nd* | > 100 | nd* | 163.47 |
| **19f** | > 100 | nd* | > 100 | nd* | 169.07 |
| **19g** | > 100 | nd* | > 100 | nd* | 168.04 |
| **19h** | 30.12 | 47.31 | 25.00 | 50.00 | 121.04 |
| **19i** | 39.52 | 40.63 | 50.00 | 50.00 | 129.06 |
| **19j** | > 100 | nd* | > 100 | nd* | 134.48 |
| **19k** | 20.33 | 43.12 | 25.00 | 50.00 | 149.32 |
| **19l** | 48.23 | nd* | 50.00 | nd* | 133.07 |
| **19m** | 56.13 | 40.09 | 50.00 | 50.00 | 145.51 |
| **19n** | 31.49 | 27.81 | 25.00 | 25.00 | 162.49 |
| **20a** | 29.51 | 70.42 | 25.00 | 50.00 | 135.62 |
| **20b** | 35.87 | 82.69 | 50.00 | 100.00 | 167.15 |
| **20c** | 98.67 | > 100 | > 100 | nd* | 189.76 |
| **20d** | > 100 | nd* | > 100 | nd* | 140.61 |
| **20e** | > 100 | nd* | > 100 | nd* | 158.43 |
| **20f** | > 100 | nd* | > 100 | nd* | 153.15 |
| **20g** | > 100 | nd* | > 100 | nd* | 179.08 |
| **23a** | > 100 | nd* | > 100 | nd* | 184.52 |
| **23b** | > 100 | nd* | > 100 | nd* | 165.09 |
| **23c** | > 100 | nd* | > 100 | nd* | 153.55 |
| **23d** | 52.37 | 43.11 | 50.00 | 50.00 | 149.39 |
| **23e** | 43.52 | 49.12 | 50.00 | 50.00 | 180.47 |
| **23f** | 30.29 | 28.73 | 25.00 | 25.00 | 181.07 |
| **23g** | 35.42 | 21.02 | 50.00 | 25.00 | 142.59 |
| **INH**[a] | 0.40 | > 100 | 0. 39 | > 100 | 73.09 |
| **RIF**[b] | 0.01 | 0.04 | 0.02 | 0.08 | 63.15 |

* Not determined.
** Microplate Alamer Blue Assay (for replicating form of *Mtb*).
*** Low Oxygen Recovery Assay (for non-replicating form of *Mtb*).
[a] INH: Isoniazid.
[b] RIF: Rifampin.

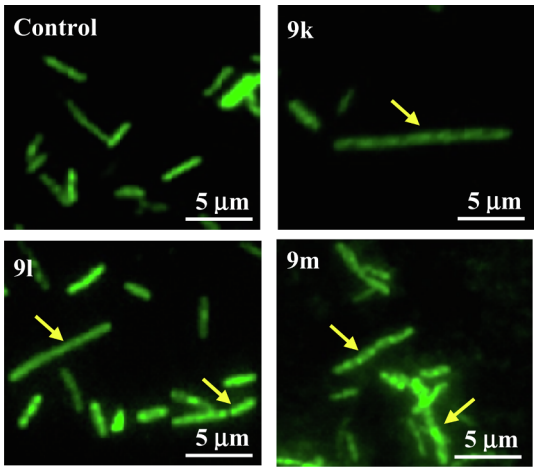



**Fig. 2.** Effect of the compounds **9k**, **9l** and **9m** on the cell morphology (H37Ra). Cells were grown for 7 days without any compound (control) and with 2xMIC of **9k**, **9l** and **9m**. 10 μl of FDA solution was used to take fluorescence image.

longer than the untreated *Mtb* (2.5 – 3 μm). This finding was in well agreement with their respective MIC values against replicating *Mtb*.

### 2.4. Gtpase activity of the FtsZ in the presence of active molecules

Cell division occurs through a septa formation at the division site, which is formed through the polymerization of the FtsZ enzyme. FtsZ is a GTPase enzyme, which converts GTP to GDP and thereby harnesses the energy to generate the key constructive force for bacterial cell division. Therefore, we measured the GTPase activity of FtsZ (*Mtb*) in the presence of our synthesized molecules to find out the reason (target) for their anti-mycobacterium activity against replicating *Mtb*. Compounds **9k**, **9l** and **9m** (MIC < 3 μg/ml against replicating *Mtb*) were selected for this assay, where we quantified and compared the inorganic phosphate content in the presence of FtsZ with and without the synthesized compounds. The best $IC_{50}$ value was obtained for compound **9k** (32 μM), which indeed showed the optimum elongation of *Mtb* (Fig. 3).

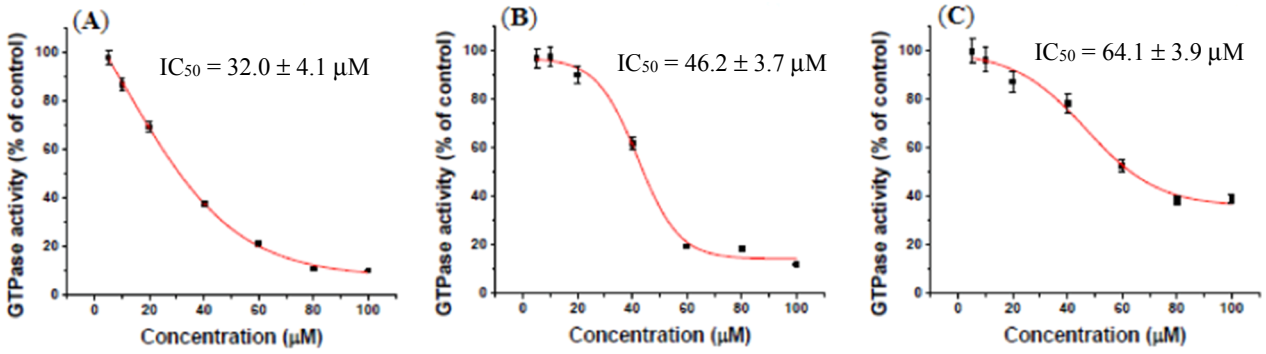



**Fig. 3.** Concentration-response curve of GTPase activity for FtsZ (*Mtb*) in the presence of comp. **9k** (A), **9l** (B) and **9m** (C). Assay composition: 3.5 μM FtsZ with varying concentrations of the **9k**, **9l** and **9m** (5–100 μM) in 50 μM MOPS buffer for 10 min at 25 °C, followed by the addition of 500 μM GTP in 5 μM $MgCl_2$ and 200 μM KCl. Each point represents the mean of three independent assays, and the vertical bars show the standard derivation of the mean.

### 2.5. Docking study with Mtb-FtsZ with *9k, 9l and 9n*

After the FtsZ inhibition assay we proceeded for the docking study with **9k**, **9l** and **9n** to visualize their binding conformation within the protein. This docking study revealed that all the three molecules bind at the active site (GTPase domain) of FtsZ protein. However, their modes of bindings were quite different with each other. Compared to the conformation of GTPγS in FtsZ (PDB ID: 1RLU) [45], the alkenyl chain of **9k** was found to occupy the same pocket (T1 to T4 loops) as for the γ-thiophosphate, although the guanine and benzoimidazole moieties were found to get projected at perpendicular with each other (Fig. 4B). On the other hand, in the docked conformation of **9l** and **9n** we observed that the benzoimidazole moiety of these compounds resided remarkably close to T6 loop like guanine (for GTPγS) (Fig. 4C and D). Nevertheless, the alkenyl chains of these molecules were found to get exposed in an opposite direction compared to the γ-thiophosphate (T1-T4 loop), which is presumably because of the increase of hydrophobicity of the flanking chain. Therefore, we observed a decreased

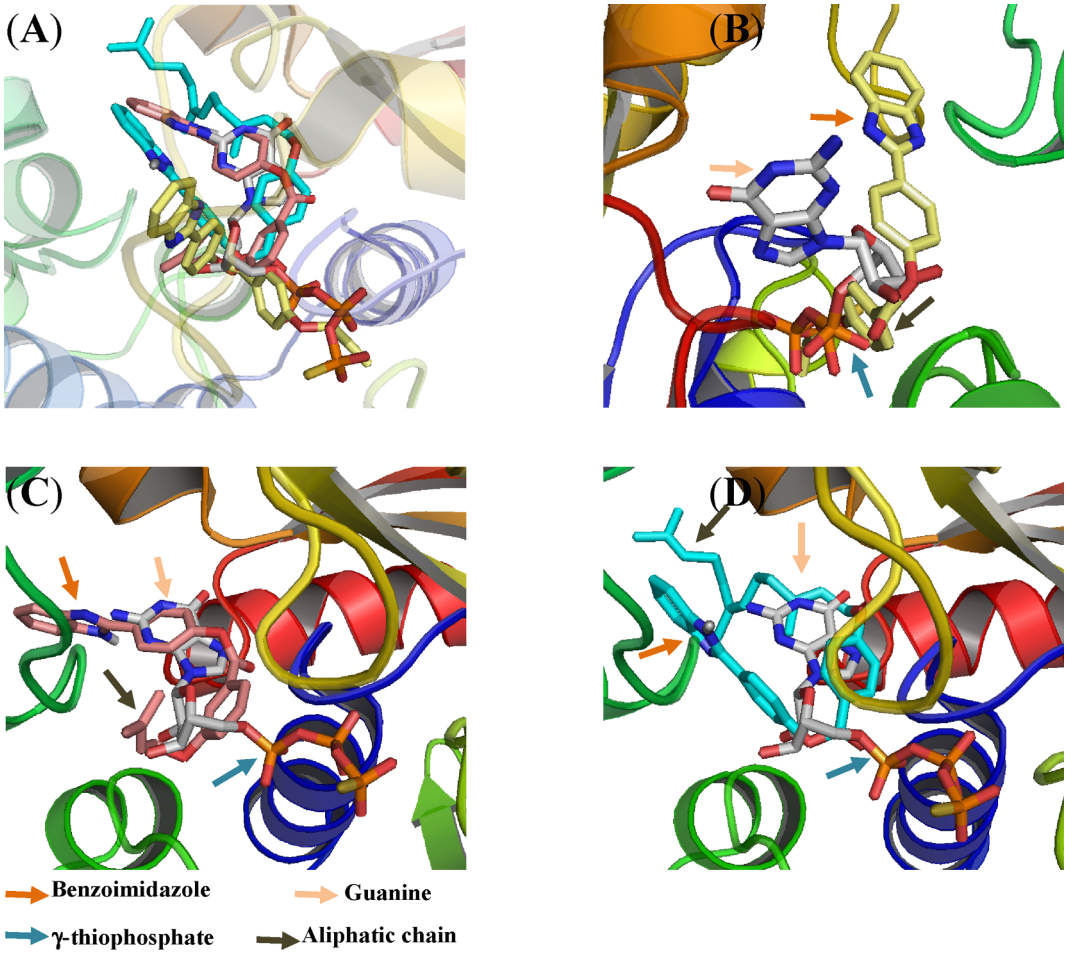



**Fig. 4.** Docking conformation and comparison of GTPγS binding with **9k**, **9l** and **9m**. (A) Conformations of GTPγS, **9k**, **9l** and **9m** together in Mtb-FtsZ. (B) Relative conformation between GTPγS (white) and **9k** (Yellow); (C) Relative conformation between GTPγS (white) and **9l** (Red); (D) Relative conformation between GTPγS (white) and **9n** (Cyan). Energy minimization and docking was performed using AutoDock software. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

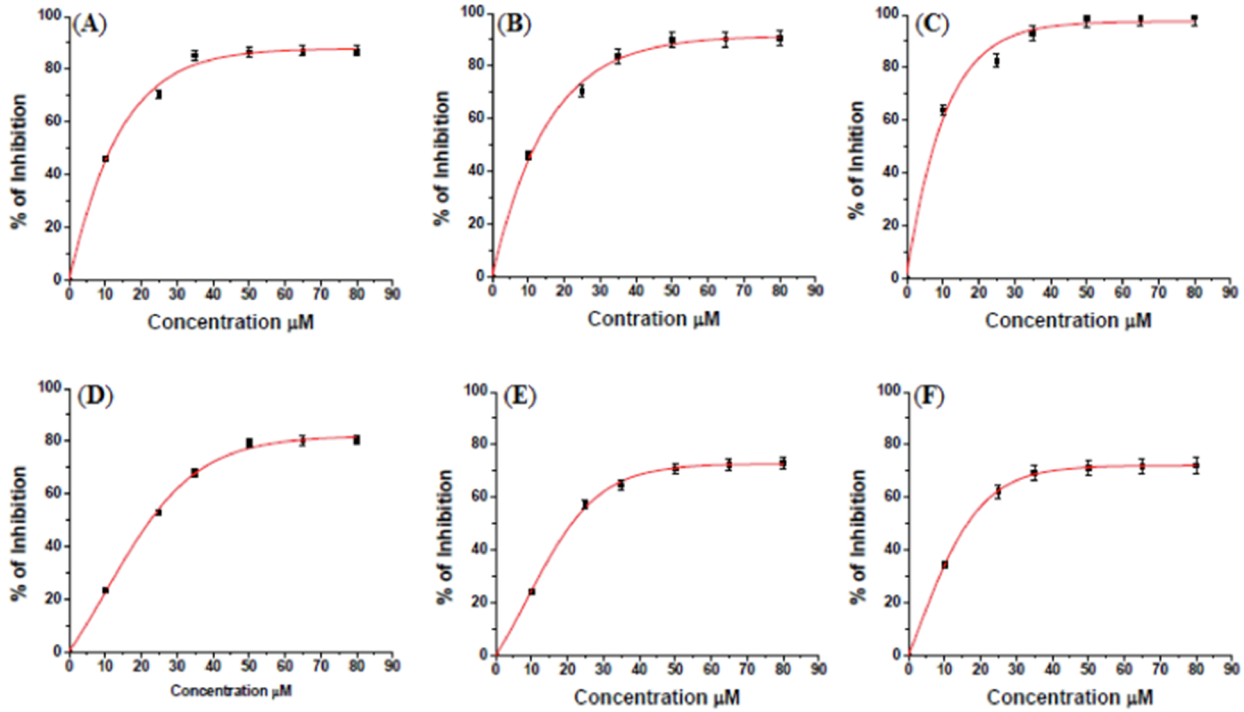



**Fig. 5.** The $IC_{50}$ curve for the MenG inhibition assay by synthesized compound; (A) Comp. **9l**, (B) Comp. **9m**, (C) Comp. **9n**, (D) Comp. **10m**, (E) Comp. **10n** and (F) Comp. **14n**, using H37Ra membrane fraction. Substrate **A** (500 μM) was mixed with 500 μM SAM and 100 μl membrane fraction and incubated for 3 h at 37 °C. Each point represents the mean of three independent assays, and the vertical bars show the standard derivation of the mean.

activity of compound **9l** and **9n** compared with compound **9k** on FtsZ, and it is in well corroboration with our previous observation (change in cell morphology).

### 2.6. Effect of the synthesized molecules on MenG

To understand the plausible reason of their activity against non-replication *Mtb,* we tested the active molecules against the respiratory system, as it remains active in the dormant state. Hence, our synthesized molecules have structural resemblance with MenG substrate; therefore, we performed the MenG inhibition study with compounds **9l**, **9m**, **9n**, **10m**, **10n**, **14m**, **14n** and **18n** (LORA MIC ≤ 12.5 μg/ml; MABA MIC ≤ 25 μg/ml against H37Ra). The MenG inhibition values ($IC_{50}$) were determined by HPLC based assay, which is quite similar to the MenA inhibition assay except the use of DMMQ and SAM (methyl transferring agent) [46]. MenG is the final enzyme in the menaquinone biosynthesis pathway, which converts the DMMQ to MQ in the presence of SAM. The MQ accepts two electrons from NADH and get converted to its reduced form, finally it again reversibly converted to MQ by transferring these electrons to the other electron acceptors present in the electron transport system. Therefore, inhibition of this enzyme is expected to perturb the respiratory system of *Mtb* through which it harnesses its required energy in the latent or non-replicating state [47].

**Table 2**
Effect of the synthesized molecules on the MenG inhibition.

| Compound | Men G Inhibition; $IC_{50}$ (μM) H37Ra |
|---|---|
| **9l** | 12.59 ± 0.49 |
| **9m** | 11.62 ± 0.21 |
| **9n** | 7.49 ± 0.37 |
| **10m** | 23.29 ± 1.03 |
| **10n** | 21.37 ± 0.71 |
| **14m** | 32.53 ± 0.14 |
| **14n** | 16.57 ± 0.09 |
| **18n** | 36.61 ± 1.23 |

The substrate and the product were prepared separately (SI-I) [35,48] for calibration and identification purpose. The retention times for substrate (comp. **A)** and product (comp. **B)** were 5.713 min and 6.400 min respectively, which was found good to determine the $IC_{50}$ value using HPLC system. The membrane fraction (according to the reported protocol) [49] of *Mtb* (H37Ra) was used as a source of membrane bound MenG. Representative $IC_{50}$ profiles for effective compounds are shown in Fig. 5 (and SI-I). The $IC_{50}$ calculation was based on the conversion of **A** with respect to the control set (without inhibitor molecule) and given in Table 2.

In this assay the conversion of the model substrate (comp. **A**; DMMQ) by MenG (from H37Ra) to the corresponding product (Comp. **B**; MQ) was monitored at 250 nm (by HPLC) in the presence of 6 different concentrations of the synthesized molecules and the corresponding $IC_{50}$ values were calculated by non-linear regression analysis (Table 2).

The best activity was observed for compound **9n** ($IC_{50}$ 7.49 μM) with farnesyl side chain. However, comparative activity of **9n**, **10n**, **14n** and **18n** against MenG showed that it was not only the farnesyl group but the presence of heteroatom in the benzazole ring and the overall orientation (*meta* or *para*) of the molecule played a decisive role for inhibition of MenG activity.

To find out the consequence of MQ biosynthesis inhibition in the dormant state of *Mtb*, we prepared the dormant H37Ra following the reported protocol [50] and performed the Vit-K2 rescue experiment. Vit-K2 (MQ) is the only quinone present in the electron transport chain of *Mtb*. Thus, inhibition of the MQ synthesis is expected to affect the energy harnessing process in its non-replicating state. Whereas, co-culture of *Mtb* with Vit-K2 is used to provide the electron carrier externally and by virtue of this supplement *Mtb* becomes able to convert ATP to ADP despite the inhibition of the MQ biosynthesis. In the presence of Vit-K2 (1 mM), the growth of the H37Ra (dormant form) did not significantly affected after 10 days exposure (Fig. 6; left panel). However, when they were incubated with **9l**, **9m**, **9n** and **14n** (20 μg/ml) the growth was diminished to 5.3, 4.1, 2.6 and 4.8 $\log_{10}$CFU/ml respectively compared to the set with 1 mM Vit-K2 (Fig. 6; right panel).

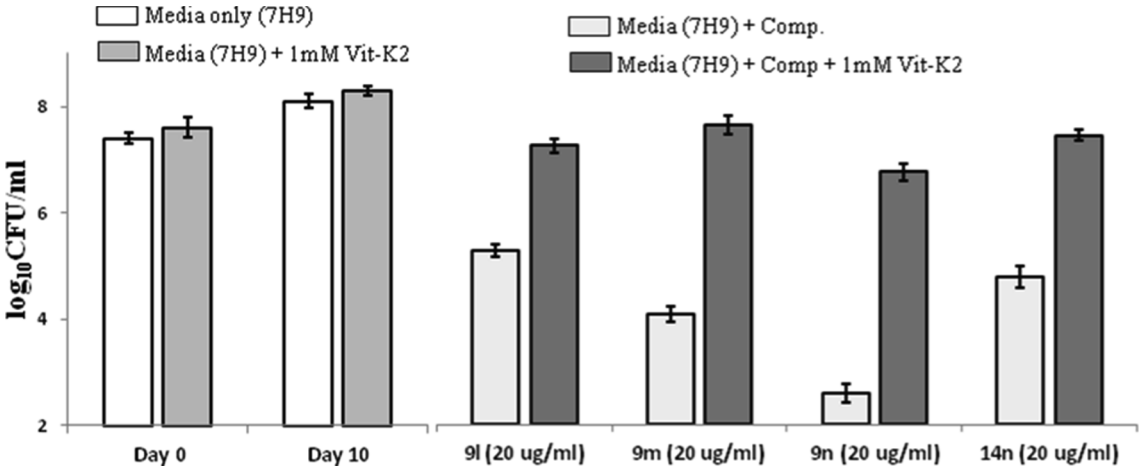



**Fig. 6.** Effect of the comp. **9l**, **9m**, **9n** and **14n** against non-replicating H37Ra: Growth of the non-replicating H37Ra in absence and in the presence of Vit-K2 (1 mM) at 0th and 10th day (Left panel); Growth of the non-replicating H37Ra in absence and in the presence of Vit-K2 (1 mM) and comp. **9l**, **9m**, **9n** and **14n** at 20 μg/ml on 10th day followed by 27 days after CFU counting on 7H10 agar plate (Right panel). Each point represents the mean of three independent assays, and the vertical bars show the standard derivation of the mean.

This provided unambiguous evidence of molecules inhibiting the biosynthesis of MenG and in turn reduced their growth in dormant state by blocking the respiratory chain of H37Ra.

Thereafter, the production of ATP was measured in presence of our best molecule **9n** ($MIC_{LORA}$ < 2 μg/ml and $IC_{50}$ (MenG) < 10 μM). The ATP/ADP ratio was varied in the range of 1.04–1.34 for the control set from day 3 to day 9 (Fig. 7). For the co-culture of the dormant H37Ra with comp. **9n** (10, 25 and 50 μg/ml), we observed continuous reduction in their ATP production level which confirms that the comp. **9n** eradicates *Mtb* in the dormant state by inhibiting the MenG biosynthesis and as a whole by reducing its ATP production.

### 2.7. Effect on resistant strains of Mtb

Finally, we tested the best molecules **9l**, **9m**, **9n** and **14n** (MABA and LORA MIC < 10 μg/ml) against the isoniazide and refampin resistant H37Rv strains (ATCC-35822 and ATCC-35838 respectively). Both these compounds showed slightly better MIC values against the resistance strains as compared to the non-resistance strain (Table 3).

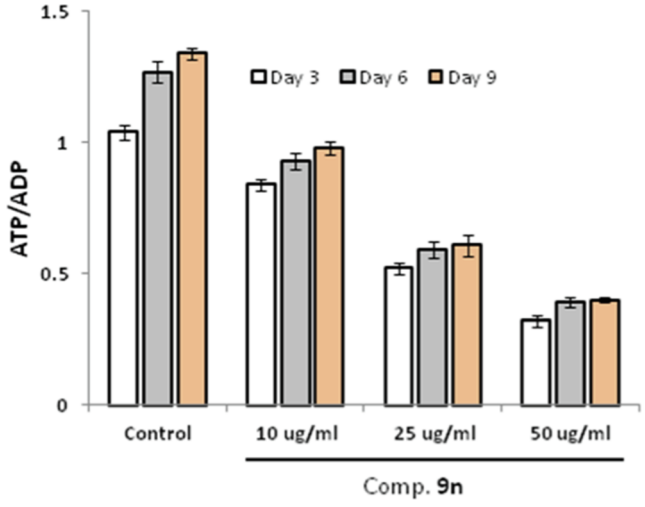



**Fig. 7.** Effect of Comp. **9n** on the ATP synthesis against non-replicating H37Ra on 3rd, 6th and 9th day at 10, 25 and 50 μg/ml. Each point represents the mean of two independent assays, and the vertical bars show the standard derivation of the mean.

**Table 3**
The MIC values of the compounds **9l**, **9m**, **9n** and **14n** against H37Rv drug resistance strains.

| Entry | Strains | MIC (μg/ml) against replicating Mtb | | | | | |
|---|---|---|---|---|---|---|---|
| | | **9l** | **9m** | **9n** | **14n** | INH[a] | RIF[b] |
| 1 | H37Rv (ATCC 27294) | 2.16 | 3.54 | 4.66 | 9.65 | 0.4 | 0.01 |
| 2 | H37Rv-INH-R(ATCC 35822) | 1.04 | 2.13 | 1.42 | 3.27 | > 8 | 0.03 |
| 3 | H37Rv-RIF-R (ATCC 35838) | 1.57 | 1.94 | 1.06 | 4.14 | 0.25 | > 2 |

[a] INH: Isoniazid.
[b] RIF: Refampin, The MIC value were calculated by agar plate dilution method.

## 3. Conclusion

In conclusion, 84 molecules were designed and synthesized to target the cell division and the respiratory system of *Mtb* simultaneously. Compounds with alkenyl chain, typically geranyl and farnesyl group showed the best activity against replicating and non-replicating *Mtb*. Out of the three heterocyclic systems, it was observed that the benzoimidazole was the most preferred one. The anti-tubercular activity for the best active molecules against replicating form was found because of the inhibition of GTPase activity of FtsZ enzyme, which was systematically substantiated by the morphological change of *Mtb* and reduction of GTPase activity of FtsZ enzyme in the presence of active molecules. Comparative activity of molecules with small aliphatic chain and prenyl group showed that the heterocyclic ring was mainly responsible for their activity against replication *Mtb*. The presence of aliphatic chain has a role in their activity to some extent as observed from the docking conformations. On the other hand, for the molecules with prenyl groups we observed a significant improvement in their activity against non-replicating Mtb, which is attributed to their better recognition by MenG enzyme. The best molecule (**9n**) against non-replicating *Mtb* showed $IC_{50}$ value as 7.49 μM for in MenG inhibition assay. The Vit-K2 rescue study for comp. **9n** with farnesyl group clearly showed the best inhibitory effect on the electron transport system at 20 μg/ml concentration which gets revived in the presence of Vit-K2. Similarly, the ATP/ADP ratio got diminished in the presence of **9n**, which plausibly confirms that these molecules (with prenyl chain) eradicate the *Mtb* in its non-replication form by affecting its electron transport system. The dual-targeted best molecules **9l**, **9m**, **9n** and **14n**

were also found to be active against INH and RIF resistant strains. This work shows that by customizing the molecular design we can perturb more than one target of *Mtb*, to counteract the emergence of resistant strain.

## 4. Experimental

### 4.1. Reagents and instrumentation

All the reagents were purchased from Sigma-Aldrich, Alfa-Aesar and Merck chemicals. Solvents were dried according to the standard protocols. TLC were performed on Merck silica gel 60, $f_{254}$ pre-coated aluminium plates. Spots were visualized under UV lamp or stained using 10% PMA in Ethanol, 5% Sulfuric acid in methanol or Iodine. Column chromatographic separations were performed using silica gel (100–200 mesh). NMR spectra were run on Bruker AVANCE II instrument using TMS as internal standard for $^{1}H$ (300 and 400 MHz) and solvent as internal standard for $^{13}C$ (75 and 100 MHz) experiments. Chemical shifts were given in ppm (δ scale) UV–vis measurements were made using a Perkin Elmer UV–vis spectrophotometer (Model Lambda 25). Mass spectra had been recorded using Waters Mass Spectrometer (model XevoG2QTof). HPLC experiments were performed using an Agilent 1200 infinity series with DAD detector with silica $C_{18}$ column (4.6x250mm) and 5 μm.

### 4.2. General procedure for methyl 4-alkenyloxy benzoates (**5a**-**5d**)

4-Hydroxy methyl benzoate (5.0 g, 32.9 mmol) was dissolved in DMF and to that Potassium carbonate (11.4 g, 82.25 mmol) was added under stirring. Finally the corresponding alkenyl halide (39.5 mmol) was added and maintained at 80 °C for 8–12 h. After completion of reaction, the reaction mass was poured into water and extracted with ethyl acetate (3x150 ml). Combined organic layer was thoroughly washed with water followed by brine solution. The organic portion was evaporated and purified by column chromatography (silica gel 100–200 mesh) using ethyl acetate in hexanes to afford the compounds.

#### 4.2.1. Methyl 4-(allyloxy)benzoate (**5a**)

Yield- 85.7%; colorless liquid; $^{1}H$ NMR (300 MHz, $CDCl_3$): $\delta$ 3.88 (s, 3H), 4.59 (dt, $J$ = 1.5, 5.4 Hz, 2H), 5.32 (dq, $J$ = 1.5, 10.5 Hz, 1H), 5.42 (dq, $J$ = 1.5, 17.4 Hz, 1H), 5.99–6.12 (m, 1H), 6.90–6.95 (m, 2ArH), 7.96–8.01 (m, 2ArH). HRMS ($ESI^+$): $m/z$ calculated for $C_{11}H_{12}O_3$ $[M+H]^+$: 192.0786; found: 1925.0790.

#### 4.2.2. Methyl 4-((3-methylbut-2-en-1-yl)oxy)benzoate (**5b**)

Yield- 87.5%; colorless liquid; $^{1}H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.76 (s, 3H), 1.81 (s, 3H), 3.88 (s, 3H), 4.56 (d, $J$ = 6.9 Hz, 2H), 5.48 (tt, $J$ = 1.5, 6.9 Hz, 1H), 6.89–6.95 (m, 2ArH) 7.96–8.01 (m, 2ArH). HRMS ($ESI^+$): $m/z$ calculated for $C_{13}H_{16}O_3$ $[M+H]^+$: 220.1099; found: 220.1101.

#### 4.2.3. Methyl-4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)benzoate (**5c**)

Yield- 83.2%; colorless liquid; $^{1}H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.61 (s, 3H), 1.68 (s, 3H), 1.75 (s, 3H), 2.05–2.14 (m, 4H), 3.88 (s, 3H), 4.59 (d, $J$ = 6.3 Hz, 2H), 5.06–5.11 (m, 1H), 5.48 (td, $J$ = 1.2, 6.6 Hz, 1H), 6.90–6.95 (m, 2ArH), 7.96–8.01 (m, 2ArH). HRMS ($ESI^+$): $m/z$ calculated for $C_{18}H_{24}O_3$ $[M+H]^+$: 288.1725; found: 288.1729.

#### 4.2.4. Methyl 4-((-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)benzoate (**5d**)

Yield- 81.6%; colorless liquid; $^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.60 (s, 6H), 1.67 (s, 3H), 1.74 (s, 3H), 1.81–2.11 (m, 8H), 3.88 (s, 3H), 4.59 (d, $J$ = 6.4 Hz, 2H), 5.09–5.12 (m, 2H), 5.48–5.51 (m, 1H), 6.87–6.93 (m, 2ArH), 7.93–7.99 (m, 2ArH). HRMS ($ESI^+$): $m/z$ calculated for $C_{23}H_{32}O_3$ $[M+H]^+$: 356.2351; found: 356.2352.

### 4.3. General procedure for 4-alkoxy benzoic acids (**6a**-**6d**)

4-alkenyloxy methyl benzoate (28.0 mmol) was dissolved in 1, 4-dioxane in water (1:1) followed by the addition of sodium hydroxide (84.0 mmol) and maintained under reflux for 24–30 h. After completion of reaction, volatiles were evaporated and the aqueous mass neutralized with concentrated hydrochloric acid. The white solid thus formed was filtered, washed thoroughly with water and dried to afford the benzoic acids.

#### 4.3.1. 4-(allyloxy)benzoic acid (**6a**)

Yield- 85.4%; white solid; m.p- 142–144 °C; $^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta$ 4.64 (d, $J$ = 5.4 Hz, 2H), 5.34–5.37 (m, 1H), 5.46–5.48 (m, 1H), 6.05–6.11 (m, 1H), 6.99 (d, $J$ = 6.8 Hz, 2ArH), 8.09 (d, $J$ = 6.8 Hz, 2ArH). HRMS ($ESI^+$): $m/z$ calculated for $C_{10}H_{10}O_3$ $[M+H]^+$: 178.0630; found: 178.0633.

#### 4.3.2. 4-((3-methylbut-2-en-1-yl)oxy)benzoic acid (**6b**)

Yield- 81.4%; white solid; m.p- 136–138 °C; $^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.79 (s, 3H), 1.84 (s, 3H), 4.62 (d, $J$ = 5.4 Hz, 2H), 5.52 (t, $J$ = 6.4 Hz, 1H), 6.98 (d, $J$ = 6.8 Hz, 2ArH), 8.09 (d, $J$ = 6.8 Hz, 2ArH). HRMS ($ESI^+$): $m/z$ calculated for $C_{12}H_{14}O_3$ $[M+H]^+$: 206.0943; found: 206.0947.

#### 4.3.3. (E)-4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)benzoic acid (**6c**)

Yield- 82.5%; white solid; m.p- 108–110 °C; $^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.61 (s, 3H), 1.68 (s, 3H), 1.76 (s, 3H), 2.06–2.15 (m, 4H) 4.62 (d, $J$ = 6.6 Hz, 2H), 5.07–5.10 (m, 1H), 5.47–5.51 (m, 1H), 6.96 (dd, $J$ = 2.4, 9.0 Hz, 2ArH), 8.05 (d, $J$ = 8.7 Hz, 2ArH), 9.87 (s, 1H COOH). HRMS ($ESI^+$): $m/z$ calculated for $C_{17}H_{22}O_3$ $[M+H]^+$: 274.1569; found: 274.1574.

#### 4.3.4. 4-(((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)benzoic acid (**6d**)

Yield- 68.8%; white solid; m.p- 56–58 °C; $^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.60 (s, 6H), 1.68 (s, 3H), 1.75 (s, 3H) 1.81–2.18 (m, 8H), 4.61 (d, $J$ = 6.6 Hz, 2H), 5.09–5.11 (m, 2H), 5.48–5.51 (m, 1H), 6.95 (d, $J$ = 9.0 Hz, 2ArH), 8.04 (d, $J$ = 8.7 Hz, 2ArH). HRMS ($ESI^+$): $m/z$ calculated for $C_{22}H_{30}O_3$ $[M+H]^+$: 342.2195; found: 342.2198.

#### 4.3.5. General procedure for the synthesis of aldehyde scaffolds **7a**-**7n** and **8a**-**8n**

3-Hydroxybenzaldehyde (for **7a**-**7n**) or 4-hydroxybenzaldehyde (for **8a**-**8n**) (1.0 g, 8.19 mmol), DMAP (0.05 g, 0.4 mmol) and the corresponding 4-alkoxy benzoic acid (8.19 mmol) were dissolved in DMF and stirred at room temperature for 15 min. Then DCC (2.0 g, 9.83 mmol) was added drop wise to the reaction mixture. After completion of reaction, the reaction mixture was diluted with ethyl acetate and filtered through celite. The filtrate was washed with water and brine solution. The organic portion was dried over sodium sulfate and concentrated under reduced pressure. The crude was then purified by column chromatography (silica gel 100–200 mesh) using ethyl acetate in hexanes to obtain the product.

#### 4.3.6. Synthesis of 3-formylphenyl 4-methoxybenzoate (**7a**)

Yield: 1.65 g, 78.6%, white solid, m.p: 78–80 °C, $^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta$ 3.91 (s, 3H), 7.01 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 7.48–7.51 (m, 1ArH), 7.60 (t, $J$ = 7.6 Hz, 1ArH), 7.75 (d, $J$ = 2.0 Hz, 1ArH), 7.79–7.81 (m, 1ArH), 8.17 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 10.04 (s, 1H CHO). HRMS ($ESI^+$): $m/z$ calculated for $C_{15}H_{13}O_4$ $[M+H]^+$: 257.0814; found: 257.0815.

#### 4.3.7. Synthesis of 3-formylphenyl 4-ethoxybenzoate (**7b**)

Yield: 1.83 g, 82.8%, white solid, m.p: 76–78 °C, $^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.47 (t, $J$ = 7.2 Hz, 3H), 4.14 (q, $J$ = 7.2 Hz, 2H), 6.98 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 7.50 (dd, $J$ = 1.2, 2.4 Hz, 1ArH) 7.60 (t,

$J$ = 7.6 Hz, 1ArH), 7.74–7.80 (m, 2ArH), 8.15 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 10.03 (s, 1H CHO). HRMS ($ESI^+$): $m/z$ calculated for $C_{16}H_{15}O_4$ $[M+H]^+$: 271.0970; found: 271.0973.

*4.3.8. Synthesis of 3-formylphenyl 4-propoxybenzoate (**7c**)*

Yield: 2.10 g, 90.1%, white solid, m.p: 72–74 °C, $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.07 (t, $J$ = 7.5 Hz, 3H), 1.85 (sextet, $J$ = 7.2 Hz, 2H) 4.02 (t, $J$ = 6.6 Hz, 2H), 6.97–7.02 (m, 2ArH), 7.49 (dq, $J$ = 1.2, 8.1 Hz, 1ArH), 7.60 (t, $J$ = 7.8 Hz, 1ArH), 7.74 (t, $J$ = 1.5 Hz, 1ArH), 7.80 (dt, $J$ = 1.2, 7.5 Hz, 1ArH), 8.12–8.17 (m, 2ArH) 10.03 (s, 1H CHO). HRMS ($ESI^+$): $m/z$ calculated for $C_{17}H_{17}O_4$ $[M+H]^+$: 285.1127; found: 285.1128.

*4.3.9. Synthesis of 3-formylphenyl 4-butoxybenzoate (**7d**)*

Yield: 2.11 g, 86.5%, white solid, m.p: 66–68 °C, $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.98 (t, $J$ = 7.2 Hz, 3H), 1.52 (sextet, $J$ = 7.2 Hz, 2H), 1.82 (quintet, $J$ = 6.4 Hz, 2H), 4.06 (t, $J$ = 6.4 Hz, 2H), 6.99 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 7.48–7.51 (m, 1ArH), 7.60 (t, $J$ = 7.6 Hz, 1ArH), 7.74 (t, $J$ = 2.0 Hz, 1ArH), 7.79 (d, $J$ = 7.6 Hz, 1ArH), 8.15 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 10.03 (s, 1H CHO). HRMS ($ESI^+$): $m/z$ calculated for $C_{18}H_{19}O_4$ $[M+H]^+$: 299.1283; found: 299.1288.

*4.3.10. Synthesis 3-formylphenyl 4-(pentyloxy)benzoate (**7e**)*

Yield: 2.18 g, 85.2%, white solid, m.p: 60–62 °C, $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 0.95 (t, $J$ = 7.2 Hz, 3H), 1.40–1.49 (m, 4H), 1.84 (quintet, $J$ = 7.5 Hz, 2H), 4.05 (t, $J$ = 6.6 Hz, 2H), 6.97–7.00 (m, 2ArH), 7.46–7.54 (m, 1ArH), 7.60 (t, $J$ = 1.5 Hz, 1ArH), 7.74 (t, $J$ = 1.5 Hz, 1ArH), 7.80 (dt, $J$ = 1.2, 7.5 Hz, 1ArH), 8.12–8.16 (m, 2ArH), 10.03 (s, 1H CHO). HRMS ($ESI^+$): $m/z$ calculated for $C_{19}H_{21}O_4$ $[M+H]^+$: 313.1440; found: 313.1445.

*4.3.11. Synthesis of 3-formylphenyl 4-(hexyloxy)benzoate (**7f**)*

Yield: 2.23 g, 83.5%, white solid, m.p: 56–58 °C, $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.92 (t, $J$ = 6.8 Hz, 3H), 1.35–1.37 (m, 4H), 1.45–1.51 (m, 2H), 1.83 (quintet, $J$ = 6.4 Hz, 2H), 4.05 (t, $J$ = 6.4 Hz, 2H), 6.99 (d, $J$ = 8.8 Hz, 2ArH), 7.49 (dd, $J$ = 1.2, 8.0 Hz, 1ArH), 7.60 (t, $J$ = 8.0 Hz, 1ArH), 7.75 (t, $J$ = 1.6 Hz, 1ArH), 7.79 (d, $J$ = 7.6 Hz, 1ArH), 8.14 (d, $J$ = 8.8 Hz, 2ArH), 10.03 (s, 1H CHO). HRMS ($ESI^+$): $m/z$ calculated for $C_{20}H_{23}O_4$ $[M+H]^+$: 327.1596; found: 327.1599.

*4.3.12. Synthesis of 3-formylphenyl 4-(heptyloxy)benzoate (**7g**)*

Yield: 2.35 g, 84.2%, white solid, m.p: 48–50 °C, $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.91 (t, $J$ = 6.8 Hz, 3H), 1.30–1.40 (m, 6H), 1.46–1.48 (m, 2H), 1.83 (t, $J$ = 6.8 Hz, 2H), 4.05 (t, $J$ = 6.8 Hz, 2H), 6.99 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 7.50 (q, $J$ = 1.2 Hz, 1ArH), 7.60 (t, $J$ = 8.0 Hz, 1ArH), 7.74 (t, $J$ = 2.0 Hz, 1ArH), 7.78–7.80 (m, 1ArH), 8.15 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 10.03 (s, 1H CHO). HRMS ($ESI^+$): $m/z$ calculated for $C_{21}H_{25}O_4$ $[M+H]^+$: 341.1753; found: 341.1754.

*4.3.13. Synthesis of 3-formylphenyl 4-(octyloxy)benzoate (**7h**)*

Yield: 2.46 g, 84.8%, white solid, m.p: 38–40 °C, $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.90 (t, $J$ = 6.8 Hz, 3H), 1.30–1.39 (m, 8H), 1.47 (sextet, $J$ = 7.2 Hz, 2H), 1.83 (quintet, $J$ = 6.8 Hz, 2H), 4.05 (t, $J$ = 6.4 Hz, 2H), 6.99 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 7.48–7.51 (m, 1ArH), 7.60 (t, $J$ = 7.6 Hz, 1ArH), 7.74 (t, $J$ = 2.0, 1ArH), 7.79 (dt, $J$ = 1.2, 7.6 Hz, 1ArH), 8.15 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 10.03 (s, 1H CHO). HRMS ($ESI^+$): $m/z$ calculated for $C_{22}H_{27}O_4$ $[M+H]^+$: 355.1909; found: 355.1911.

*4.3.14. Synthesis of 3-formylphenyl 4-(nonyloxy)benzoate (**7i**)*

Yield: 2.65 g, 88.3%, white solid, m.p: 38–40 °C, $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 0.89 (t, $J$ = 6.9 Hz, 3H), 1.29–1.33 (m, 10*H*), 1.46–1.51 (m, 2H), 1.83 (quintet, $J$ = 6.6 Hz, 2H), 4.05 (t, $J$ = 6.6 Hz, 2H), 6.96–7.01 (m, 2ArH), 7.47–7.51 (m, 1ArH), 7.60 (t, $J$ = 7.8 Hz, 1ArH), 7.74 (t, $J$ = 1.8 Hz, 1ArH), 7.50 (dd, $J$ = 1.2, 5.1 Hz, 1ArH), 8.12–8.17 (m, 2ArH), 10.03 (s, 1H CHO). HRMS ($ESI^+$): $m/z$ calculated for $C_{23}H_{29}O_4$ $[M+H]^+$: 369.2066; found: 369.2067.

*4.3.15. Synthesis of 3-formylphenyl 4-(decyloxy)benzoate (**7j**)*

Yield: 2.68 g, 85.6%, white solid, m.p: 38–40 °C, $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.89 (t, $J$ = 6.8 Hz, 3H), 1.28–1.38 (m, 12H), 1.48 (sextet, $J$ = 6.8 Hz, 2H), 1.81 (quintet, $J$ = 6.8 Hz, 2H), 4.05 (t, $J$ = 6.4 Hz, 2H), 6.99 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 7.48–7.51 (m, 1H), 7.60 (t, $J$ = 7.6 Hz, 1ArH), 7.74 (t, $J$ = 2.0 Hz, 1ArH), 7.79 (dt, $J$ = 1.2, 7.6 Hz, 1ArH), 8.15 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 10.03 (s, 1H CHO). HRMS ($ESI^+$): $m/z$ calculated for $C_{24}H_{31}O_4$ $[M+H]^+$: 383.2222; found: 383.2224.

*4.3.16. Synthesis of 3-formylphenyl 4-(allyloxy)benzoate (**7k**)*

Yield: 2.1 g, 90.9%, white solid, m.p: 58–60 °C, $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 4.64 (dt, $J$ = 1.2, 5.6 Hz, 2H), 5.33–5.37 (m, 1H), 5.43–5.48 (m, 1H), 6.04–6.11 (m, 1H), 7.02 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 7.48–7.51 (m, 1ArH), 7.60 (t, $J$ = 7.6 Hz, 1ArH), 7.74 (t, $J$ = 2.0 Hz, 1ArH), 7.80 (dt, $J$ = 1.2, 7.6 Hz, 1ArH), 8.16 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 10.03 (s, 1H CHO). HRMS ($ESI^+$): $m/z$ calculated for $C_{17}H_{15}O_4$ $[M+H]^+$: 283.0970; found: 283.0973.

*4.3.17. Synthesis of 3-formylphenyl 4-((3-methylbut-2-en-1-yl)oxy) benzoate (**7l**)*

Yield: 2.23 g, 87.8%, white solid, m.p: 72–74 °C, $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$1.78 (s, 3H), 1.82 (s, 3H), 4.62 (d, $J$ = 6.8 Hz, 2H), 5.49–5.53 (m, 1H), 7.01 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 7.50 (d, $J$ = 1.2 Hz, 1ArH), 7.58 (t, $J$ = 7.6 Hz, 1ArH), 7.74 (d, $J$ = 2.0 Hz, 1ArH), 7.80 (d, $J$ = 7.6 Hz, 1ArH), 8.15 (dd, $J$ = 2.0, 4.8 Hz, 2ArH), 10.03 (s, 1H CHO). HRMS ($ESI^+$): $m/z$ calculated for $C_{19}H_{19}O_4$ $[M+H]^+$: 311.1283; found: 311.1284.

*4.3.18. Synthesis of 3-formylphenyl −4-((3,7-dimethylocta-2,6-dien-1-yl) oxy)benzoate (**7m**)*

Yield: 2.86 g, 92.3%, pale yellow liquid, $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.62 (s, 3H), 1.69 (s, 3H), 1.77 (s, 3H), 2.12–2.15 (m, 4H), 4.65 (d, $J$ = 7.2 Hz, 2H), 5.06–5.10 (m, 1H), 5.47–5.50 (m, 1H), 7.00 (d, $J$ = 8.8 Hz, 2ArH), 7.48–7.50 (m, 1ArH), 7.60 (t, $J$ = 8.0 Hz, 1ArH), 7.74–7.81 (m, 2ArH), 8.15 (d, $J$ = 8.8 Hz, 2ArH), 10.03 (s, 1H CHO). HRMS ($ESI^+$): $m/z$ calculated for $C_{24}H_{27}O_4$ $[M+H]^+$: 379.1909; found: 379.1910.

*4.3.19. Synthesis of 3-formylphenyl 4-((3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)benzoate (**7n**)*

Yield: 3.20 g, 87.4%, pale yellow liquid, $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.60–1.61 (m, 6H), 1.68–1.69 (s, 3H), 1.77 (s, 3H), 1.96–2.17 (m, 8H), 4.60–4.65 (m, 2H), 5.10–5.11 (m, 2H), 5.50 (t, $J$ = 4.5 Hz, 1H), 7.01 (d, $J$ = 6.3 Hz, 2ArH), 7.49 (dd, $J$ = 0.9, 6.0 Hz, 1ArH), 7.60 (t, $J$ = 6.0 Hz, 1ArH), 7.74 (s, 1ArH), 7.79 (d, $J$ = 5.7 Hz, 1ArH), 8.15 (d, $J$ = 6.6 Hz, 2ArH) 10.03 (s, 1H CHO). HRMS ($ESI^+$): $m/z$ calculated for $C_{29}H_{35}O_4$ $[M+H]^+$: 447.2535; found: 447.2536.

*4.3.20. Synthesis of 4-formylphenyl 4-methoxybenzoate (**8a**)*

Yield: 1.59 g, 75.7%, white solid, m.p: 78–80 °C, $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 3.91 (s, 3H), 6.99–7.03 (m, 2ArH), 7.39–7.42 (m, 2ArH), 7.95–7.99 (m, 2ArH), 8.14–8.19 (m, 2ArH), 10.03 (s, 1H CHO). HRMS ($ESI^+$): $m/z$ calculated for $C_{15}H_{13}O_4$ $[M+H]^+$: 257.0814; found: 257.0817.

*4.3.21. Synthesis of 4-formylphenyl 4-ethoxybenzoate (**8b**)*

Yield: 1.74 g, 78.7%, white solid, m.p: 78–80 °C, $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.49 (t, $J$ = 6.8 Hz, 3H), 4.16 (q, $J$ = 6.4 Hz, 2H), 6.99–7.03 (m, 2ArH), 7.41–7.44 (m, 2ArH), 7.97–8.01 (m, 2ArH), 8.15–8.19 (m, 2ArH), 10.05 (s, 1H CHO). HRMS ($ESI^+$): $m/z$ calculated for $C_{16}H_{15}O_4$ $[M+H]^+$: 271.0970; found: 271.0974.

*4.3.22. Synthesis of 4-formylphenyl 4-propoxybenzoate (**8c**)*

Yield: 1.89 g, 87.1%, white solid, m.p: 72–74 °C, $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.07 (t, $J$ = 6.8 Hz, 3H), 1.82–1.91 (m, 2H), 4.02 (t, $J$ = 6.8 Hz, 2H), 6.99 (d, $J$ = 8.8 Hz, 2ArH), 7.40 (d, $J$ = 8.4 Hz, 2ArH), 7.97 (d, $J$ = 8.4 Hz, 2ArH), 8.14 (d, $J$ = 8.8 Hz, 2ArH), 10.02 (s, 1H CHO). HRMS (ESI$^+$): $m/z$ calculated for $C_{17}H_{17}O_4$ $[M+H]^+$: 285.1127; found: 285.1130.

*4.3.23. Synthesis of 4-formylphenyl 4-butoxybenzoate (**8d**)*

Yield: 1.98 g, 81.2%, white solid, m.p: 70–72 °C, $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.00 (t, $J$ = 7.2 Hz, 3H), 1.53 (sextet, $J$ = 7.6 Hz, 2H), 1.82 (quintet, $J$ = 7.6 Hz, 2H), 4.06 (t, $J$ = 6.8 Hz, 2H), 6.99 (dd, $J$ = 1.6, 6.8 HZ, 2ArH), 7.40 (dd, $J$ = 1.6, 6.8 Hz, 2ArH), 7.97 (dd, $J$ = 1.6, 6.4 Hz, 2ArH), 8.14 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 10.02 (s, 1H CHO). HRMS (ESI$^+$): $m/z$ calculated for $C_{18}H_{19}O_4$ $[M+H]^+$: 299.1283; found: 299.1287.

*4.3.24. Synthesis of 4-formylphenyl 4-(pentyloxy)benzoate (**8e**)*

Yield: 2.05 g, 80.1%, white solid, m.p: 64–66 °C, $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.95 (t, $J$ = 7.2 Hz, 3H), 1.38–1.51 (m, 4H), 1.84 (quintet, $J$ = 6.4 Hz, 2H), 4.05 (t, $J$ = 6.4 Hz, 2H), 6.97–7.00 (m, 2ArH), 7.39–7.42 (m, 2ArH), 7.95–7.98 (m, 2ArH), 8.12–8.16 (m, 2ArH), 10.02 (s, 1H CHO). HRMS (ESI$^+$): $m/z$ calculated for $C_{19}H_{21}O_4$ $[M+H]^+$: 313.1440; found: 313.1441.

*4.3.25. Synthesis of 4-formylphenyl 4-(hexyloxy)benzoate (**8f**)*

Yield: 2.10 g, 78.7%, white solid, m.p: 52–54 °C, $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.92 (t, $J$ = 7.2 Hz, 3H), 1.35–1.38 (m, 4H), 1.49 (sextet, $J$ = 7.2 Hz, 2H), 1.83 (quintet, $J$ = 6.8 Hz, 2H), 4.05 (t, $J$ = 6.8 Hz, 2H), 6.99 (dd, $J$ = 2.0, 7.2 Hz, 2ArH), 7.40 (dd, $J$ = 1.6, 6.8 Hz, 2ArH), 7.97 (dd, $J$ = 2.0, 6.4 Hz, 2ArH), 8.14 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 10.02 (s, 1H CHO). HRMS (ESI$^+$): $m/z$ calculated for $C_{20}H_{23}O_4$ $[M+H]^+$: 327.1596; found: 327.1598.

*4.3.26. Synthesis of 4-formylphenyl 4-(heptyloxy)benzoate (**8g**)*

Yield: 2.20 g, 78.9%, white solid, m.p: 50–52 °C, $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.95 (t, $J$ = 7.2 Hz, 3H), 1.30–1.40 (m, 6H), 1.46–1350 (m, 2H), 1.81–1.85 (m, 2H), 4.05 (t, $J$ = 6.4 Hz, 2H), 6.97–7.00 (m, 2ArH), 7.40–7.41 (m, 2ArH), 7.85–7.98 (m, 2ArH), 8.14 (dd, $J$ = 2.0, 4.8 Hz, 2ArH), 10.02 (s, 1H CHO). HRMS (ESI$^+$): $m/z$ calculated for $C_{21}H_{25}O_4$ $[M+H]^+$: 341.1753; found: 341.1756.

*4.3.27. Synthesis of 4-formylphenyl 4-(octyloxy)benzoate (**8h**)*

Yield: 2.20 g, 75.9%, white solid, m.p: 50–52 °C, $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.90 (t, $J$ = 6.8 Hz, 3H), 1.30–1.36 (m, 8H), 1.48 (sextet, $J$ = 7.2 Hz, 2H), 1.83 (quintet, $J$ = 7.2 Hz, 2H), 4.05 (t, $J$ = 6.4 Hz, 2H), 6.98 (dd, $J$ = 1.6, 6.8 Hz, 2ArH), 7.40 (dd, $J$ = 1.6, 6.8 Hz, 2ArH), 7.97 (dd, $J$ = 2.0, 6.8 Hz, 2H), 8.14 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 10.02 (s, 1H CHO). HRMS (ESI$^+$): $m/z$ calculated for $C_{22}H_{27}O_4$ $[M+H]^+$: 355.1909; found: 355.1912.

*4.3.28. Synthesis of 4-formylphenyl 4-(nonyloxy)benzoate (**8i**)*

Yield: 2.40 g, 80.0%, white solid, m.p: 52–54 °C, $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.89 (t, $J$ = 6.8 Hz, 3H), 1.30–1.39 (m, 10*H*), 1.44–1.49 (m, 2H), 1.83 (quintet, $J$ = 7.2 Hz, 2H), 4.05 (t, $J$ = 6.8 Hz, 2H), 6.98 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 7.40 (dd, $J$ = 1.6, 6.8 Hz, 2ArH), 7.97 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 8.14 (dd, $J$ = 2.0, 6.8 Hz, 2ArH), 10.02 (s, 1H, CHO). HRMS (ESI$^+$): $m/z$ calculated for $C_{23}H_{29}O_4$ $[M+H]^+$: 369.2066; found: 369.2069.

*4.3.29. Synthesis of 4-formylphenyl 4-(decyloxy)benzoate (**8j**)*

Yield: 2.45 g, 78.3%, white solid, m.p: 52–54 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.91 (t, $J$ = 6.6 Hz, 3H), 1.28–1.45 (m, 12H), 1.48–1.50 (m, 2H), 1.83 (quintet, $J$ = 6.6 Hz, 2H), 4.05 (t, $J$ = 6.6 Hz, 2H), 6.91–7.01 (m, 2ArH), 7.38–7.42 (m, 2ArH), 7.95–7.99 (m, 2ArH), 8.12–8.17 (m, 2ArH), 10.02 (s, 1H CHO). HRMS (ESI$^+$): $m/z$ calculated for $C_{24}H_{31}O_4$ $[M+H]^+$: 383.2222; found: 383.2223.

*4.3.30. Synthesis of 4-formylphenyl 4-(allyloxy)benzoate (**8k**)*

Yield: 1.89 g, 81.8%, white solid, m.p: 86–88 °C, $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.63–4.65 (m, 2H), 5.3–5.37 (m, 1H), 5.43–5.48 (m, 1H), 6.04–6.11 (m, 1H), 7.01 (dd, $J$ = 2.0, 5.2 Hz, 2ArH), 7.40 (dd, $J$ = 2.0, 5.2 Hz, 2ArH), 7.95–7.98 (m, 2ArH), 8.13–8.17 (m, 2ArH), 10.02 (s, 1H CHO). HRMS (ESI$^+$): $m/z$ calculated for $C_{17}H_{15}O_4$ $[M+H]^+$: 283.0970; found: 283.0972.

*4.3.31. Synthesis of 4-formylphenyl 4-((3-methylbut-2-en-1-yl)oxy) benzoate (**8l**)*

Yield: 2.10 g, 82.7%, white solid, m.p: 108–110 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.78 (s, 3H), 1.82 (s, 3H), 4.61 (d, $J$ = 6.8 Hz, 2H), 5.49–5.52 (m, 1H), 7.00 (d, $J$ = 8.8 Hz, 2ArH), 7.40 (d, $J$ = 8.4 Hz, 2ArH), 7.97 (d, $J$ = 8.4 Hz, 2ArH), 8.14 (d, $J$ = 8.8 Hz, 2ArH), 10.02 (s, 1H CHO). HRMS (ESI$^+$): $m/z$ calculated for $C_{19}H_{19}O_4$ $[M+H]^+$: 311.1283; found: 311.1284.

*4.3.32. Synthesis of 4-formylphenyl-4-((3,7-dimethylocta-2,6-dien-1-yl) oxy)benzoate (**8m**)*

Yield: 2.78 g, 89.7%, white solid, m.p: 44–46 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.64 (s, 3H), 1.71 (s, 3H), 1.79 (s, 3H), 2.11–2.1 (m, 4H), 4.67 (d, $J$ = 7.2 Hz, 2H),5.10–5.12 (m, 1H), 5.50–5.54 (m, 1H), 7.03 (d, $J$ = 6.8 Hz, 2ArH), 7.43 (d, $J$ = 6.8 Hz, 2ArH), 7.99 (d, $J$ = 6.8 Hz, 2ArH), 8.17 (d, $J$ = 6.4 Hz, 2ArH), 10.05 (s, 1H CHO). HRMS (ESI$^+$): $m/z$ calculated for $C_{24}H_{27}O_4$ $[M+H]^+$: 379.1909; found: 379.1911.

*4.3.33. Synthesis of 4-formylphenyl −4-((3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)benzoate (**8n**)*

Yield: 3.33 g, 90.1%, pale yellow liquid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.61 (s, 6H), 1.69 (s, 3H), 1.77 (s, 3H), 1.96–2.17 (m, 8H), 4.64 (d, $J$ = 6.4 Hz, 2H), 5.09–5.11 (m, 2H), 5.50 (t, $J$ = 6.4 Hz, 1H), 7.00 (d, $J$ = 8.4 Hz, 2ArH), 7.40 (d, $J$ = 8.4 Hz, 2ArH), 7.97 (d, $J$ = 8.4 Hz, 2ArH), 8.14 (d, $J$ = 8.4 Hz, 2ArH), 10.02 (s, 1H CHO). HRMS (ESI$^+$): $m/z$ calculated for $C_{29}H_{35}O_4$ $[M+H]^+$: 447.2535; found: 447.2538.

*4.3.34. 3-(1H-benzo[d]imidazol-2-yl)phenyl 4-methoxybenzoate (**9a**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **7a** (0.118 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 28% ethyl acetate in hexanes. Yield: 0.113 g, 71.5%, pale brown solid, m.p: 156–158 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.92 (s, 3H), 6.96–7.02 (m, 2ArH), 7.23–7.29 (m, 3ArH), 7.42 (t, $J$ = 7.5 Hz, 1ArH), 7.61 (bs, 2ArH), 7.85–7.90 (m, 2ArH), 8.13–8.18 (m, 2ArH), 10.10 (bs, 1 N−H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 55.5, 113.9, 120.2, 121.2, 122.9, 123.2, 124.0, 130.0, 131.4, 132.4, 150.8, 151.3, 164.1, 165.4. HRMS (ESI) $m/z$ calculated for $C_{21}H_{17}N_2O_3$ $(M+H)^+$: 345.1239; found: 345.1240.

*4.3.35. 3-(1H-benzo[d]imidazol-2-yl)phenyl 4-ethoxybenzoate (**9b**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **7b** (0.124 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction(TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography on silica gel (100–200 mesh) using 28% ethyl acetate in hexanes. Yield: 0.128 g, 78.0%, pale brown solid, m.p: 186–188 °C. $^1$H NMR (300 MHz, $CDCl_3$ + acetone$d_6$): $\delta$ 1.48 (t, $J$ = 7.2 Hz, 3H), 4.14 (q, $J$ = 6.9 Hz, 2H), 6.96–6.99 (m, 2ArH), 7.24–7.29 (m, 4ArH), 7.43 (t, $J$ = 7.8 Hz, 1ArH), 7.78 (bs,

1ArH), 7.86 (dd, $J$ = 1.2, 8.7 Hz, 1ArH), 7.90 (t, $J$ = 2.1 Hz, 1ArH), 8.13–8.16 (m, 2ArH), 9.99 (bs, 1 N−H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.6, 63.8, 114.3, 120.2, 121.2, 122.7, 123.2, 123.9, 129.9, 131.6, 132.2, 150.9, 151.5, 163.5, 164.8.HRMS (ESI) $m/z$ calculated for $C_{22}H_{19}N_2O_3$ $(M+H)^+$: 359.1396; found:359.1399.

*4.3.36. 3-(1H-benzo[d]imidazol-2-yl)phenyl 4-propoxybenzoate (**9c**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **7c** (0.131 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 28% ethyl acetate in hexanes. Yield: 0.115 g, 67.2%, pale brown solid, m.p: 154–156 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.00 (t, $J$ = 7.5 Hz, 3H), 1.73–1.85 (m, 2H), 4.08 (t, $J$ = 6.6 Hz, 2H), 7.00–7.12 (m, 1ArH), 7.14–7.17 (m, 2ArH), 7.22–7.27 (m, 2ArH), 7.40–7.43 (m, 1ArH), 7.56–7.59 (m, 1ArH), 7.65–7.68 (m, 2ArH), 8.05–8.08 (m, 1ArH), 8.13 (d, $J$ = 9.0 Hz, 2ArH), 13.00 (s, 1 N−H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 10.8, 22.4, 69.9, 115.1, 120.4, 121.1, 123.9, 124.3, 130.7, 132.1, 132.5, 132.6, 150.8, 151.6, 163.8, 164.7. HRMS (ESI) $m/z$ calculated for $C_{23}H_{21}N_2O_3$ $(M+H)^+$: 373.1552; found: 373.1554.

*4.3.37. 3-(1H-benzo[d]imidazol-2-yl)phenyl 4-butoxybenzoate (**9d**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **7d** (0.137 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 28% ethyl acetate in hexanes. Yield: 0.122 g, 68.5%, pale brown solid, m.p: 118–120 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.99 (t, $J$ = 6.9 Hz, 3H), 1.52 (quintet, $J$ = 6.6 Hz, 2H), 1.82 (sextet, $J$ = 6.6 Hz, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.92–6.94 (2ArH), 7.04–7.15 (m, 1ArH), 7.22–7.41 (m, 3ArH), 7.45–7.54 (m, 1ArH), 7.54–7.60 (m, 1ArH), 7.84–7.87 (m, 1ArH), 7.90 (t, $J$ = 1.8 Hz, 1ArH), 8.05–8.14 (m, 2ArH), 10.31 (bs, 1 N−H).$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 13.9, 19.2, 31.2, 68.1, 114.3, 120.2, 121.5, 123.0, 126.2, 131.1, 150.7, 151.3, 162.4, 163.7, 164.8, 165.2. HRMS (ESI) $m/z$ calculated for $C_{24}H_{23}N_2O_3$ $(M+H)^+$: 387.1709; found: 387.1711.

*4.3.38. 3-(1H-benzo[d]imidazol-2-yl)phenyl 4-(pentyloxy)benzoate (**9e**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **7e** (0.144 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 28% ethyl acetate in hexanes. Yield: 0.099 g, 53.8%, off white solid, m.p: 148–150 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.96 (t, $J$ = 6.9 Hz, 3H), 1.41–1.49 (m, 4H), 1.82–1.84 (m, 2H), 4.05 (t, $J$ = 6.6 Hz, 2H), 6.92–6.98 (m, 2ArH), 7.21–7.30 (m, 4ArH), 7.34–7.40 (m, 1ArH), 7.60–7.61 (m, 1ArH), 7.83–7.87 (m, 1ArH), 7.90 (t, $J$ = 1.8 Hz, 1ArH), 8.05–8.14 (m, 2ArH) $^{13}$C NMR (75 MHz, $CDCl_3$ + DMSO-$d_6$): $\delta$ 13.0, 21.3, 27.0, 27.6, 67.2, 113.4, 120.3, 121.4, 122.1, 128.8, 131.2, 150.2, 150.5, 162.6, 163.5. HRMS (ESI) $m/z$ calculated for $C_{25}H_{25}N_2O_3$ $(M+H)^+$: 401.1865; found: 401.1866.

*4.3.39. 3-(1H-benzo[d]imidazol-2-yl)phenyl 4-(hexyloxy)benzoate (**9f**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **7f** (0.150 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 28% ethyl acetate in hexanes. Yield: 0.156 g, 82.1%, pale brown solid, m.p:142–144 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.93 (t, $J$ = 6.9 Hz, 3H), 1.35–1.40 (m, 4H), 1.45–1.55 (m, 2H), 1.84 (quintet, $J$ = 6.9 Hz, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.96–7.00 (m, 2ArH), 7.23–7.29 (m, 3ArH), 7.42 (t, $J$ = 7.8 Hz, 2ArH), 7.79 (bs, 1ArH), 7.85 (dt, $J$ = 1.2, 7.8 Hz, 1ArH), 7.90 (t, $J$ = 2.1 Hz, 1ArH), 8.12–8.17 (m, 2ArH), 9.98 (bs, 1 N−H). $^{13}$C NMR (75 MHz, $CDCl_3$ + DMSO-$d_6$): $\delta$ 13.5, 22.0, 25.0, 28.4, 30.9, 67.8, 113.8, 120.5, 121.7, 121.8, 127.5, 131.7, 150.8, 151.6, 163.1, 164.1. HRMS (ESI) $m/z$ calculated for $C_{26}H_{27}N_2O_3$ $(M+H)^+$: 415.2022; found: 415.2023.

*4.3.40. 3-(1H-benzo[d]imidazol-2-yl)phenyl 4-(heptyloxy)benzoate (**9g**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **7g** (0.157 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC) the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 28% ethyl acetate in hexanes. Yield: 0.148 g, 75.1%, pale brown solid, m.p: 128–130 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.91 (t, $J$ = 6.6 Hz, 3H), 1.33–1.49 (m, 8H), 1.84 (quintet, $J$ = 6.6 Hz, 2H), 4.05 (t, $J$ = 6.6 Hz, 2H), 6.97 (d, $J$ = 8.4 Hz, 2ArH), 7.21–7.23 (m, 3ArH), 7.37 (t, $J$ = 8.1 Hz, 1ArH), 7.60 (bs, 2ArH), 7.84 (d, $J$ = 7.2 Hz, 1ArH), 7.90 (s, 1ArH), 8.12 (d, $J$ = 8.4 Hz, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.6, 26.0, 29.0, 29.1, 31.8, 68.4, 114.4, 120.2, 121.0, 122.9, 123.2, 123.9, 130.0, 131.4, 132.4, 150.7, 151.4, 163.8, 165.4. HRMS (ESI) $m/z$ calculated for $C_{27}H_{29}N_2O_3$ $(M+H)^+$: 429.2178; found: 429.2179.

*4.3.41. 3-(1H-benzo[d]imidazol-2-yl)phenyl 4-(octyloxy)benzoate (**9h**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **7h** (0.163 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC) the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 25% ethyl acetate in hexanes. Yield: 0.154 g, 75.5%, pale brown solid, m.p: 112–114 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.90 (t, $J$ = 6.3 Hz, 3H), 1.31–1.49 (m, 10*H*), 1.79–1.88 (m, 2H), 4.05 (t, $J$ = 6.6 Hz, 2H), 6.97 (d, $J$ = 9.0 Hz, 2ArH), 7.20–7.25 (m, 3ArH), 7.36 (t, $J$ = 8.1 Hz, 1ArH), 7.60 (bs, 2ArH), 7.82 (d, $J$ = 7.8 Hz, 1ArH), 7.89 (t, $J$ = 1.8 Hz, 1ArH), 8.13 (d, $J$ = 9.0 Hz, 2ArH), 10.16 (bs, 1 N−H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.4, 29.7, 31.8, 68.2, 113.8, 120.0, 121.6, 121.7, 122.0, 123.0,130.1, 131.3,132.4, 150.7, 151.4, 163.8, 165.4. HRMS (ESI) $m/z$ calculated for $C_{28}H_{31}N_2O_3$ $(M+H)^+$: 443.2335; found: 443.2338.

*4.3.42. 3-(1H-benzo[d]imidazol-2-yl)phenyl 4-(nonyloxy)benzoate (**9i**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **7i** (0.169 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 25% ethyl acetate in hexanes. Yield: 0.148 g, 70.5%, pale brown solid, m.p: 128–130 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.90 (t, $J$ = 6.9 Hz, 3H), 1.30–1.44 (m, 10*H*), 1.47–1.51 (m, 2H), 1.82 (quintet, $J$ = 6.6 Hz, 2H), 4.05 (t, $J$ = 6.6 Hz, 2H), 6.97 (dd, $J$ = 1.2, 9.0 Hz, 2ArH), 7.19–7.28 (m, 3ArH), 7.32–7.42 (m, 1ArH), 7.61 (bs, 2ArH), 7.83 (t, $J$ = 6.9 Hz, 1ArH), 7.89 (s, 1ArH), 8.13 (dd, $J$ = 2.4, 9.0 Hz,

2ArH), 10.16 (bs, 1 N−H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.3, 29.4, 29.6, 31.9, 68.4, 114.4, 115.3, 120.2, 120.9, 123.0, 123.3, 123.9, 130.1, 131.1, 132.4, 138.8, 150.6, 151.4, 163.8, 165.5. HRMS (ESI) *m/z* calculated for $C_{29}H_{33}N_2O_3$ $(M+H)^+$: 457.2491; found: 457.2491.

*4.3.43. 3-(1H-benzo[d]imidazol-2-yl)phenyl 4-(decyloxy)benzoate (**9j**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **7j** (0.176 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC) the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 25% ethyl acetate in hexanes. Yield: 0.125 g, 57.8%, pale brown solid, m.p: 96–98 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.89 (t, $J$ = 6.9 Hz, 3H), 1.25–1.49 (m, 12H), 1.44–1.49 (m, 2H), 1.84 (quintet, $J$ = 6.3 Hz, 2H), 4.05 (t, $J$ = 6.6 Hz, 2H), 6.96–6.99 (m, 2ArH), 7.23–7.29 (m, 4ArH), 7.41 (t, $J$ = 8.1 Hz, 1ArH), 7.61 (bs, 2ArH), 7.86 (d, $J$ = 7.8 Hz, 1ArH), 7.89 (t, $J$ = 1.8 Hz, 1ArH), 8.12–8.15 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.3, 29.4, 29.6, 29.7, 31.9, 68.4, 114.4, 120.2, 121.0, 123.0, 123.3, 123.9, 130.1, 131.2, 132.4, 150.6, 151.4, 163.8, 165.4. HRMS (ESI) *m/z* calculated for $C_{30}H_{35}N_2O_3$ $(M+H)^+$: 471.2648; found: 471.2651.

*4.3.44. 3-(1H-benzo[d]imidazol-2-yl)phenyl 4-(allyloxy)benzoate (**9k**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **7k** (0.130 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC) the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 30% ethyl acetate in hexanes. Yield: 0.096 g, 56.5%, off white solid, m.p:, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.64 (td, $J$ = 1.5, 8.4 Hz, 2H), 5.26 (dd, $J$ = 1.2, 10.5 Hz, 1H), 5.49 (dd, $J$ = 1.5, 15.9 Hz, 1H), 6.02–6.15 (m, 1H), 6.96–7.02 (m, 2ArH), 7.19–7.26 (m, 3ArH), 7.35 (t, $J$ = 7.8 Hz, 1ArH), 7.60 (bs, 2ArH), 7.82 (d, $J$ = 8.1 Hz, 1ArH), 7.89 (t, $J$ = 1.8 Hz, 1ArH), 8.09–8.15 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 68.6, 114.3, 117.9, 120.1, 121.3, 122.2, 122.8, 123.8, 129.5, 131.7, 131.9, 132.1, 150.7, 151.1, 162.7, 164.4. HRMS (ESI) *m/z* calculated for $C_{23}H_{19}N_2O_3$ $(M+H)^+$: 371.1396; found: 371.1399.

*4.3.45. 3-(1H-benzo[d]imidazol-2-yl)phenyl 4-((3-methylbut-2-en-1-yl) oxy)benzoate (**9l**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **7l** (0.143 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC) the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 30% ethyl acetate in hexanes. Yield: 0.129 g, 70.5%, brown solid, m.p: 106–108 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.79 (s, 3H), 1.83 (s, 3H), 4.62 (d, $J$ = 6.9 Hz, 2H), 5.50–5.54 (m, 1H), 6.96–7.01 (m, 2ArH), 7.22–7.29 (m, 3ArH), 7.41 (t, $J$ = 7.8 Hz, 1ArH), 7.61 (bs, 2ArH), 7.84 (d, $J$ = 7.8 Hz, 1ArH), 7.89 (t, 2.1 Hz, 1ArH), 8.13–8.16 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 17.7, 25.7, 65.2, 114.6, 118.7, 120.1, 121.1, 123.0, 123.3, 123.6, 123.9, 124.3, 124.4, 130.1, 131.4, 131.7, 132.4, 135.6, 135.8, 142.1, 150.6, 151.4, 163.6, 165.4. HRMS (ESI) *m/z* calculated for $C_{25}H_{23}N_2O_3$ $(M+H)^+$: 399.1709; found: 399.1711.

*4.3.46. 3-(1H-benzo[d]imidazol-2-yl)phenyl (E)-4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)benzoate (**9m**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **7m** (0.174 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC) the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 22% ethyl acetate in hexanes. Yield: 0.165 g, 76.7%, pale brown solid, m.p: 112–114 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.63 (s, 3H), 1.69 (s, 3H), 1.78 (s, 3H), 2.13–2.15 (m, 4H), 4.65 (d, $J$ = 6.6 Hz, 2H), 5.09–5.11 (m, 1H), 5.49–5.53 (m, 1H), 6.99–7.03 (m, 2ArH), 7.27–7.30 (m, 3ArH), 7.48 (t, $J$ = 8.1 Hz, 2ArH), 7.80 (bs, 1ArH), 7.88–7.91 (m, 2ArH), 8.16–8.18 (m, 2ArH), 9.89 (bs, 1 N−H). $^{13}$C NMR (75 MHz, $CDCl_3$ + DMSO-$d_6$): $\delta$ 16.2, 17.2, 25.2, 25.7, 64.7, 114.1, 115.2, 118.2, 119.9, 120.7, 122.0, 122.6, 123.2, 123.6, 129.3, 131.2, 131.4, 131.7, 141.4, 150.5, 151.0, 162.9, 164.2.HRMS (ESI) *m/z* calculated for $C_{30}H_{31}N_2O_3$ $(M+H)^+$: 467.2335; found: 467.2336.

*4.3.47. 3-(1H-benzo[d]imidazol-2-yl)phenyl 4-(((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)benzoate (**9n**)*

*o*-phenylenediamine (0.05 g, 0.46 mmol), aldehyde **7n** (0.205 g, 0.46 mmol) and *p*-Toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC) the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 22% ethyl acetate in hexanes. Yield: 0.154 g, 62.8%, pale brown solid, m.p: 154–156 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.61–1.62 (m, 6H), 1.69 (s, 3H), 1.84 (s, 3H), 2.01–2.14 (m, 8H), 4.61–4.66 (m, 2H), 5.10–5.12 (m, 2H), 5.51 (t, $J$ = 6.6 Hz, 1H), 6.96–7.02 (m, 2ArH), 7.26–7.30 (m, 4ArH), 7.46 (t, $J$ = 7.8 Hz, 1ArH), 7.61–7.62 (m, 1ArH), 7.87–7.91 (m, 2ArH), 8.12–8.17 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 16.1, 16.8, 17.7, 25.7, 26.1, 26.7, 39.6, 39.9, 65.2, 114.6, 118.7, 120.2, 121.0, 122.9, 123.1, 123.6, 124.0, 130.0, 131.3, 131.7, 132.4, 135.6, 142.1, 150.8, 151.3, 163.6, 165.6. HRMS (ESI) *m/z* calculated for $C_{35}H_{39}N_2O_3$ $(M+H)^+$: 535.2961; found: 535.2963.

*4.3.48. 4-(1H-benzo[d]imidazol-2-yl)phenyl 4-methoxybenzoate (**10a**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **8a** (0.118 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 35% ethyl acetate in hexanes. Yield: 0.096 g, 60.7%, pale brown solid, m.p: 216–218 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.92 (s, 3H), 6.99–7.03 (m, 2ArH), 7.27–7.33 (m, 4ArH), 7.64 (q, $J$ = 3.0 Hz, 2ArH), 8.04–8.07 (m, 2ArH), 8.15–8.19 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$ + DMSO-$d_6$): $\delta$ 54.6, 113.0, 120.3, 121.3, 121.4, 127.0, 131.3, 150.3, 151.2, 163.1, 163.5. HRMS (ESI) *m/z* calculated for $C_{21}H_{17}N_2O_3$ $(M+H)^+$: 345.1239; found: 345.1241.

*4.3.49. 4-(1H-benzo[d]imidazol-2-yl)phenyl 4-ethoxybenzoate compound (**10b**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **8b** (0.124 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 35% ethyl acetate in hexanes. Yield: 0.121 g, 73.3%, pale brown solid, m.p: 218–220 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.48 (t, $J$ = 6.9 Hz, 3H), 4.14 (q, $J$ = 6.9 Hz, 2H), 6.99 (d, $J$ = 9.0 Hz, 2ArH), 7.28–7.30 (m, 2ArH), 7.31–7.36 (m, 2ArH), 7.50 (bs, 1ArH), 7.82 (bs, 1ArH), 8.06–8.09 (m, 2ArH), 8.14–8.18 (m, 2ArH), 9.74 (bs, 1 N−H).

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.3, 63.5, 114.0, 120.9, 121.9, 122.0, 127.7, 132.0, 151.0, 151.9, 163.1, 164.3. HRMS (ESI) *m/z* calculated for $C_{22}H_{19}N_2O_3$ $(M+H)^+$: 359.1396; found: 359.1398.

*4.3.50. 4-(1H-benzo[d]imidazol-2-yl)phenyl 4-propoxybenzoate (**10c**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **8c** (0.131 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 35% ethyl acetate in hexanes. Yield: 0.112 g, 65.5%, pale brown solid, m.p: 172–174 °C, $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.01 (t, $J$ = 7.2 Hz, 3H), 1.75–1.82 (m, 2H), 4.06 (q, $J$ = 6.6 Hz, 2H), 7.11 (d, $J$ = 9.0 Hz, 2ArH), 7.13–7.27 (m, 2ArH), 7.48 (d, $J$ = 9.0 Hz, 2ArH), 7.55 (d, $J$ = 7.2 Hz, 1ArH), 7.69 (d, $J$ = 6.9 Hz, 1ArH), 8.03 (d, $J$ = 8.7 Hz, 2ArH), 8.26 (d, $J$ = 8.7 Hz, 2ArH), 12.97 (s, 1 N−H). $^{13}$C NMR (75 MHz, DMSO-$d_6$ + $CDCl_3$): $\delta$ 9.2, 21.0, 68.4, 113.2, 119.7, 121.0, 121.1, 121.2, 125.9, 126.7, 129.1, 130.8, 130.9, 149.9, 150.9, 162.3, 163.1. HRMS (ESI) *m/z* calculated for $C_{23}H_{21}N_2O_3$ $(M+H)^+$: 373.1552; found: 373.1552.

*4.3.51. 4-(1H-benzo[d]imidazol-2-yl)phenyl 4-butoxybenzoate (**10d**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **8d** (0.137 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 28% ethyl acetate in hexanes. Yield: 0.118 g, 66.3%, pale brown solid, m.p: 220–222 °C. $^1$H NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$): $\delta$ 1.00 (t, $J$ = 7.2 Hz, 3H), 1.47–1.57 (m, 2H), 1.82 (quintet, $J$ = 6.9 Hz, 2H), 4.07 (t, $J$ = 6.6 Hz, 2H), 6.95–7.02 (m, 2ArH), 7.19 (s, 1ArH), 7.27–7.31 (m, 2ArH), 7.34–7.37 (m, 2ArH), 7.74–7.89 (m, 1ArH), 8.06–8.11 (m, 2ArH), 8.14–8.18 (m, 2ArH), 11.30 (bs,1N-H). $^{13}$C NMR (75 MHz, $CDCl_3$ + DMSO-$d_6$): $\delta$ 12.9, 18.2, 30.1, 63.8, 113.5, 120.8, 121.4, 121.9, 127.1, 131.3, 151.1, 151.8, 163.3, 163.5.HRMS (ESI) *m/z* calculated for $C_{24}H_{23}N_2O_3$ $(M+H)^+$: 387.1709; found: 387.1710.

*4.3.52. 4-(1H-benzo[d]imidazol-2-yl)phenyl 4-(pentyloxy)benzoate (**10e**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **8e** (0.144 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel (100–200 mesh) using 28% ethyl acetate in hexanes. Yield: 0.132 g, 71.7%, brown solid, m.p: 108–110 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.96 (t, $J$ = 6.9 Hz, 3H), 1.41–1.49 (m, 4H), 1.82–1.84 (m, 2H), 4.05 (t, $J$ = 6.6 Hz, 2H), 6.92–6.98 (m, 2ArH), 7.21–7.30 (m, 4ArH), 7.34–7.40 (m, 1ArH), 7.60–7.61 (m, 1ArH), 7.83–7.87 (m, 1ArH), 7.90 (t, $J$ = 1.8 Hz, 1ArH), 8.05–8.14 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.0, 22.5, 28.1, 28.8, 68.4, 114.3, 1207, 121.2, 121.5, 127.0, 127.3, 128.8, 130.5, 136.0, 136.9, 137.6, 143.0, 151.1, 152.5, 163.6, 165.2. HRMS (ESI) *m/z* calculated for $C_{25}H_{25}N_2O_3$ $(M+H)^+$: 401.1865; found: 401.1868.

*4.3.53. 4-(1H-benzo[d]imidazol-2-yl)phenyl 4-(hexyloxy)benzoate (**10f**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **8f** (0.150 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction by TLC, the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 28% ethyl acetate in hexanes. Yield: 0.123 g, 64.7%, pale brown solid, m.p: 184–186 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.92 (t, $J$ = 6.9 Hz, 3H), 1.35–1.38 (m, 4H), 1.49–1.52 (m, 2H), 1.83 (quintet, $J$ = 6.9 Hz, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.97–7.01 (m, 2ArH), 7.26–7.30 (m, 2ArH), 7.31–7.36 (m, 2ArH), 7.61–7.89 (bs, 2ArH), 8.07–8.10 (m, 2ArH), 8.14–8.18 (m, 2ArH), 9.83 (bs, 1 N−H). $^{13}$C NMR (75 MHz, $CDCl_3$ + DMSO-$d_6$): $\delta$ 13.4, 21.9, 24.9, 28.3, 30.8, 67.7, 113.7, 120.4, 121.6, 121.8, 127.1, 127.4, 131.6, 150.6, 151.6, 163.0, 163.9. HRMS (ESI) *m/z* calculated for $C_{26}H_{27}N_2O_3$ $(M+H)^+$: 415.2022; found: 415.2024.

*4.3.54. 4-(1H-benzo[d]imidazol-2-yl)phenyl 4-(heptyloxy)benzoate (**10g**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **8g** (0.157 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 25% ethyl acetate in hexanes. Yield: 0.131 g, 66.5%, pale brown solid, m.p: 192–194 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.91 (t, $J$ = 6.6 Hz, 3H), 1.32–1.50 (m, 6H), 1.51–1.53 (m, 2H), 1.84 (quintet, $J$ = 6.6 Hz, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.98–7.01 (m, 2ArH), 7.28–7.31 (m, 2ArH), 7.33–7.36 (m, 2ArH), 7.49 (bs, 1ArH), 7.81 (bs, 1ArH), 8.05–8.08 (m, 2ArH), 8.14–8.18 (m, 2ArH), 9.81 (bs, 1 N−H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.0, 25.5, 25.9, 28.9, 29.0, 31.7, 68.3, 114.3, 121.1, 122.2, 128.0, 128.1, 132.2, 151.3, 152.2, 163.7, 164.7. HRMS (ESI) *m/z* calculated for $C_{27}H_{29}N_2O_3$ $(M+H)^+$: 429.2178; found: 429.2180.

*4.3.55. 4-(1H-benzo[d]imidazol-2-yl)phenyl 4-(octyloxy)benzoate (**10h**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **8h** (0.163 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography on silica gel (100–200 mesh) using 25% ethyl acetate in hexanes. Yield: 0.136 g, 67.0%, pale brown solid, m.p: 108–110 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.89 (t, $J$ = 6.3 Hz, 3H), 1.26–1.33 (m, 8H), 1.42–1.48 (m, 2H), 1.83 (quintet, $J$ = 6.3 Hz, 2H), 4.05 (t, $J$ = 6.3 Hz, 2H), 6.95–7.00 (m, 2ArH), 7.19 (s, 1ArH), 7.28–7.37 (m, 3ArH), 7.61 (bs, 1ArH), 7.75 (d, $J$ = 8.7 Hz, 1ArH), 7.88 (d, $J$ = 7.5 Hz, 1ArH), 8.06–8.11 (m, 1ArH), 8.15 (dd, $J$ = 1.5, 9.0 Hz, 2ArH), 10.13 (bs, 1 N−H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.2, 29.3, 31.8, 68.4, 114.4, 121.0, 122.4, 123.0, 127.2, 128.0, 132.3, 150.6, 151.0, 152.5, 163.8, 165.0. HRMS (ESI) *m/z* calculated for $C_{28}H_{31}N_2O_3$ $(M+H)^+$: 443.2335; found: 443.2336.

*4.3.56. 4-(1H-benzo[d]imidazol-2-yl)phenyl 4-(nonyloxy)benzoate (**10i**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **8i** (0.169 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 25% ethyl acetate in hexanes. Yield: 0.126 g, 60.0%, pale brown solid, m.p:, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.89 (t, $J$ = 6.9 Hz, 3H), 1.20–1.30 (m, 10*H*), 1.44–1.48 (m, 2H), 1.78–1.88 (m, 2H), 4.05 (t, $J$ = 6.3 Hz, 2H), 6.95–7.00 (m, 2ArH), 7.18–7.33 (m, 5ArH), 7.30–7.60 (m, 1ArH), 8.03–8.06 (m, 2ArH), 8.14–8.18 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.3, 29.4, 29.5, 31.9, 68.4, 114.5, 121.0, 122.4, 122.9, 127.6, 128.0, 132.4, 151.2, 152.3, 163.9,

165.2. HRMS (ESI) *m/z* calculated for $C_{29}H_{33}N_2O_3$ $(M+H)^+$: 457.2491; found: 457.2494.

*4.3.57. 4-(1H-benzo[d]imidazol-2-yl)phenyl 4-(decyloxy)benzoate (**10j**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **8j** (0.176 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 25% ethyl acetate in hexanes. Yield: 0.130 g, 60.2%, pale brown solid, m.p: 142–144 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.89 (t, $J$ = 6.9 Hz, 3H), 1.29–1.34 (m, 12H), 1.42–1.48 (m, 2H), 1.83 (quintet, $J$ = 6.6 Hz, 2H), 4.05 (t, $J$ = 6.3 Hz, 2H), 6.97 (d, $J$ = 9.0 Hz, 2ArH), 7.25–7.28 (m, 4H), 7.64–7.67 (m, 2ArH), 8.09–8.13 (m, 4ArH).$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.3, 29.4, 29.6, 29.7, 31.9, 68.4, 114.5, 115.2, 121.0, 122.4, 123.0, 127.3, 128.0, 132.4, 139.0, 151.1, 152.4, 163.9, 165.2. HRMS (ESI) *m/z* calculated for $C_{30}H_{35}N_2O_3$ $(M+H)^+$: 471.2648; found: 471.2649.

*4.3.58. 4-(1H-benzo[d]imidazol-2-yl)phenyl 4-(allyloxy)benzoate (**10k**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **8k** (0.130 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 30% ethyl acetate in hexanes. Yield: 0.106 g, 62.3%, pale brown solid, m.p:, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.62–4.66 (m, 2H), 5.32–5.34 (m, 1H), 5.42–5.51 (m, 1H), 6.03–6.09 (m, 1H), 6.98–7.03 (m, 2ArH), 7.19 (s, 1ArH), 7.28–7.36 (m, 3ArH), 7.66 (bs, 1ArH), 7.76 (d, $J$ = 8.7 Hz, 1ArH), 7.87 (d, $J$ = 8.7 Hz, 1ArH), 8.07–8.18 (m, 3ArH). $^{13}$C NMR (75 MHz, $CDCl_3$ + DMSO-$d_6$): $\delta$ 68.3, 114.0, 117.6, 120.9, 121.6, 121.7, 121.9, 122.6, 126.4, 127.4, 129.7, 131.6, 131.7, 133.0, 135.4, 142.4, 149.9, 150.7, 162.3, 162.4, 163.8. HRMS (ESI) *m/z* calculated for $C_{23}H_{19}N_2O_3$ $(M+H)^+$: 371.1396; found: 371.1397.

*4.3.59. 4-(1H-benzo[d]imidazol-2-yl)phenyl 4-((3-methylbut-2-en-1-yl) oxy)benzoate (**10l**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **8l** (0.143 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 30% ethyl acetate in hexanes. Yield: 0.103 g, 56.3%, brown solid, m.p: 202–204 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.78 (s, 3H), 1.82 (s, 3H), 4.62 (d, $J$ = 6.3 Hz, 2H), 5.49–5.53 (m, 1H), 6.97–7.02 (m, 2ArH), 7.18–7.34 (m, 4ArH), 7.60–7.62 (m, 2ArH), 8.03–8.06 (m, 2ArH), 8.14–8.17 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$ + DMSO-$d_6$): $\delta$ 17.5, 25.0, 64.3, 113.8, 118.2, 120.3, 121.6, 122.5, 129.6, 131.4, 138.0, 150.5, 151.5, 162.6, 163.8. HRMS (ESI) *m/z* calculated for $C_{25}H_{23}N_2O_3$ $(M+H)^+$: 399.1709; found: 399.1710.

*4.3.60. 4-(1H-benzo[d]imidazol-2-yl)phenyl (E)-4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)benzoate (**10m**)*

*o*-Phenylenediamine (0.05 g, 0.46 mmol), aldehyde **8m** (0.174 g, 0.46 mmol) and *p*-toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 25% ethyl acetate in hexanes. Yield: 0.124 g, 57.7%, pale brown solid, m.p: 128–130 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.62 (s, 3H), 1.69 (s, 3H), 1.77 (s, 3H), 2.09–2.21 (m, 4H), 4.65 (d, $J$ = 6.6 Hz, 2H), 5.08–5.11 (m, 1H), 5.50 (t, $J$ = 5.4 Hz, 1H), 6.97–7.03 (m, 2ArH), 7.24–7.29 (m, 4ArH), 7.61 (bs, 2ArH), 8.04 (d, $J$ = 7.8 Hz, 2ArH), 8.14–8.18 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 16.8, 17.7, 25.7, 26.3, 39.5, 65.2, 114.7, 115.1, 118.7, 121.1, 122.6, 123.4, 123.7, 128.1, 132.0, 132.4, 142.1, 150.5, 152.8, 163.6, 164.9. HRMS (ESI) *m/z* calculated for $C_{30}H_{31}N_2O_3$ $(M+H)^+$: 467.2335; found: 467.2339.

*4.3.61. 4-(1H-benzo[d]imidazol-2-yl)phenyl 4-(((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)benzoate (**10n**)*

*o*-phenylenediamine (0.05 g, 0.46 mmol), aldehyde **8n** (0.205 g, 0.46 mmol) and *p*-Toluenesulfonic acid (0.044 g, 0.23 mmol) were dissolved in DMF and maintained at 80 °C for 4 h. After completion of reaction (TLC), the reaction mass was diluted with ethyl acetate and partitioned with water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 25% ethyl acetate in hexanes. Yield: 0.105 g, 42.9%, pale brown solid, m.p:, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.61 (s, 6H), 1.69 (s, 3H), 1.77 (s, 3H), 1.98–2.18 (m, 8H), 4.65 (d, $J$ = 6.3 Hz, 2H), 5.11 (d, $J$ = 6.3 Hz, 2H), 5.53 (t, $J$ = 6.6 Hz, 1H), 6.97–7.02 (m, 2ArH), 7.16–7.19 (m, 1ArH), 7.27–7.42 (m, 3ArH), 7.63–7.66 (m, 2ArH), 8.06 (d, $J$ = 8.7 Hz, 2ArH), 8.13–8.18 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 16.1, 16.8, 17.7, 26.6, 65.2, 114.7, 118.7, 121.2, 122.5, 123.1, 123.5, 124.3, 124.4, 127.3, 127.9, 128.8, 131.4, 132.4, 135.6, 142.1, 150.8, 152.6, 163.6, 164.9.HRMS (ESI) *m/z* calculated for $C_{35}H_{39}N_2O_3$ $(M+H)^+$: 535.2961; found: 535.2964.

*4.3.62. Synthesis of compound 2-((4-methoxybenzylidene)amino)phenol (**11a**)*

2-Aminophenol (5 g, 45.82 mmol) and *p*-anisaldehyde (6.24 g, 45.82 mmol) were dissolved in methanol and stirred at room temperature in the presence of catalytic amount of acetic acid for 3 h. The solid thus formed was filtered and washed with cold methanol and air dried to get compound **11a** (8.43 g, 81.0%) as yellow solid, m.p: 80–82 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.89 (s, 3H), 6.90 (td, $J$ = 1.5, 7.8 Hz, 1ArH), 7.01 (dd, $J$ = 1.8, 9.0 Hz, 3ArH), 7.17 (td, $J$ = 1.5, 9.0 Hz, 1ArH), 7.29 (d, $J$ = 1.2 Hz, 1ArH), 7.88 (dd, $J$ = 2.4, 11.4 Hz, 2ArH), 8.63 (s, 1H). HRMS ($ESI^+$): *m/z* calculated for $C_{17}H_{22}O_3$ $[M+H]^+$: 274.1569; found: 274.1574.

*4.3.63. Synthesis of compound 2-((3-nitrobenzylidene)amino)phenol (**11b**)*

2-Aminophenol (5 g, 45.8 mmol) and *m*-nitrobenzaldehyde (6.92 g, 45.82 mmol) were dissolved in methanol and stirred at room temperature in the presence of catalytic amount of acetic acid for 3 h. The solid thus formed was filtered and washed with cold methanol and air dried to get compound **11b** (9.3 g, 84.5%) as yellow solid, m.p: 118–120 °C. The compound was used as such for the next step. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.95 (td, $J$ = 1.2, 8.1 Hz, 1ArH), 7.06 (dd, $J$ = 1.2, 8.1 Hz, 1ArH), 7.16 (s, 1O-H), 7.24–7.30 (m, 1ArH), 7.35 (dd, $J$ = 1.2, 8.1 Hz, 1ArH), 7.69 (t, $J$ = 8.1 Hz, 1ArH), 8.26 (d, $J$ = 7.8 Hz, 1ArH), 8.35 (dq, $J$ = 1.2, 8.1 Hz, 1ArH), 8.75 (t, $J$ = 1.8 Hz, 1ArH), 8.79 (s, 1H). HRMS ($ESI^+$): *m/z* calculated for $C_{13}H_8N_2O_3$ $[M+H]^+$: 240.0535; found: 240.0539.

*4.3.64. Synthesis of compound 2-(4-methoxyphenyl)benzo[d]oxazole (**12**)*

Compound **11** (8.0 g, 35.2 mmol) was dissolved in DCM and to that DDQ (8.79 g, 38.7 mmol) was added and stirred at room temperature for 2 h. After completion of reaction, the mass was diluted with DCM and washed with water. Aqueous layer again extracted with DCM (3x150 mL). Combined organic layer was washed with water followed by brine solution. The organic portion was dried over sodium sulfate and concentrated under reduced pressure. The crude was then purified

by column chromatography (silica gel 100–200 mesh) using ethyl acetate in hexanes (25%) to afford compound **12** (6.7 g, 84.5%) as pale brown solid, m.p: 86–88 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.90 (s, 3H), 7.04 (d, $J$ = 9.2 Hz, 2ArH), 7.32–7.36 (m, 2ArH), 7.55–7.57 (m, 1ArH), 7.73–7.75 (m, 1ArH), 8.20 (dd, $J$ = 1.6, 8.8 Hz, 2ArH). HRMS ($ESI^+$): $m/z$ calculated for $C_{14}H_{11}NO_2$ $[M+H]^+$: 225.0790; found: 225.0795.

*4.3.65. Synthesis of compound 4-(benzo[d]oxazol-2-yl)phenol (**13**)*

Compound **12** (6 g, 26.6 mmol) was suspended in hydrobromic acid (50% in acetic acid) and maintained at 80 °C for 12 h. After completion of reaction the mass was poured into water and the solid was filtered. The solid thus obtained was dissolved in ethyl acetate and washed with 10% sodium carbonate solution. The organic layer was further washed with water, brine solution and dried over sodium sulfate. The organic portion was then concentrated and purified by column chromatography (silica gel 100–200 mesh) using ethyl acetate in hexanes (32%) to afford compound **13** (4.4 g, 78.3%) as off white solid, m.p: > 200 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 5.52 (bs, 1O-H), 6.97 (d, $J$ = 8.8, 2ArH), 7.32–7.34 (m, 2ArH), 7.55–7.57 (m, 1ArH), 7.73–7.75 (m, 1ArH), 8.15–8.22 (m, 2ArH). HRMS ($ESI^+$): $m/z$ calculated for $C_{13}H_9NO_2$ $[M+H]^+$: 211.0633; found: 211.0634.

*4.3.66. Synthesis of compound 2-(3-nitrophenyl)benzo[d]oxazole (**15**)*

Compound **11b** (9.0 g, 37.2 mmol) was dissolved in DCM and to that DDQ (9.29 g, 40.9 mmol) was added and stirred at RT for 2 h. After completion of reaction, the mass was diluted with DCM and washed with water. Aqueous layer was again extracted with DCM (3x150 mL). Combined organic layer was washed with water followed by brine solution. The organic portion was dried over sodium sulfate and concentrated under reduced pressure. The crude was purified by column chromatography (silica gel 100–200 mesh) using ethyl acetate in hexanes (25%) to afford compound **15** (7.64 g, 85.5%) as pale yellow solid, m.p: 168–170 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.38–7.45 (m, 2ArH), 7.62–7.68 (m, 1ArH), 7.74 (t, $J$ = 7.8 Hz, 1ArH), 7.80–7.85 (m, 1ArH), 8.39 (dq, $J$ = 0.9, 8.1 Hz, 1ArH), 8.60 (dt, $J$ = 1.2, 7.8 Hz, 1ArH), 9.11 (s, 1ArH). HRMS ($ESI^+$): $m/z$ calculated for $C_{13}H_8N_2O_3$ $[M+H]^+$: 240.0535; found: 240.0539.

*4.3.67. Synthesis of compound 3-(benzo[d]oxazol-2-yl)aniline (**16**)*

Compound **15** (7 g, 29.14 mmol) was dissolved in methanol and chlroform (3:2) and cooled to 0–5 °C and then Nickel chloride hexahydrate (0.345 g, 1.46 mmol) was added and stirred for 10 min. Then sodium borohydride (3.31 g, 87.42 mmol) was added in 5 lots over a period of 30 min and stirred at room temperature for another 1 h. Then the reaction mixture was then filtered through celite bed and the bed washed with warm methanol. The filtrate was evaporated and partitioned between ethyl acetate and water (3x200 mL). Combined organic layer washed with water and then with brine. The organic portion was dried over sodium sulfate and concentrated under reduced pressure to get the product **16** (5.45 g, 88.9%) as brown solid, m.p: 162–164 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.25 (bs, 2 NH), 6.84–6.86 (m, 1ArH), 7.31–7.36 (m, 3ArH), 7.59–7.60 (m, 2ArH), 7.66–7.68 (m, 1ArH), 7.82–7.85 (m, 1ArH). HRMS ($ESI^+$): $m/z$ calculated for $C_{13}H_{10}N_2O$ $[M+H]^+$: 210.0793; found: 210.0791.

*4.3.68. Synthesis of compound 3-(benzo[d]oxazol-2-yl)phenol (**17**)*

Compound **16** (5 g, 23.8 mmol) was dissolved in 5% aqueous HCl (30 mL) and cooled to 5 °C for 15 min. Then aqueous solution of sodium nitrite (1.97 g, 28.5 mmol) was added drop wise to the reaction mass and stirred for 15 min. It was heated to 80 °C, and maintained for 6 h. After completion of the reaction by TLC the aqueous phase was extracted with ethyl acetate (3x150). Combined organic layer was washed with water and then with brine. Evaporated and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes to get the product **17** (3.9 g, 77.5%) as pale brown solid m.p: 196–198 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.03–7.06 (m, 1ArH), 7.33–7.37 (m, 4ArH), 7.57–7.59 (m, 1ArH), 7.72–7.77 (m, 2ArH), 9.15 (bs, 1O-H). HRMS ($ESI^+$): $m/z$ calculated for $C_{13}H_9NO_2$ $[M+H]^+$: 211.0633; found: 211.0636.

*4.3.69. 4-(Benzo[d]oxazol-2-yl)phenyl 4-methoxybenzoate (**14a**)*

To a stirred solution of 4-methoxybenzoic acid (0.072 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **13** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.125 g, 77.1%, white solid, m.p: 144–146 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.91 (s, 3H), 6.98–7.03 (m, 2ArH), 7.34–7.42 (m, 4ArH), 7.57–7.63 (m, 1ArH), 7.76–7.81 (m, 1ArH), 8.15–8.20 (m, 2ArH), 8.31–8.36 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 55.6, 110.6, 114.0, 120.0, 121.4, 122.5, 124.7, 125.2, 129.0, 132.4, 142.1, 150.8, 153.7, 162.4, 164.1, 164.5. HRMS (ESI) $m/z$ calculated for $C_{21}H_{16}NO_4$ $(M+H)^+$: 346.1079; found: 346.1081.

*4.3.70. 4-(Benzo[d]oxazol-2-yl)phenyl 4-ethoxybenzoate (**14b**)*

To a stirred solution of 4-ethoxybenzoic acid (0.079 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **13** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.139 g, 82.2%, white solid, m.p: 170–172 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.47 (t, $J$ = 6.9 Hz, 3H), 4.14 (q, $J$ = 6.9 Hz, 2H), 6.97–7.01 (m, 2 ArH), 7.34–7.42 (m, 4 ArH), 7.57–7.63 (m, 1ArH), 7.75–7.81 (m, 1 ArH), 8.14–8.19 (m, 2ArH), 8.31–8.36 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.7, 63.9, 110.6, 114.4, 120.0, 121.2, 122.5, 124.7, 125.2, 129.0, 132.4, 142.1, 150.8, 153.7, 162.4, 163.6, 164.5. HRMS (ESI) $m/z$ calculated for $C_{22}H_{18}NO_4$ $(M+H)^+$: 360.1236; found: 360.1239.

*4.3.71. 4-(Benzo[d]oxazol-2-yl)phenyl 4-propoxybenzoate (**14c**)*

To a stirred solution of 4-propoxybenzoic acid (0.085 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **13** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.118 g, 67.2%, white solid, m.p: 170–172 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.08 (t, $J$ = 7.5 Hz, 3H), 1.87 (sextet, $J$ = 7.5 Hz, 2H), 4.03 (t, $J$ = 6.6 Hz, 2H), 7.00 (td, $J$ = 1.8, 4.8 Hz, 2H), 7.36–7.39 (m, 2H), 7.41 (dd, $J$ = 0.9, 4.8 Hz, 1H), 7.57–7.62 (m, 2H), 7.75–7.81 (m, 1H), 8.13 (t, $J$ = 1.8 Hz, 1H), 8.17 (td, $J$ = 1.8,5.1 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 10.5, 22.5, 69.8, 110.6, 114.4, 120.0, 121.1, 122.5, 124.7, 125.2, 129.0, 132.4, 142.1, 150.8, 153.7, 162.5, 163.8, 164.5. HRMS (ESI) $m/z$ calculated for $C_{23}H_{20}NO_4$ $(M+H)^+$: 374.1392; found: 374.1395.

*4.3.72. 4-(Benzo[d]oxazol-2-yl)phenyl 4-butoxybenzoate (**14d**)*

To a stirred solution of 4-butoxybenzoic acid (0.091 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **13** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room

temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.142 g, 77.2%, white solid, m.p:, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.00 (t, $J$ = 7.5 Hz, 3H), 1.54 (sextet, $J$ = 7.5 Hz, 2H), 1.82 (quintet, $J$ = 7.8 Hz, 2H), 4.07 (t, $J$ = 6.6 Hz, 2H), 6.97–7.02 (m, 2ArH), 7.32–7.42 (m, 4ArH), 7.55–7.63 (m, 1ArH), 7.73–7.81 (m, 1ArH), 8.14–8.22 (m, 2ArH), 8.31–8.35 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 18.8, 19.2, 31.1, 68.1, 110.6, 114.4, 120.0, 121.1, 122.5, 124.7, 125.2, 129.0, 132.4, 142.1, 150.8, 153.7, 162.5, 163.8, 164.5. HRMS (ESI) $m/z$ calculated for $C_{24}H_{22}NO_4$ $(M+H)^+$: 388.1549; found: 388.1551.

#### 4.3.73. 4-(Benzo[d]oxazol-2-yl)phenyl 4-(pentyloxy)benzoate (14e)

To a stirred solution of 4-pentoxybenzoic acid (0.098 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **13** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.151 g, 79.9%, white solid, m.p: 120–122 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.95 (t, $J$ = 6.9 Hz, 3H), 1.42–1.48 (m, 4H), 1.82–1.86 (m, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.97–7.02 (m, 2ArH), 7.34–7.42 (m, 4ArH), 7.57–7.63 (m, 1ArH), 7.76–7.81 (m, 1ArH), 8.14–8.19 (m, 2ArH), 8.31–8.36 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.0, 22.5, 28.1, 28.8, 68.4, 110.6, 114.4, 120.0, 121.1, 122.5, 124.6, 125.2, 129.0, 132.4, 142.1, 150.8, 153.7, 162.4, 163.8, 164.5. HRMS (ESI) $m/z$ calculated for $C_{25}H_{24}NO_4$ $(M+H)^+$: 402.1705; found: 402.1706.

#### 4.3.74. 4-(Benzo[d]oxazol-2-yl)phenyl 4-(hexyloxy)benzoate (14f)

To a stirred solution of 4-hexyloxybenzoic acid (0.104 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **13** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.163 g, 83.6%, white solid, m.p: 118–120 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.92 (t, $J$ = 6.9 Hz, 3H), 1.33–1.39 (m, 4H), 1.46–1.51 (m, 2H), 1.83 (quintet, $J$ = 6.9 Hz, 2H), 4.06 (t, $J$ = 6.3 Hz, 2H), 6.98–7.02 (m, 2ArH), 7.31–7.41 (m, 4ArH), 7.58–7.63 (m, 1ArH), 7.77–7.81 (m, 1ArH), 8.14–8.19 (m, 2ArH), 8.31–8.36 (m, 2ArH) $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 14.1, 22.6, 25.7, 29.1, 31.6, 68.4, 110.6, 114.4, 120.0, 121.1, 122.5, 124.7, 125.2, 129.0, 129.4, 132.4, 142.1, 15.08, 153.7, 162.5, 163.8, 164.5. HRMS (ESI) $m/z$ calculated for $C_{26}H_{26}NO_4$ $(M+H)^+$: 416.1862; found: 416.1866.

#### 4.3.75. 4-(Benzo[d]oxazol-2-yl)phenyl 4-(heptyloxy)benzoate (14g)

To a stirred solution of 4-heptyloxybenzoic acid (0.111 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **13** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0158 g, 78.2%, white solid, m.p: 106–108 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.91 (t, $J$ = 6.9 Hz, 3H), 1.33–1.37 (m, 6H), 1.40–1.51 (m, 2H), 1.84 (quintet, $J$ = 6.6 Hz, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.98–7.01 (m, 2ArH), 7.34–7.42 (m, 4ArH), 7.57–7.62 (m, 1ArH), 7.76–7.82 (m, 1ArH), 8.14–8.18 (m, 2ArH), 8.31–8.35 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.6, 26.0, 29.0, 29.1, 31.8, 68.4, 110.6, 114.4, 120.0, 121.1, 122.5, 124.7, 125.2, 129.0, 132.4, 142.1, 150.8, 153.7, 162.5, 163.8, 164.5. HRMS (ESI) $m/z$ calculated for $C_{27}H_{28}NO_4$ $(M+H)^+$: 430.2018; found:430.2020.

#### 4.3.76. 4-(Benzo[d]oxazol-2-yl)phenyl 4-(octyloxy)benzoate (14h)

To a stirred solution of 4-octyloxybenzoic acid (0.118 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **13** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.163 g, 78.4%, appearance, m.p: 118–120 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.90 (t, $J$ = 6.6 Hz, 3H), 1.30–1.35 (m, 8H), 1.60–1.61 (m, 2H), 1.83 (quintet, $J$ = 6.6 Hz, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.97–7.02 (m, 2ArH), 7.34–7.42 (m, 4ArH), 7.57–7.63 (m, 1ArH), 7.76–7.81 (m, 1ArH), 8.14–8.18 (m, 2ArH), 8.31–8.36 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.2, 29.3, 31.8, 68.4, 110.6, 114.4, 120.0, 121.1, 122.5, 124.6, 125.2, 129.0, 132.4, 142.1, 150.8, 153.7, 162.5, 163.8, 164.5. HRMS (ESI) $m/z$ calculated for $C_{28}H_{30}NO_4$ $(M+H)^+$: 444.2175; found:444.2177.

#### 4.3.77. 4-(Benzo[d]oxazol-2-yl)phenyl 4-(nonyloxy)benzoate (14i)

To a stirred solution of 4-nonyloxybenzoic acid (0.124 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **13** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.187 g, 87.0%, white solid, m.p: 84–86 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.89 (t, $J$ = 6.6 Hz, 3H), 1.26–1.39 (m, 10*H*), 1.46–1.48 (m, 2H), 1.83 (quintet, $J$ = 6.6 Hz, 2H), 4.05 (t, $J$ = 6.6 Hz, 2H), 6.97–7.02 (m, 2ArH), 7.33–7.41 (m, 4ArH), 7.54–7.63 (m, 1ArH), 7.73–7.81 (m, 1ArH), 8.14–8.22 (m, 2ArH), 8.31–8.35 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.3, 29.4, 29.5, 31.9, 68.4, 110.6, 114.4, 120.0, 121.9, 122.5, 124.7, 125.2, 129.0, 129.4, 132.4, 142.1, 150.8, 153.7, 162.5, 163.8, 164.5. HRMS (ESI) $m/z$ calculated for $C_{29}H_{32}NO_4$ $(M+H)^+$: 458.2331; found: 458.2333.

#### 4.3.78. 4-(Benzo[d]oxazol-2-yl)phenyl 4-(decyloxy)benzoate (14j)

To a stirred solution of 4-decyloxybenzoic acid (0.131 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **13** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.183 g, 82.4%, white solid, m.p: 96–98 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.89 (t, $J$ = 6.9 Hz, 3H), 1.25–1.34 (m, 12H), 1.43–1.49 (m, 2H), 1.83 (quintet, $J$ = 6.9 Hz, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.97–7.02 (m, 2ArH), 7.34–7.42 (m, 4ArH), 7.56–7.63

(m, 1ArH), 7.74–7.82 (m, 1ArH), 8.14–8.19 (m, 2ArH), 8.31–8.36 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.3, 29.4, 29.6, 29.7, 31.9, 68.4, 110.6, 114.4, 120.0, 121.1, 122.5, 124.7, 125.2, 129.0, 132.4, 142.1, 150.8, 153.7, 162.5, 163.8, 164.5. HRMS (ESI) *m/z* calculated for $C_{30}H_{34}NO_4$ $(M+H)^+$: 472.2488; found: 472.2450.

#### *4.3.79. 4-(Benzo[d]oxazol-2-yl)phenyl 4-(allyloxy)benzoate (**14k**)*

To a stirred solution of 4-allyloxybenzoic acid (0.084 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **13** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.152 g, 87.4%, white solid, m.p: 128–130 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.65 (dt, $J$ = 1.5, 5.4 Hz, 2H), 5.33–5.37 (m, 1H), 5.42–5.50 (m, 1H), 6.04–6.13 (m,1H), 7.01–7.05 (m, 2ArH), 7.36–7.42 (m, 4ArH), 7.59–7.62 (m, 1ArH), 7.77–7.80 (m, 1ArH), 8.15–8.20 (m, 2ArH), 8.31–8.36 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 69.0, 110.6, 114.7, 118.3, 120.0, 121.5, 122.5, 124.6, 124.7, 125.2, 129.0, 132.4, 142.1, 150.8, 153.7, 162.4, 163.1, 164.4. HRMS (ESI) *m/z* calculated for $C_{23}H_{18}NO_4$ $(M+H)^+$: 372.1236; found: 372.1239.

#### *4.3.80. 4-(Benzo[d]oxazol-2-yl)phenyl 4-((3-methylbut-2-en-1-yl)oxy) benzoate (**14l**)*

To a stirred solution of 4-prenyloxybenzoic acid (0.097 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **13** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.148 g, 78.7%, pale yellow solid, m.p: 148–150 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.78 (s, 3H), 1.83 (s, 3H), 4.62 (d, $J$ = 6.6 Hz, 2H), 5.49–5.54 (m, 1H), 6.99–7.03 (m, 2ArH), 7.34–7.41 9 (m, 4ArH), 7.57–7.63 (m, 1ArH), 7.76–7.81 (m, 1ArH), 8.14–8.19 (m, 2ArH), 8.31–8.35 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 18.3, 25.9, 65.1, 110.6, 114.6, 118.9, 120.0, 121.2, 122.5, 124.7, 125.2, 129.0, 132.4, 139.1, 142.1, 150.8, 153.7, 162.4, 163.5, 164.5. HRMS (ESI) *m/z* calculated for $C_{25}H_{22}NO_4$ $(M+H)^+$: 400.1549; found: 400.1550.

#### *4.3.81. 4-(Benzo[d]oxazol-2-yl)phenyl (E)-4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)benzoate (**14m**)*

To a stirred solution of 4-geranyloxybenzoic acid (0.129 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **13** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.165 g, 75.0%, pale yellow solid, m.p: 110–112 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.62 (s, 3H), 1.69 (s, 3H), 1.77 (s, 3H), 2.12–2.14 (m, 4H), 4.65 (d, $J$ = 6.3 Hz, 2H), 5.10 (t, $J$ = 1.5 Hz, 1H), 5.50 (t, $J$ = 1.2 Hz, 1H), 6.99–7.03 (m, 2ArH), 7.34–7.42 (m, 4ArH), 7.57–7.63 (m, 1ArH), 7.75–7.81 (m, 1ArH), 8.15–8.19 (m, 2ArH), 8.31–8.36 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 16.8, 17.7, 25.7, 26.3, 39.5, 65.2, 110.6, 114.7, 118.7, 120.0, 121.2, 122.5, 123.7, 124.7, 125.2, 129.0, 132.0, 132.4, 142.1, 142.1, 150.8, 153.7, 162.5, 163.5, 164.5. HRMS (ESI) *m/z* calculated for $C_{30}H_{30}NO_4$ $(M+H)^+$: 468.2175; found: 468.2178.

#### *4.3.82. 4-(Benzo[d]oxazol-2-yl)phenyl 4-(((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)benzoate (**14n**)*

To a stirred solution of 4-farnesyloxybenzoic acid (0.161 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **13** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.205 g, 81.3%, pale yellow solid, m.p: 60–62 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.62 (s, 6H), 1.68 (s, 3H), 1.77 (s, 3H), 1.98–2.18 (m, 8H), 4.65 (d, $J$ = 6.6 Hz, 2H), 5.07–5.09 (m, 2H), 5.51 (t, $J$ = 6.6 Hz, 1H), 6.99–7.02 (m, 2ArH), 7.34–7.41 (m, 4ArH), 7.57–7.63 (m, 1ArH), 7.76–7.81 (m, 1ArH), 8.16 (t, $J$ = 8.7 Hz, 2ArH), 8.31–8.36 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 16.1, 16.8, 17.7, 23.4, 26.1, 26.2, 32.0, 39.5, 39.7, 65.2, 110.6, 114.6, 118.7, 120.0, 121.2, 122.5, 123.6, 124.3, 124.3, 124.7, 125.2, 129.0, 131.4, 132.4, 135.6, 142.1, 150.8, 153.7, 162.5, 163.5, 164.5. HRMS (ESI) *m/z* calculated for $C_{35}H_{38}NO_4$ $(M+H)^+$: 536.2801; found: 536.2805.

#### *4.3.83. 3-(Benzo[d]oxazol-2-yl)phenyl 4-methoxybenzoate (**18a**)*

To a stirred solution of 4-methoxybenzoic acid (0.072 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **17** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.124 g, 76.5%, white solid, m.p: 138–140 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.92 (s, 3H), 6.99–7.04 (m, 2ArH), 7.34–7.38 (m, 2ArH), 7.39–7.43 (m, 1ArH), 7.57–7.62 (m, 2ArH), 7.77–7.80 (m, 1ArH), 8.13 (t, $J$ = 1.8 Hz, 1ArH), 8.16–8.20 (m, 3ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 55.6, 110.7, 114.0, 120.2, 121.2, 121.5, 124.7, 124.9, 125.1, 125.4, 128.6, 130.1, 132.4, 142.0, 150.8, 151.5, 162.2, 164.1, 164.7. HRMS (ESI) *m/z* calculated for $C_{21}H_{16}NO_4$ $(M+H)^+$: 346.1079; found: 346.1082.

#### *4.3.84. 3-(Benzo[d]oxazol-2-yl)phenyl 4-ethoxybenzoate (**18b**)*

To a stirred solution of 4-ethoxybenzoic acid (0.079 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **17** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.118 g, 69.8%, white solid, m.p: 80–82 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.48 (t, $J$ = 6.9 Hz, 3H), 4.14 (q, $J$ = 6.9 Hz, 2H), 6.98–7.02 (m, 2 ArH), 7.34–7.43 (m, 2 ArH), 7.48–7.58 (m, 2 ArH), 7.92 (d, $J$ = 8.1 Hz, 1 ArH), 7.96–7.99 (m, 2 ArH), 8.07 (d, $J$ = 8.1 Hz, 1 ArH), 8.06–8.20 (m, 2 ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.7, 63.9, 114.4, 120.9, 121.3, 121.7, 123.4, 124.5, 124.9, 125.4, 126.4, 130.0, 132.4, 135.1, 151.6, 154.0, 163.5, 164.7, 166.9. HRMS (ESI) *m/z* calculated for $C_{22}H_{18}NO_4$ $(M+H)^+$: 360.1236; found: 360.1237.

#### *4.3.85. 3-(Benzo[d]oxazol-2-yl)phenyl 4-propoxybenzoate compound (**18c**)*

To a stirred solution of 4-propoxybenzoic acid (0.085 g, 0.47 mmol)

in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **17** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.139 g, 79.0%, white solid, m.p: 116–118 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.08 (t, $J$ = 7.5 Hz, 3H), 1.83 (sextet, $J$ = 7.2 Hz, 2H), 4.03 (t, $J$ = 6.6 Hz, 2H), 6.98–7.03 (m, 2ArH), 7.34–7.38 (m, 2ArH), 7.39–7.43 (m, 1ArH), 7.57–7.59 (m, 1ArH), 7.60–7.62 (m, 1ArH), 7.75–7.81 (m, 1ArH), 8.13 (t, $J$ = 1.8 Hz, 1ArH), 8.15–8.20 (m, 3ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 10.5, 22.5, 69.8, 110.7, 114.4, 120.2, 121.2, 124.7, 124.9, 125.1, 125.4, 128.6, 130.1, 132.4, 142.0, 150.8, 151.5, 162.2, 163.7, 164.7.HRMS (ESI) *m/z* calculated for $C_{23}H_{20}NO_4$ $(M+H)^+$: 374.1392; found: 374.1393.

#### *4.3.86. 3-(Benzo[d]oxazol-2-yl)phenyl 4-butoxybenzoate compound **(18d)***

To a stirred solution of 4-butoxybenzoic acid (0.091 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **17** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.134 g, 73.6%, white solid, m.p: 102–104 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.98 (t, $J$ = 6.9 Hz, 3H), 1.47–1.57 (m, 2H), 1.78–1.87 (m, 2H), 4.07 (t, $J$ = 6.6 Hz, 2H), 6.97–7.02 (m, 2ArH), 7.34–7.38 (m, 2ArH), 7.39–7.43 (m, 1ArH), 7.57–7.62 (m, 2ArH), 7.75–7.81 (m, 1ArH), 8.12 (t, $J$ = 1.8 Hz, 1ArH), 8.15–8.20 (m, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 13.8, 19.2, 31.2, 68.1, 110.7, 114.4, 120.2, 121.2, 124.7, 124.9, 125.1, 125.4, 128.6, 130.1, 132.4, 142.0, 150.8, 151.5, 162.2, 163.7, 164.7.HRMS (ESI) *m/z* calculated for $C_{24}H_{22}NO_4$ $(M+H)^+$: 388.1549; found: 388.1551.

#### *4.3.87. 3-(Benzo[d]oxazol-2-yl)phenyl 4-(pentyloxy)benzoate compound **(18e)***

To a stirred solution of 4-pentoxybenzoic acid (0.098 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **17** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.145 g, 76.7%, white solid, m.p: 95–97 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.96 (t, $J$ = 6.9 Hz, 3H), 1.43–1.48 (m, 4H), 1.85 (quintet, $J$ = 6.9 Hz, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.97–7.01 (m, 2ArH), 7.34–7.43 (m, 3ArH), 7.56–7.62 (m, 2ArH), 7.75–7.81 (m, 1ArH), 8.12 (t, $J$ = 1.8 Hz, 1ArH), 8.16–8.19 (m, 3ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.0, 22.5, 28.2, 28.8, 68.4, 110.7, 114.4, 120.2, 121.2, 124.7, 124.9, 125.1, 125.4, 128.6, 130.1, 132.4, 142.0, 150.8, 151.5, 162.2, 163.7, 164.7. HRMS (ESI) *m/z* calculated for $C_{25}H_{24}NO_4$ $(M+H)^+$: 402.1705; found: 402.1708.

#### *4.3.88. 3-(Benzo[d]oxazol-2-yl)phenyl 4-(hexyloxy)benzoate **(18f)***

To a stirred solution of 4-hexyloxybenzoic acid (0.104 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **17** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.158 g, 81.0%, white solid, m.p: 106–108 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.93 (t, $J$ = 7.2 Hz, 3H), 1.37 (sextet, $J$ = 3.6 Hz, 4H), 1.45–1.54 (m, 2H), 1.84 (pentet, $J$ = 6.6 Hz, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.97–7.02 (m, 2ArH), 7.34–7.38 (m, 2ArH), 7.39–7.42 (m, 1ArH), 7.56–7.62 (m, 2ArH), 7.75–7.81 (m, 1ArH), 8.12 (t, $J$ = 1.8 Hz, 1ArH), 8.15–8.19 (m, 3ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.0, 22.6, 25.7, 29.1, 31.6, 68.4, 110.7, 114.4, 120.2, 121.2, 124.7, 124.9, 125.1, 125.4, 128.6, 130.1, 132.4, 142.0, 150.8, 151.5, 162.2, 163.7, 164.7. HRMS (ESI) *m/z* calculated for $C_{26}H_{26}NO_4$ $(M+H)^+$: 416.1862; found: 416.1865.

#### *4.3.89. 3-(Benzo[d]oxazol-2-yl)phenyl 4-(heptyloxy)benzoate compound **(18g)***

To a stirred solution of 4-heptyloxybenzoic acid (0.111 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **17** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.162 g, 80.1%, appearance, m.p: 90–92 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.91 (t, $J$ = 6.6 Hz, 3H), 1.33–1.41 (m, 6H), 1.46–1.49 (m, 2H), 1.81 (pentet, $J$ = 6.6 Hz, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.97–7.01 (m, 2ArH), 7.34–7.43 (m, 3ArH), 7.56–7.62 (m, 2ArH), 7.75–7.81 (m, 1ArH), 8.12 (t, $J$ = 1.5 Hz, 1ArH), 8.15–8.21 (m, 3ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.6, 26.0, 29.0, 29.1, 31.8, 68.4, 110.7, 114.4, 120.2, 121.2, 124.7, 124.9, 125.1, 125.4, 128.6, 130.1, 132.4, 142.0, 150.8, 151.5, 162.2, 163.7, 164.7. HRMS (ESI) *m/z* calculated for $C_{27}H_{28}NO_4$ $(M+H)^+$: 430.2018; found: 430.2021.

#### *4.3.90. 3-(Benzo[d]oxazol-2-yl)phenyl 4-(octyloxy)benzoate **(18h)***

To a stirred solution of 4-octyloxybenzoic acid (0.118 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **17** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.157 g, 75.5%, white solid, m.p: 78–80 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.90 (t, $J$ = 6.9 Hz, 3H), 1.31–1.35 (m, 8H), 1.46–1.49 (m, 2H), 1.82 (pentet, $J$ = 6.9 Hz, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.98–7.01 (m, 2ArH), 7.34–7.43 (m, 3ArH), 7.56–7.62 (m, 2ArH), 7.75–7.81 (m, 1ArH), 8.12 (t, $J$ = 1.5 Hz, 1ArH), 8.15–8.18 (m, 3ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.2, 29.3, 31.8, 68.4, 110.7, 114.4, 120.2, 121.2, 124.9, 125.1, 125.4, 128.6, 130.1, 132.4, 142.0, 150.8, 151.3, 162.2, 163.7, 164.7. HRMS (ESI) *m/z* calculated for $C_{28}H_{30}NO_4$ $(M+H)^+$: 444.2175; found: 444.2175.

#### *4.3.91. 3-(Benzo[d]oxazol-2-yl)phenyl 4-(nonyloxy)benzoate **(18i)***

To a stirred solution of 4-nonyloxybenzoic acid (0.124 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **17** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer

was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.174 g, 80.9%, white solid, m.p: 84–86 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.90 (t, $J$ = 6.9 Hz, 3H), 1.30–1.34 (m, 10*H*), 1.46–1.49 (m, 2H), 1.83 (pentet, $J$ = 6.9 Hz, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.97–7.00 (m, 2ArH), 7.34–7.43 (m, 3ArH), 7.56–7.62 (m, 2ArH), 7.75–7.81 (m, 1ArH), 8.12 (t, $J$ = 2.1 Hz, 1ArH), 8.16–8.18 (m, 3ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.3, 29.4, 29.5, 31.9, 68.4, 110.7, 114.4, 120.2, 121.2, 124.7, 125.1, 128.6, 130.1, 132.4, 142.0, 150.8, 151.5, 162.2, 163.7, 164.7. HRMS (ESI) *m/z* calculated for $C_{29}H_{32}NO_4$ $(M+H)^+$: 458.2331; found: 458.2335.

#### *4.3.92. 3-(Benzo[d]oxazol-2-yl)phenyl 4-(decyloxy)benzoate compound **(18j)***

To a stirred solution of 4-decyloxybenzoic acid (0.131 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **17** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.185 g, 83.7%, white solid, m.p: 76–78 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.89 (t, $J$ = 6.9 Hz, 3H), 1.29–1.34 (m, 12H), 1.44–1.49 (m, 2H), 1.84 (pentet, $J$ = 6.6 Hz, 2H), 4.06 (t, $J$ = 6.3 Hz, 2H), 6.98–7.00 (m, 2ArH), 7.34–7.42 (m, 3ArH), 7.56–7.62 (m, 2ArH), 7.75–7.80 (m, 1ArH), 8.12 (t, $J$ = 1.8 Hz, 1ArH), 8.16–8.18 (m, 3ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.3, 29.4, 29.6, 68.4, 110.7, 114.4, 120.2, 121.2, 124.9,125.1, 125.4, 128.6, 130.1, 132.4, 142.0, 150.8, 151.5, 162.2, 163.7, 164.7. HRMS (ESI) *m/z* calculated for $C_{30}H_{34}NO_4$ $(M+H)^+$: 472.2488; found: 472.2491.

#### *4.3.93. 3-(Benzo[d]oxazol-2-yl)phenyl 4-(allyloxy)benzoate compound **(18k)***

To a stirred solution of 4-allyloxybenzoic acid (0.084 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **17** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.128 g, 73.6%, white solid, m.p: 120–122 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.65 (dt, $J$ = 1.5, 5.4 Hz, 2H), 5.35 (dd, $J$ = 1.2, 10.5 Hz, 1H), 5.46 (dd, $J$ = 1.5, 17.4 Hz, 1H), 6.02–6.15 (m, 1H), 7.00–7.05 (m, 2ArH), 7.34–7.43 (m, 3ArH), 7.56–7.62 (m, 2ArH), 7.75–7.81 (m, 1ArH), 8.12 (t, $J$ = 1.8 Hz, 1ArH), 8.16–8.20 (m, 3ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 69.0, 110.7, 114.7, 118.3, 120.2, 121.1, 121.6, 124.7, 124.9, 125.1, 125.4, 128.6, 130.1, 132.4, 132.4, 142.0, 150.8, 151.5, 162.2, 163.1, 164.6. HRMS (ESI) *m/z* calculated for $C_{23}H_{18}NO_4$ $(M+H)^+$: 372.1236; found: 372.1238.

#### *4.3.94. 3-(Benzo[d]oxazol-2-yl)phenyl 4-((3-methylbut-2-en-1-yl)oxy) benzoate **(18l)***

To a stirred solution of 4-prenyloxybenzoic acid (0.097 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **17** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.132 g, 70.6%, pale yellow solid, m.p: 118–120 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.79 (s, 3H), 1.83 (s, 3H), 4.62 (d, $J$ = 6.9 Hz, 2H), 5.49–5.55 (m, 1H), 6.99–7.04 (m, 2ArH), 7.34–7.38 (m,2H), 7.39–7.43 (m, 1ArH), 7.57–7.62 (m, 2ArH), 7.75–7.81 (m, 1ArH), 8.12 (t, $J$ = 1.8 Hz, 1ArH), 8.15–8.17 (m, 3ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 18.3, 25.9, 65.1, 110.7, 114.6, 118.9, 120.2, 121.2, 121.3, 124.7, 124.9, 125.1, 125.4, 128.6, 130.1, 132.4, 139.1, 142.0, 150.8, 151.5, 162.2, 163.4, 164.7. HRMS (ESI) *m/z* calculated for $C_{25}H_{22}NO_4$ $(M+H)^+$: 400.1549; found: 400.1553.

#### *4.3.95. 3-(Benzo[d]oxazol-2-yl)phenyl (E)-4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)benzoate **(18m)***

To a stirred solution of 4-geranyloxybenzoic acid (0.129 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **17** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.168 g, 76.7%, pale yellow solid, m.p: 90–92 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.62 (s, 3H), 1.69 (s, 3H), 1.78 (s, 3H), 2.09–2.20 (m, 4H), 4.65 (d, $J$ = 6.6 Hz, 2H), 5.09–5.11 (m, 1H), 5.51 (t, $J$ = 6.6 Hz, 1H), 6.70–7.03 (m, 2ArH), 7.36–7.38 (m, 2H), 7.39–7.43 (m, 1ArH), 7.57–7.62 (m, 2ArH), 7.77–7.80 (m, 1ArH), 8.12 (t, $J$ = 1.8 Hz, 1ArH), 8.15–8.19 (m, 3ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 16.8, 17.7, 25.7, 26.3, 39.6, 65.2, 110.7, 114.6, 118.7, 120.2, 121.2, 121.3, 123.7, 124.7, 124.9, 125.1, 125.4, 128.6, 130.1, 132.0, 132.4, 142.0, 142.1, 150.8, 151.5, 162.2, 163.5, 164.7. HRMS (ESI) *m/z* calculated for $C_{30}H_{30}NO_4$ $(M+H)^+$: 468.2175; found: 468.2176.

#### *4.3.96. 3-(Benzo[d]oxazol-2-yl)phenyl 4-(((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)benzoate **(18n)***

To a stirred solution of 4-farnesyloxybenzoic acid (0.161 g, 0.47 mmol) in THF, DMAP (0.005 g, 0.047 mmol) and EDC.HCl (0.118 g, 0.62 mmol) were added and stirred at room temperature for 15 min. Then **17** (0.1 g, 0.47 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. Dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.189 g, 75.3%, pale yellow solid, m.p: 52–54 °C, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.61–1.62 (m, 6H), 1.69 (s, 3H), 1.78 (s, 3H), 1.96–2.18 (m, 8H), 4.65 (d, $J$ = 6.3 Hz, 2H), 5.08–5.12 (m, 2H), 5.51 (t, $J$ = 6.3 Hz, 1H), 7.01 (dd, $J$ = 2.4, 9.0 Hz, 2ArH), 7.34–7.43 (m, 3ArH), 7.56–7.62 (m, 2ArH), 7.75–7.81 (m, 1ArH), 8.12 (t, $J$ = 1.8 Hz, 1ArH), 8.16–8.19 (m, 3ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 16.1, 16.8, 23.4, 26.1, 26.2, 32.0, 39.6, 39.7, 65.2, 110.7, 114.6, 118.8, 120.2, 121.2, 121.3, 123.6, 124.3, 124.4, 124.7, 124.9, 125.1, 125.4, 128.6, 130.1, 131.4, 131.6, 132.4, 135.6, 142.0, 150.8, 151.5, 162.2, 163.5, 164.7. HRMS (ESI) *m/z* calculated for $C_{35}H_{38}NO_4$ $(M+H)^+$: 536.2801; found: 536.2803.

#### *4.3.97. 2-(4-Methoxyphenyl)benzo[d]thiazole **(21)***

2-Aminothiophenol (4 g, 31.95 mmol), *p*-anisaldehyde (4.35 g, 31.95 mmol) were mixed thoroughly in a mortar with pestle for 5 min. Then ceric ammonium nitrate (0.088 g, 0.16 mmol) was added and ground well. To that 30% Hydrogen peroxide (3 mL) was added and further ground for 10 min. Reaction mass dissolved with ethyl acetate and washed thoroughly with water. Then washed with brine solution and dried over Sodium sulfate. It was then purified by column chromatography using ethyl acetate in hexanes (8%) to afford the product **21** (5.30 g, 89.2%) as pale yellow solid, m.p: 104–106 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.89 (s, 3H), 7.01 (dd, $J$ = 2.0, 4.8 Hz, 2ArH),

7.35–7.45 (m, 1ArH), 7.47 (t, $J$ = 7.2 Hz, 1ArH), 7.88 (d, $J$ = 7.6 Hz, 1ArH), 8.02–8.06 (m, 3ArH). HRMS ($ESI^+$): $m/z$ calculated for $C_{14}H_{12}NOS$ $[M+H]^+$: 242.0640; found: 242.0642.

*4.3.98. 4-(Benzo[d]thiazol-2-yl)phenol (**22**)*

Compound **21** (4 g, 16.6 mmol) was suspended in hydrobromic acid (33% in acetic acid) and maintained at 80 °C for 12 h. After completion of reaction the mass was poured into water and was filtered. The solid thus obtained was dissolved in ethyl acetate and washed with 10% sodium carbonate solution. The organic layer was washed with water and then with brine solution. It was then dried over sodium sulfate, concentrated and purified by column chromatography (silica gel 100–200 mesh) using ethyl acetate in hexanes (25%) to afford compound **22** (2.8 g, 74.3%) as off white solid, 200–202 °C. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 6.94–6.97 (m, 2 ArH), 7.31–7.45 (m, 1ArH), 7.44–7.45 (m, 1ArH), 7.86 (dd, $J$ = 2.4, 5.6 Hz, 1ArH), 7.92–7.96 (m, 2ArH), 8.00 (dd, $J$ = 2.4, 5.6 Hz, 1ArH), 9.32 (s, 1O-H). HRMS ($ESI^+$): $m/z$ calculated for $C_{13}H_{10}NOS$ $[M+H]^+$: 228.0483; found: 228.0487.

*4.3.99. 3-(Benzo[d]thiazol-2-yl)phenyl 4-methoxybenzoate (**19a**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **7a** (0.103 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.114 g, 79.2%, white solid, m.p: 116–118 °C. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 3.91 (s, 3H), 6.99–7.03 (m, 2ArH), 7.35–7.38 (m, 1ArH), 7.40–7.43 (m, 1ArH), 7.48–7.51 (m, 1ArH), 7.53–7.58 (m, 1ArH), 7.90–7.93 (m, 1ArH), 7.96–7.99 (m, 2ArH), 8.08 (td, $J$ = 0.6, 6.9 Hz, 1ArH), 8.16–8.21 (m, 2ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 55.6, 113.9, 120.9, 121.5, 121.7, 123.4, 124.5, 124.9, 125.4, 126.4, 130.1, 132.4, 135.1, 135.1, 151.6, 154.0, 164.1, 164.7, 166.9. HRMS (ESI) $m/z$ calculated for $C_{21}H_{16}NO_3S$ $(M+H)^+$: 362.0851; found: 362.0853.

*4.3.100. 3-(Benzo[d]thiazol-2-yl)phenyl 4-ethoxybenzoate (**19b**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **7b** (0.108 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.124 g, 82.7%, white solid, m.p: 124–126 °C. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.48 (t, $J$ = 6.9 Hz, 3H), 4.14 (q, $J$ = 6.9 Hz, 2H), 6.97–7.02 (m, 2ArH), 7.34–7.38 (m, 1ArH), 7.40–7.43 (m, 1ArH), 7.48–7.52 (m, 1ArH), 7.53–7.58 (m, 1ArH), 7.92 (dd, $J$ = 0.6, 8.1 Hz, 1ArH), 7.96–7.99 (m, 2ArH), 8.07 (d, $J$ = 8.1 Hz, 1ArH), 8.15–8.20 (m, 2ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 14.7, 63.9, 114.4, 120.9, 121.3, 121.7, 123.4, 124.5, 124.9, 125.4, 126.4, 130.1, 132.4, 135.1, 135.1, 151.6, 154.0, 151.6, 154.0, 163.5, 164.7, 166.9HRMS (ESI) $m/z$ calculated for $C_{22}H_{18}NO_3S$ $(M+H)^+$: 376.1007; found: 376.1009.

*4.3.101. 3-(Benzo[d]thiazol-2-yl)phenyl 4-propoxybenzoate (**19c**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **7c** (0.114 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.12 g, 76.9%, white solid, m.p: 108–110 °C. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.08 (t, $J$ = 7.5 Hz, 3H), 1.87 (sextet, $J$ = 7.2 Hz, 2H), 4.03 (t, $J$ = 6.6 Hz, 2H), 6.98–7.01 (m, 2ArH), 7.35–7.38 (m, 1ArH), 7.40–7.43 (m, 1ArH), 7.48–7.51 (m, 1ArH), 7.53–7.58 (m, 1ArH), 7.92 (dq, $J$ = 0.9,6.0 Hz, 1ArH) 7.96 (t, $J$ = 0.9 Hz, 1ArH) 7.98–7.99 (m,1ArH) 8.08 (dq, $J$ = 0.6,6.6 Hz, 1ArH) 8.16–8.19 (m, 2ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 10.5, 22.5, 69.8, 114.4, 120.9, 121.2, 121.7, 123.4, 124.5, 124.9, 125.4, 126.4, 130.1, 132.4, 135.1, 135.1, 151.6, 154.1, 163.7, 164.8, 166.9. HRMS (ESI) $m/z$ calculated for $C_{23}H_{20}NO_3S$ $(M+H)^+$: 390.1164; found: 390.1165.

*4.3.102. 3-(Benzo[d]thiazol-2-yl)phenyl 4-butoxybenzoate (**19d**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **7d** (0.119 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.138 g, 85.7%, pale yellow solid, m.p: 106–108 °C. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.01 (t, $J$ = 7.5 Hz, 3H) 1.47–1.57 (m, 2H), 1.78–1.87 (m, 2H), 4.07 (t, $J$ = 6.6 Hz, 2H), 6.97–7.02 (m, 2ArH), 7.35–7.38 (m, 1ArH), 7.40–7.43 (m, 1ArH), 7.48–7.52 (m, 1ArH), 7.53–7.58 (m, 1ArH), 7.91–7.93 (m, 1ArH), 7.96–7.99 (m, 2ArH), 8.06–8.09 (m, 1ArH) 8.15–8.20 (m,2ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 13.8, 19.2, 31.2, 68.1, 114.4, 120.9, 121.2, 121.7, 123.4, 124.5, 124.9, 125.4, 126.4, 130.0, 132.4, 135.1, 135.1, 151.6, 154.1, 163.7, 164.8, 166.9. HRMS (ESI) $m/z$ calculated for $C_{24}H_{22}NO_3S$ $(M+H)^+$: 404.1320; found: 404.1323.

*4.3.103. 3-(Benzo[d]thiazol-2-yl)phenyl 4-(pentyloxy)benzoate (**19e**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **7e** (0.125 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.133 g, 79.6%, pale yellow solid, m.p: 112–114 °C. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 0.96 (t, $J$ = 6.9 Hz, 3H), 1.42–1.46 (m, 4H), 1.82–1.84 (m, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.98–7.02 (m, 2ArH), 7.34–7.43 (m, 2ArH), 7.48–7.58 (m, 2ArH), 7.90–7.93 (m, 1ArH), 7.96–7.99 (m, 2ArH), 8.06–8.09 (m, 1ArH), 8.15–8.19 (m, 2ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 14.0, 22.5, 28.2, 28.8, 68.4, 114.4, 120.9, 121.2, 121.7, 123.4, 124.5, 124.9, 125.4, 126.4, 130.0, 132.4, 135.1, 135.1, 151.6, 154.0, 163.7, 164.8, 166.9, HRMS (ESI) $m/z$ calculated for $C_{25}H_{24}NO_3S$ $(M+H)^+$: 418.1477; found: 418.1477.

*4.3.104. 3-(Benzo[d]thiazol-2-yl)phenyl 4-(hexyloxy)benzoate (**19f**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **7f** (0.130 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 10% ethyl acetate in hexanes. Yield: 0.142 g, 82.1%, pale yellow solid, m.p: 96–98 °C. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 0.93 (t, $J$ = 6.9 Hz,3H), 1.35–1.38 (m, 4H), 1.49–1.59 (m, 2H), 1.84 (quintet, $J$ = 6.9 HZ, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.98–7.02 (m, 2ArH), 7.35–7.43 (m, 2ArH), 7.48–7.52 (m, 1ArH), 7.53–7.58 (m, 1ArH), 7.92 (d, $J$ = 7.2 Hz, 1ArH), 7.96–7.99 (m, 2ArH), 8.07 (t, $J$ = 7.8 Hz, 1ArH), 8.15–8.19 (m, 2ArH). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.6, 25.7, 29.1, 31.6, 68.4, 114.4, 120.9, 121.2, 121.7, 123.4, 124.5, 124.9, 125.4, 126.4, 130.0, 132.4, 135.1, 151.6, 154.1, 163.7,

164.8, 166.9. HRMS (ESI) *m/z* calculated for $C_{26}H_{26}NO_3S$ $(M+H)^+$: 432.1633; found: 432.1637.

*4.3.105. 3-(Benzo[d]thiazol-2-yl)phenyl 4-(heptyloxy)benzoate (**19g**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **7g** (0.136 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 10% ethyl acetate in hexanes. Yield: 0.145 g, 81.5%, white solid, m.p: 130–132 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.91 (t, $J$ = 6.9 Hz, 3H), 1.33–1.37 (m, 6H), 1.40–1.58 (m, 2H), 1.81–1.86 (m, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.97–7.00 (m, 2ArH), 7.35–7.43 (m, 3ArH), 7.51 (dt, $J$ = 1.2, 8.1 Hz, 1ArH), 7.91–7.93 (m, 1ArH), 8.07–8.09 (m, 1ArH), 8.15–8.18 (m, 4ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.6, 26.0, 29.0, 29.1, 31.8, 68.4, 114.4, 121.2, 121.7, 122.5, 123.2, 125.2, 126.4, 128.8, 131.2, 132.4, 135.2, 153.3, 154.2, 163.8, 164.6, 167.1. HRMS (ESI) *m/z* calculated for $C_{27}H_{28}NO_3S$ $(M+H)^+$: 446.1790; found: 446.1793.

*4.3.106. 3-(Benzo[d]thiazol-2-yl)phenyl 4-(octyloxy)benzoate (**19h**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **7h** (0.142 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 10% ethyl acetate in hexanes. Yield: 0.136 g, 74.3%, white solid, m.p: 88–90 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.90 (t, $J$ = 6.9 Hz, 3H), 1.29–1.35 (m, 8H), 1.43–1.60 (m, 2H), 1.83 (quintet, $J$ = 6.9 Hz, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.97–7.02 (m, 2ArH), 7.34–7.38 (m, 1ArH), 7.40–7.43 (m, 1ArH), 7.48–7.52 (m, 1ArH), 7.53–7.58 (m, 1ArH), 7.92 (dd, $J$ = 0.6, 7.8 Hz, 1ArH), 7.96–7.99 (m, 2ArH), 8.07 (dd, $J$ = 0.6, 7.8 Hz, 1ArH), 8.15–8.19 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.3, 29.4, 31.8, 68.4, 114.4, 120.9, 121.2, 121.7, 123.4, 124.5, 124.9, 125.4, 126.4, 130.0, 132.4, 135.1, 135.1, 151.6, 154.1, 163.7, 164.8, 166.9. HRMS (ESI) *m/z* calculated for $C_{28}H_{30}NO_3S$ $(M+H)^+$: 460.1946; found: 460.1947.

*4.3.107. 3-(Benzo[d]thiazol-2-yl)phenyl 4-(nonyloxy)benzoate (**19i**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **7i** (0.147 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 10% ethyl acetate in hexanes. Yield: 0.154 g, 81.5%, white solid, m.p: 72–74 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.89 (t, $J$ = 6.9 Hz, 3H), 1.25–1.33 (m, 10*H*), 1.44–1.51 (m, 2H), 1.79–1.86 (m, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.98–7.00 (m, 2ArH), 7.34–7.43 (m, 2ArH), 7.48–7.58 (m, 2ArH), 7.90–7.93 (m, 1ArH), 7.96–7.98 (m, 2ArH), 8.06–8.09 (m, 1ArH), 8.15–819 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.3, 29.4, 29.5, 31.9, 68.4, 114.4, 120.9, 121.2, 121.7, 123.4, 124.5 124.9, 125.4, 126.4, 130.0, 132.4, 135.1, 135.1, 151.6, 154.1, 163.7, 164.8, 166.9. HRMS (ESI) *m/z* calculated for $C_{29}H_{32}NO_3S$ $(M+H)^+$: 474.2103; found: 474.2104.

*4.3.108. 3-(Benzo[d]thiazol-2-yl)phenyl 4-(decyloxy)benzoate (**19j**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **7j** (0.153 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 10% ethyl acetate in hexanes. Yield: 0.142 g, 72.8%, white solid, m.p: 92–94 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.89 (t, $J$ = 6.9 Hz, 3H), 1.25–1.33 (m, 14H), 1.81–1.83 (m, 2H), 4.06 (t, $J$ = 6.3 Hz, 2H), 6.98–7.02 (m, 2ArH), 7.34–7.38 (m, 1ArH), 7.40–7.43 (m, 1ArH), 7.48–7.51 (m, 1ArH), 7.53–7.58 (m, 1ArH), 7.90–7.93 (m, 1ArH), 7.97–7.99 (m, 2ArH), 8.07–8.09 (m, 1ArH), 8.16–8.19 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.3, 29.4, 29.6, 31.9, 68.4, 114.4, 120.9, 121.2, 121.7, 123.4, 124.5, 124.9, 125.4, 126.4, 130.0, 132.4, 135.1, 135.2, 151.6, 154.0, 163.7, 164.8, 166.9. HRMS (ESI) *m/z* calculated for $C_{30}H_{34}NO_3S$ $(M+H)^+$: 488.2259; found: 488.2260.

*4.3.109. 3-(Benzo[d]thiazol-2-yl)phenyl 4-(allyloxy)benzoate (**19k**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **7k** (0.113 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.127 g, 81.9%, white solid, m.p: 122–124 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.65 (td, $J$ = 1.5, 2.4 Hz, 2H), 5.35 (dd, $J$ = 1.5, 9.3 Hz, 1H), 5.46 (dd, $J$ = 1.5, 15.6 Hz, 1H), 6.04–6.14 (m, 1H), 7.00–7.05 (m, 2ArH), 7.34–7.43 (m, 2ArH), 7.48–7.58 (m, 2ArH), 7.92 (d, $J$ = 7.8 Hz, 1ArH), 7.97–7.99 (m, 2ArH), 8.07 (d, $J$ = 7.8 Hz, 1ArH), 8.16–8.21 (m, 2Ar-H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 69.0, 114.6, 118.3, 120.8, 121.6, 121.7, 123.4, 124.5, 124.9, 125.4, 126.5, 130.1, 132.4, 132.4, 135.1,135.1,151.6, 154.0, 163.1, 164.7, 166.9.HRMS (ESI) *m/z* calculated for $C_{23}H_{18}NO_3S$ $(M+H)^+$: 388.1007; found: 388.1009.

*4.3.110. 3-(Benzo[d]thiazol-2-yl)phenyl 4-((3-methylbut-2-en-1-yl)oxy) benzoate (**19l**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **7l** (0.124 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 10% ethyl acetate in hexanes. Yield: 0.126 g, 75.9%, white solid, m.p: 96–98 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.79 (s, 3H), 1.83 (s, 3H), 4.62 (d, $J$ = 6.9 Hz, 2H), 5.52 (t, $J$ = 6.6 Hz, 1H), 7.01 (d, $J$ = 8.7 Hz, 2ArH), 7.35–7.43 (m, 2ArH), 7.48–7.58 (m, 2ArH), 7.92 (d, $J$ = 7.5 Hz, 1ArH), 7.97–7.99 (m, 2ArH), 8.08 (d, $J$ = 7.8 Hz, 1ArH), 8.18 (d, $J$ = 9.0 Hz, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 18.3, 25.9, 65.1, 114.6, 118.9, 120.9, 121.4, 121.7, 123.4, 124.5, 124.9, 125.4, 126.4, 130.1, 132.4, 135.1, 135.1, 139.1, 151.6, 154.0, 163.4, 164.7, 166.9. HRMS (ESI) *m/z* calculated for $C_{25}H_{22}NO_3S$ $(M+H)^+$: 416.1320; found: 416.1322.

*4.3.111. 3-(Benzo[d]thiazol-2-yl)phenyl (E)-4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)benzoate (**19m**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **7m** (0.151 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 10% ethyl acetate in hexanes. Yield:

0.142 g, 73.6%, off white solid, m.p: 42–44 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.62 (s, 3H), 1.69 (s, 3H), 1.78 (s, 3H), 2.13–2.14 (m, 4H), 4.65 (d, $J$ = 6.3 Hz, 2H), 5.08–5.11 (m, 1H), 5.51 (t, $J$ = 6.6 Hz, 1H), 7.00–7.03 (m, 2ArH), 7.34–7.43 (m, 2ArH), 7.49 (dd, $J$ = 1.2,6.0 Hz, 1ArH), 7.55 (t, $J$ = 6.3 Hz, 1ArH), 7.92 (td, $J$ = 0.6,6.6 Hz, 1ArH), 7.96–7.99 (m, 2ArH), 8.08 (d, $J$ = 7.5 Hz, 1ArH), 8.15–8.20 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 16.8, 17.7, 25.7, 26.3, 39.6, 65.2, 114.6, 118.7, 120.9, 121.3, 121.7, 123.4, 123.7, 124.5, 125.4, 126.4, 130.1, 132.0, 132.4, 135.1, 135.1, 142.1, 151.6, 154.0, 163.4, 164.8, 166.9. HRMS (ESI) *m/z* calculated for $C_{30}H_{30}NO_3S$ $(M+H)^+$: 484.1946; found: 484.1947.

#### *4.3.112. 3-(Benzo[d]thiazol-2-yl)phenyl 4-(((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)benzoate (**19n**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **7n** (0.179 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 10% ethyl acetate in hexanes. Yield: 0.168, 76.4%, pale yellow solid, m.p: 154–156 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.60 (d, $J$ = 4.5 Hz,6H), 1.69 (s, 3H), 1.78 (s, 3H), 1.98–2.18 (m,8H), 4.60–4.66 (m, 2H), 5.10 (t, $J$ = 6.9 Hz, 2H), 5.51 (t, $J$ = 6.6 Hz, 1H), 6.99–7.03 (m, 2ArH), 7.34–7.43 (m, 2ArH), 7.48–7.58 (m, 2ArH), 7.92 (dd, $J$ = 0.6,7.2 Hz, 1ArH), 7.96–7.99 (m, 2ArH), 8.09 (dd, $J$ = 0.6,7.2 Hz, 1ArH), 8.16–8.19 (m, 2ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 16.1, 16.8, 17.7, 25.7, 26.1, 26.7, 39.6, 39.8, 65.2, 114.6, 118.7, 121.3, 121.7, 123.4, 123.6, 124.3, 124.4, 124.5, 124.9, 125.4, 126.5, 130.1, 131.4, 132.4, 135.1, 135.6, 142.1, 151.6, 154.0, 163.4, 164.8, 166.9. HRMS (ESI) *m/z* calculated for $C_{35}H_{38}NO_3S$ $(M+H)^+$: 552.2572; found: 552.2574.

#### *4.3.113. 4-(Benzo[d]thiazol-2-yl)phenyl 4-methoxybenzoate (**20a**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **8a** (0.103 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.121 g, 84.0%, white solid, m.p: 178–180 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.91 (s, 3H), 6.99–7.02 (m, 2ArH), 7.35–7.42 (m, 3ArH), 7.51 (t, $J$ = 8.1 Hz, 1ArH), 7.92 (d, $J$ = 8.1 Hz, 1ArH), 8.08 (d, $J$ = 8.1 Hz, 1ArH), 8.15–8.19 (m, 4ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 54.7, 113.1, 120.9, 121.7, 122.1, 124.4, 125.5, 127.7, 130.1, 131.4, 134.0, 152.2, 153.1, 163.2. 164.3, 167.2 HRMS (ESI) *m/z* calculated for $C_{21}H_{16}NO_3S$ $(M+H)^+$: 362.0851; found: 362.0852.

#### *4.3.114. 4-(Benzo[d]thiazol-2-yl)phenyl 4-ethoxybenzoate (**20b**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **8b** (0.108 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.113 g, 75.3%, white solid, m.p: 168–170 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.47 (t, $J$ = 6.9 Hz, 3H), 4.14 (q, $J$ = 6.9 Hz, 2H), 6.98–7.00 (m, 2ArH), 7.36–7.39 (m, 2ArH), 7.43–7.49 (m, 1ArH), 7.52 (td, $J$ = 1.2, 8.4 Hz, 1ArH), 7.92 (d, $J$ = 7.8 Hz, 1ArH), 8.10 (d, $J$ = 8.1 Hz, 1ArH), 8.14–8.19 (m, 4ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.7, 63.9, 114.4, 121.2, 121.7, 122.5, 123.2, 125.3, 126.4, 128.8, 131.1, 132.4, 135.1, 153.3, 154.1, 163.5, 164.6, 167.1. HRMS (ESI) *m/z* calculated for $C_{22}H_{18}NO_3S$ $(M+H)^+$: 376.1007; found: 376.1008.

#### *4.3.115. 4-(Benzo[d]thiazol-2-yl)phenyl 4-propoxybenzoate (**20c**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **8c** (0.114 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.076 g, 48.7%, white solid, m.p: 92–94 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.07 (t, $J$ = 7.5 Hz, 3H), 1.86 (sextet, $J$ = 7.2 Hz, 2H), 4.02 (t, $J$ = 6.6 Hz, 2H), 6.99 (d, $J$ = 8.7 Hz, 2ArH), 7.35–7.43 (m, 3ArH), 7.51 (td, $J$ = 1.5, 8.4 Hz, 1ArH), 7.92 (d, $J$ = 7.8 Hz, 1ArH), 8.08 (d, $J$ = 7.8 Hz, 1ArH), 8.16 (d, $J$ = 8.7 Hz, 4ArH). $^{13}$C NMR (75 MHz, $CDCl_3$ + DMSO-$d_6$): $\delta$ 10.0, 21.9, 69.3, 113.9, 120.5, 121.2, 122.0, 122.6, 124.8, 125.9, 128.2, 130.5, 131.8, 134.5, 152.7, 153.6, 163.2, 164.0, 166.4. HRMS (ESI) *m/z* calculated for $C_{23}H_{20}NO_3S$ $(M+H)^+$: 390.1164; found: 390.1167.

#### *4.3.116. 4-(Benzo[d]thiazol-2-yl)phenyl 4-butoxybenzoate (**20d**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **8d** (0.119 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.062 g, 38.5%, pale yellow solid, m.p: 170–172 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.00 (t, $J$ = 7.5 Hz, 3H), 1.47–1.57 (m, 2H), 1.84 (quintet, $J$ = 6.9 Hz, 2H), 4.07 (t, $J$ = 6.6 Hz, 2H), 6.97–7.02 (m, 2ArH), 7.34–7.39 (m, 2ArH), 7.40–7.43 (m, 1ArH), 7.48–7.54 9 m, 1ArH), 7.91–7.94 (m, 1ArH), 8.07–8.10 (m, 1ArH), 8.14–8.19 (m, 4ArH). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 13.8, 19.2, 31.1, 68.1, 114.4, 121.1, 121.7, 122.5, 123.2, 125.3, 126.4, 128.8, 131.1, 132.4, 135.1, 153.3, 154.1, 163.8, 164.6, 167.2. HRMS (ESI) *m/z* calculated for $C_{24}H_{22}NO_3S$ $(M+H)^+$: 404.1320; found: 404.1321.

#### *4.3.117. 4-(Benzo[d]thiazol-2-yl)phenyl 4-(pentyloxy)benzoate (**20e**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **8e** (0.125 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.056 g, 33.5%, white solid, m.p: 158–160 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.95 (t, $J$ = 7.2 Hz, 3H), 1.40–1.48 (m, 4H), 1.84 (quintet, $J$ = 6.9 Hz, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.99 (d, $J$ = 9.0 Hz, 2ArH), 7.34–7.3 (m, 2ArH), 7.39–7.43 (m, 1ArH), 7.51 (td, $J$ = 1.2, 7.2 Hz, 1ArH), 7.92 (d, $J$ = 7.2 Hz, 1ArH), 8.08 (d, $J$ = 7.8 Hz, 1ArH), 8.13–8.18 (m, 4ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.0, 22.5, 28.1, 28.8, 68.4, 114.4, 121.2, 121.7, 122.5, 123.2, 125.3, 126.4, 128.8, 131.2, 132.4, 135.2, 153.3, 154.2, 163.8, 164.6, 167.1. HRMS (ESI) *m/z* calculated for $C_{25}H_{24}NO_3S$ $(M+H)^+$: 418.1477; found: 418.1478.

#### *4.3.118. 4-(Benzo[d]thiazol-2-yl)phenyl 4-(hexyloxy)benzoate (**20f**)*

2-Aminothiophenol (0.05 g, 0.40 mmol) and aldehyde **8f** (0.125 g, 0.40 mmol) were crushed in a mortar and pestle for 5 min. To that CAN (0.011 g, 0.02 mmol) and 30% $H_2O_2$ (0.5 mL) were added and crushed for another 5 min. After completion of reaction (TLC), the crude mass was partitioned between ethyl acetate and water (2 times). Combined

organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: white solid, m.p: 144–146 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.92 (t, $J$ = 6.9 Hz, 3H), 1.33–1.39 (m, 4H), 1.47–1.52 (m, 2H), 1.83 (pentet, $J$ = 6.9 Hz, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.97–7.00 (m, 2ArH), 7.34–7.38 (m, 2ArH), 7.40 (dt, $J$ = 0.9, 7.8 Hz, 1ArH), 7.51 (dt, $J$ = 1.2, 7.5 Hz, 1ArH), 7.92 (d, $J$ = 7.8 Hz, 1ArH), 8.08 (d, $J$ = 8.1 Hz, 1ArH), 8.15–8.18 (m, 4ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.6, 25.7, 29.1, 31.6, 68.4, 114.4, 121.2, 121.7, 122.5, 123.3, 125.3, 126.4, 128.8, 131.2, 132.4, 135.2, 153.3, 154.2, 163.8, 164.6, 167.1.HRMS (ESI) $m/z$ calculated for $C_{26}H_{26}NO_3S$ $(M+H)^+$: 432.1633; found: 432.1635.

*4.3.119. 4-(Benzo[d]thiazol-2-yl)phenyl 4-(heptyloxy)benzoate (**20g**)*

To a stirred solution of **8g** (0.098 g, 0.44 mmol) in THF, DMAP (0.005 g, 0.04 mmol) and EDC.HCl (0.100 g, 0.53 mmol) were added and stirred at room temperature for 15 min. Then **22** (0.100 g, 0.44 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 20% ethyl acetate in hexanes. Yield: 0.12 g, 63.1%, off white solid, m.p: 136–138 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.91 (t, $J$ = 6.9 Hz, 3H), 1.33–1.43 (m, 6H), 1.46–1.51 (m, 2H), 1.81 (quintet, $J$ = 6.6 Hz, 2H), 4.06 (t, $J$ = 6.6 Hz, 2H), 6.99 (d, $J$ = 8.7 Hz, 2ArH), 7.35–7.38 (m, 2ArH), 7.39–7.43 (m, 1ArH), 7.51 (dt, $J$ = 1.5, 8.4 Hz, 1ArH), 7.92 (d, $J$ = 7.8 Hz, 1ArH), 8.08 (d, $J$ = 7.8 Hz, 1ArH), 8.15–8.18 (m, 4ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.6, 26.0, 29.0, 29.1, 31.8, 68.4, 114.4, 121.2, 121.7, 122.5, 123.3, 125.2, 126.4, 128.8, 131.2, 132.4, 135.2, 153.3, 154.2, 163.8, 164.6, 167.1. HRMS (ESI) $m/z$ calculated for $C_{27}H_{28}NO_3S$ $(M+H)^+$: 446.1790; found: 446.1791.

*4.3.120. 4-(Benzo[d]thiazol-2-yl)phenyl 4-(octyloxy)benzoate (**23a**)*

To a stirred solution of octanoic acid (0.104 g, 0.44 mmol) in THF, DMAP (0.005, 0.04 mmol) and EDC.HCl (0.100 g, 0.53 mmol) were added and stirred at room temperature for 15 min. Then **22** (0.100 g, 0.44 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 20% ethyl acetate in hexanes. Yield: 0.128 g, 63.6%, off white solid, m.p: 132–134 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.90 (t, $J$ = 6.9 Hz, 3H), 1.30–1.35 (m, 8H), 1.42–1.50 (m, 2H), 1.83 (pentet, $J$ = 6.6 Hz, 2H), 4.05 (t, $J$ = 6.6 Hz, 2H), 6.97–7.00 (m, 2ArH), 7.34–7.43 (m, 3ArH), 7.51 (dt, $J$ = 1.2, 8.4 Hz, 1ArH), 7.92 (d, $J$ = 8.1 Hz, 1ArH), 8.08 (d, $J$ = 8.1 Hz, 1ArH), 8.15–8.18 (m, 4ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.2, 29.4, 31.8, 68.4, 114.4, 121.1, 121.7, 122.5, 123.3, 125.3, 126.4, 128.8, 131.2, 132.4, 135.2, 153.3, 154.2, 163.8, 164.6, 167.1.HRMS (ESI) $m/z$ calculated for $C_{28}H_{30}NO_3S$ $(M+H)^+$: 460.1946; found: 460.1948.

*4.3.121. 4-(Benzo[d]thiazol-2-yl)phenyl 4-(nonyloxy)benzoate (**23b**)*

To a stirred solution of nonanoic acid (0.106 g, 0.44 mmol) in THF, DMAP (0.005 g, 0.04 mmol) and EDC.HCl (0.100 g, 0.53 mmol) were added and stirred at room temperature for 15 min. Then **22** (0.100 g, 0.44 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 20% ethyl acetate in hexanes. Yield: 0.142 g, 68.3%, pale yellow solid, m.p: 118–120 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.88 (t, $J$ = 6.9 Hz, 3H), 1.29–1.48 (m, 10*H*), 1.50–1.58 (m, 2H), 1.83 (pentet, $J$ = 6.6 Hz, 2H), 4.05 (t, $J$ = 6.6 Hz, 2H), 6.97–7.00 (m, 2ArH), 7.35–7.43 (m, 3ArH), 7.51 (dt, $J$ = 1.2, 8.1 Hz, 1ArH), 7.92 (d, $J$ = 8.1 Hz, 1ArH), 8.08 (d, $J$ = 8.1 Hz, 1ArH), 8.15–8.18 (m, 4ArH), $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.3, 29.5, 29.7, 31.9, 68.4, 114.4, 121.1, 121.7, 122.5, 123.3, 125.3, 126.4, 128.8, 131.2, 132.4, 135.1, 153.3, 154.2, 163.8, 164.6, 167.1. HRMS (ESI) $m/z$ calculated for $C_{29}H_{32}NO_3S$ $(M+H)^+$: 474.2103; found: 474.2105.

*4.3.122. 4-(Benzo[d]thiazol-2-yl)phenyl 4-(decyloxy)benzoate (**23c**)*

To a stirred solution of decanoic acid (0.122 g, 0.44 mmol) in THF, DMAP (0.005 g, 0.04 mmol) and EDC.HCl (0.100 g, 0.53 mmol) were added and stirred at room temperature for 15 min. Then **22** (0.100 g, 0.44 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 20% ethyl acetate in hexanes. Yield: 0.148 g, 69.2%, off white solid, m.p: 120–122 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.89 (t, $J$ = 6.9 Hz, 3H), 1.22–1.33 (m, 12H), 1.42–1.50 (m, 2H), 1.82 (pentet, $J$ = 6.6 Hz, 2H), 4.05 (t, $J$ = 6.6 Hz, 2H), 6.97–7.00 (m, 2ArH), 7.35–7.43 (m, 3ArH), 7.51 (dt, $J$ = 1.2, 8.1 Hz, 1ArH), 7.92 (d, $J$ = 8.1 Hz, 1ArH), 8.08 (d, $J$ = 8.1 Hz, 1ArH), 8.15–8.18 (m, 4ArH).$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.1, 22.7, 26.0, 29.1, 29.3, 29.4, 29.6, 29.7, 31.9, 68.4, 114.4, 121.1, 121.7, 122.5, 123.3, 125.2, 126.4, 128.8, 131.2, 132.4, 135.2, 153.3, 154.2, 163.8, 164.6, 167.1.HRMS (ESI) $m/z$ calculated for $C_{30}H_{34}NO_3S$ $(M+H)^+$: 488.2259; found: 488.2261.

*4.3.123. 4-(Benzo[d]thiazol-2-yl)phenyl 4-(allyloxy)benzoate (**23d**)*

To a stirred solution of **6a** (0.078 g, 0.44 mmol) in THF, DMAP (0.005 g, 0.04 mmol) and EDC.HCl (0.100 g, 0.53 mmol) were added and stirred at room temperature for 15 min. Then **22** (0.1 g, 0.44 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 15% ethyl acetate in hexanes. Yield: 0.124 g, 73.0%, white solid, m.p: 148–150 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.63–4.66 (m, 2H), 5.33 (dd, $J$ = 1.2, 10.5 Hz, 1H), 5.46 (dd, $J$ = 1.2, 17.1 Hz, 1H), 6.02–6.14 (m, 1H), 7.00–7.03 (m, 2ArH), 7.34–7.43 (m, 3ArH), 7.51 (td, $J$ = 1.2, 8.4 Hz, 1ArH), 7.91–7.93 (m, 1ArH), 8.07–8.10 (m, 1ArH), 8.14–8.19 (m, 4ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 69.0, 114.7, 118.3, 121.6, 121.7, 122.5, 123.3, 126.4, 128.8, 131.2, 132.4, 135.2, 153.2, 154.2, 163.1, 164.5, 167.1. HRMS (ESI) $m/z$ calculated for $C_{23}H_{18}NO_3S$ $(M+H)^+$: 388.1007; found: 388.1010.

*4.3.124. 4-(Benzo[d]thiazol-2-yl)phenyl 4-((3-methylbut-2-en-1-yl)oxy) benzoate (**23e**)*

To a stirred solution of **6b** (0.091 g, 0.44 mmol) in THF, DMAP (0.005 g, 0.04 mmol) and EDC.HCl (0.100 g, 0.53 mmol) were added and stirred at room temperature for 15 min. Then **22** (0.100 g, 0.44 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 10% ethyl acetate in hexanes. Yield: 0.105 g, 57.9%, white solid, m.p: 172–174 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.78 (s, 3H), 1.83 (s, 3H), 4.62 (d, $J$ = 6.9 Hz, 2H), 5.49–5.54 (m, 1H), 6.99–7.03 (m, 2ArH), 7.34–7.39

(m, 2ArH), 7.40–7.43 (m, 1ArH), 7.48–7.54 (m, 1ArH), 7.91–7.93 (m, 1ArH), 8.07–8.09 (m, 1ArH), 8.14–8.19 (m, 4ArH). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 18.4, 25.7, 65.1, 114.6, 118.7, 121.3, 121.7, 122.5, 123.2, 125.3, 126.4, 128.8, 131.2, 132.4, 135.3, 139.3, 153.2, 154.2, 163.5, 164.5, 167.1. HRMS (ESI) *m/z* calculated for $C_{25}H_{22}NO_3S$ $(M+H)^+$: 416.1320; found: 416.1321.

#### 4.3.125. 4-(Benzo[d]thiazol-2-yl)phenyl (E)-4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)benzoate (23f)

To a stirred solution of **6e** (0.121 g, 0.44 mmol) in THF, DMAP (0.005 g, 0.04 mmol) and EDC.HCl (0.100 g, 0.53 mmol) were added and stirred at room temperature for 15 min. Then **22** (0.100 g, 0.44 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 10% ethyl acetate in hexanes. Yield: 0.152 g, 72.6%, white solid, m.p: 130–132 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.62 (s, 3H), 1.69 (s, 3H), 1.77 (s, 3H), 2.12–2.16 (m, 4H), 4.65 (d, $J$ = 6.6 Hz, 2H), 5.10 (t, $J$ = 1.2 Hz, 1H), 5.50–5.53 (m, 1H), 6.98–7.02 (m, 2ArH), 7.34–7.43 (m, 3ArH), 7.51(td, $J$ = 1.2, 8.1 Hz, 1ArH), 7.92 (dd, $J$ = 0.6, 8.1 Hz, 1ArH), 8.09 (d, $J$ = 7.5 Hz, 1ArH), 8.14–8.19 (m, 4ArH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 16.8, 17.7, 25.7, 26.3, 39.5, 65.2, 114.6, 118.7, 121.2, 121.7, 122.5, 123.2, 123.7, 125.3, 126.4, 128.8, 131.1, 132.0, 132.4, 135.1, 142.1, 153.3, 154.1, 163.5, 164.6, 167.1. HRMS (ESI) *m/z* calculated for $C_{30}H_{30}NO_3S$ $(M+H)^+$: 484.1946; found: 484.1949.

#### 4.3.126. 4-(Benzo[d]thiazol-2-yl)phenyl 4-(((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)benzoate (23g)

To a stirred solution of **6f** (0.137 g, 0.44 mmol) in THF, DMAP (0.005 g, 0.04 mmol) and EDC.HCl (0.100 g, 0.53 mmol) were added and stirred at room temperature for 15 min. Then **22** (0.100 g, 0.44 mmol) was added and stirred for 3 h at room temperature. After completion of reaction (TLC), volatiles evaporated and the crude mass was partitioned between ethyl acetate and 10% sodium bicarbonate solution (2 times). Combined organic layer was washed with water and brine. The organic portion was dried over sodium sulfate and purified by column chromatography (silica gel 100–200 mesh) using 10% ethyl acetate in hexanes. Yield: 0.163 g, 67.2%, white solid, m.p: 74–76 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.57 (s, 3H), 1.61 (s, 3H), 1.68 (s, 3H), 1.78 (s, 3H), 1.96–2.19 (m, 8H), 4.65 (d, $J$ = 6.6 Hz, 2H), 5.10 (t, $J$ = 6.6 Hz, 2H), 5.51 (t, $J$ = 6.6 Hz, 1H), 6.99–7.02 (m, 2ArH), 7.36 (dd, $J$ = 1.8, 6.9 Hz, 2ArH), 7.42 (dt, $J$ = 1.2, 6.9 Hz, 1ArH), 7.51 (dt, $J$ = 1.2, 8.1 Hz, 1ArH), 7.92 (d, $J$ = 8.1 Hz, 1ArH), 8.08 (d, $J$ = 8.1 Hz, 1ArH), 8.14–8.18 (m, 4ArH).$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 16.1, 16.8, 17.7, 25.7, 26.2, 26.7, 39.6, 39.7, 65.2, 114.6, 118.7, 121.2, 121.7, 122.5, 123.6, 124.3, 125.3, 126.4, 128.8, 131.2, 131.4, 132.4, 135.2, 135.6, 142.1, 153.3, 154.2, 163.5, 164.6, 167.1. HRMS (ESI) *m/z* calculated for $C_{35}H_{38}NO_3S$ $(M+H)^+$: 552.2572; found: 552.2573.

### 4.4. Drug susceptibility on replicating M. tuberculosis H37Rv by MABA assay

The MIC evaluation of the synthesized molecules against replicating H37Rv was performed by MABA assay. The bacteria were grown using the 7H12 media instead of the 7H9 + glycerol + casitone + OADC supplement. Luciferase reporter strains [47] of H37Rv were used for compounds with intrinsic background fluorescence and the intracellular ATP levels measured. Compounds were used as a stock solution in DMSO, and two fold serial dilutions of the compounds were used for the assay. Cultures along with different compounds of varying concentrations were incubated in 200 µl medium in 96-well plates for 7 days at 37 °C. Alamar Blue and Tween 80 were added and incubation was continued for 24 h at 37 °C. Fluorescence was determined at excitation/emission wavelengths of 530/590 nm respectively. The MIC was calculated as the lowest concentration effecting a reduction in fluorescence (or luminescence) of 90% relative to controls. Isoniazid and rifampin were run as the control experiments.

### 4.5. Drug susceptibility on non replicating M. tuberculosis H37Rv by LORA assay

Low Oxygen Recovery Assay was used to determine the anti mycobacterial efficiency of a substance against the non replicating bacilli. The strain used for LORA is a recombinant H37Rv strain pFCA-LuxAB which makes direct luminescence measurements to determine the MIC. Briefly the strain was cultured in 7H12 media under humidified atmosphere (37 °C, 5% $CO_2$). Cultures were incubated in 200 µl medium in 96-well plates evacuated in an anaerobic jar for producing hypoxic environment using anaerobic gas mixture of 10% $H_2$, 5% $CO_2$ and 85% $N_2$ for 10 days at 37 °C. Then the culture was subjected to a recovery phase in 5% $CO_2$ and 95% humidity in a $CO_2$ incubator. Then 1% *n*-decanal was added and luminescence measured in a luminometer [29].

### 4.6. Drug susceptibility on replicating M. tuberculosis H37Ra by MABA assay

The MIC evaluation of the synthesized molecules against replicating H37Ra was performed by MABA assay. Briefly the bacteria were grown using the 7H9 media supplemented with OADC. at 37 °C. For minimum inhibitory concentration (MIC) testing, two fold serial dilutions of compounds were prepared in 360 mL in optically clear, round bottom 96-well plates. An equivalent volume of mid loge phase H37Ra culture (diluted to an optical density at 570 nm of 0.01 was added to achieve a final drug concentration range of 100–0.78 µg/ml in 7H9 broth, with a control. Plates were incubated in ambient air at 37 °C for 7 day, at which Alamar Blue and Tween 80 were added and incubation was continued for 24 h at 37 °C. Fluorescence was determined at excitation/emission wavelengths of 530/590 nm respectively. The MIC was calculated as the lowest concentration effecting a reduction in fluorescence (or luminescence) of 90% relative to controls. Isoniazid and rifampin were run as the reference drug.

### 4.7. Cytotoxicity study

Cytotoxicity studies were performed against the PBMC cells isolated from blood. The PBMC cells were propagated in RPMI media in a humidified incubator (37 °C, 5% $CO_2$). After scrapping the cells with a cell scraper, they were collected by centrifugation (1000 rpm for 5 min), resuspended in fresh medium at ~1 × $10^6$ cells/mL, dispensed into 96-well microplates (100 µl/well) and incubated for 24 h at 37 °C before being used for cytotoxicity assays. Test compounds were subsequently added at concentrations ranging from 400 to 0.2 µg/mL and incubation continued for another 72 h before the cytopathic effects of compounds was determined using the MTT Cell Proliferation Assay (ATCC). The cytotoxic $IC_{50}$ defined as the concentration causing 50% reduction in PBMC viability, was obtained from a dose–response curve plotted from percentage activity versus $\log_{10}$ concentration.

### 4.8. Whole cell based morphology assay

The effect of best molecules (**9k**, **9l** and **9m**) on the cell division of the bacilli was evaluated by the comparison of its morphology between the control set and the treated set. In brief *Mtb* (H37Ra) culture having $OD_{600}$ = 0.5 was incubated with a concentration of 2 times of the MIC of the compounds **9k**, **9l** and **9m**. After incubating for a period of 7 days, the culture was centrifuged and washed 3 times with PBS buffer and then suspended in 20 µl of PBS. 10 µl of the culture was mixed with 10 µl of FDA solution and spread on a glass slide and fluorescence image was recorded at a magnification of 100X. The elongation in the

morphology of the molecule treated set shows the influence of these molecules on the bacterial cell division [51].

### 4.9. Gtpase activity

FtsZ being a GTPase utilises GTP and releases inorganic phosphate and produces GDP. A quantification of inorganic phosphate is a direct measure of a molecule's GTPase activity. A molecule inhibiting FtsZ leads to low inorganic phosphate content. A plot of molecule's concentration to the GTPase activity can be utilized for evaluating the $IC_{50}$ of that molecule for GTPase inhibition. Briefly 3.5 μM FtsZ (*Mtb*) [32,52,53] was incubated with varying concentrations of the molecule under investigation in 50 μM (MOPS) buffer for 10 min at 25 °C. Then 500 μM GTP in 5 μM $MgCl_2$ and 200 μM KCl was added and incubated for 30 min at 37 °C. Then 100 μl of cytophos reagent was added and the OD at 650 nm was recorded. A plot of GTPase inhibition and compound concentration gave the $IC_{50}$ of that compound.

### 4.10. MenG inhibition assay

The inhibitory activity of the synthesized molecules against MenG was evaluated by a HPLC based assay by monitoring S-Adenosyl Methionine (SAM) mediated methylation of Comp **A** (representative molecule for DMMQ) in the presence of the molecule under investigation. In brief for 200 μl assay mixture, 500 μM Comp **A** (20 μl) was incubated with 5 μM (20 μl) $MgCl_2$, 5 mM DTT (20 μl) and 0.1% CHAPS (20 μl) in 100 mM Tris buffer (pH = 8). To that 500 μM SAM (10 μl) was added along with the inhibitor molecule with varying concentration (10 μl) and the reaction was initiated by adding 100 μl of H37Ra membrane bound protein (obtained by disrupting H37Ra cell using probe sonicator) separately. The mixture was incubated for 3 h and then quenched by adding 0.1 M acetic acid in methanol. The reaction mixture was then extracted with ether and injected to the HPLC (Agilent) and quantified the conversion of Comp **A** to Comp **B**. The same experiment was repeated with the synthesized molecules in increasing concentrations (10, 25, 35, 50, 65 and 80 μM) and the corresponding $IC_{50}$ was determined from non-linear regression analysis. We had used HyperClone 5 μm BDS C18 130 Å column from Phenomenex (250 × 4.6 mm) with the solvent system ACN/Water (90:10) with 0.05% TFA. The flow rate was maintained at 1 mL/min.

### 4.11. Vit-K2 rescue assay

The activity of Comp. **9l**, **9m**, **9n** and **14n** against nonreplicating *Mtb* (H37Ra) was determined by using resazurin reduction assay. The effects of Vit-K2 supplementation were investigated using medium supplemented with 1 mM Vit-K2 (as a control set). The growth was measured by plating and counting the CFU from 0 and 10 days of culture. Similarly, the growth in the presence of comp. **9l**, **9m**, **9n** and **14n** (20 μg/ml) was measured at 10th day with 1 mM Vit-K2 supplementation. In this case the cultures (incubated with **9l**, **9m**, **9n** and **14n** individually + 1 mM Vit-K2) were grown for 10 days followed by 27 days after CFU counting on 7H10 agar plates.

### 4.12. Determination of the ATP production

H37Ra was cultured for 12 days (with 25 rpm at 37 °C) in 7H9 broth till $OD_{600}$ = 0.8. Thereafter, we incubated H37Ra ($OD_{600}$ = 0.8; 2 mL) with three different concentrations of comp. **9n** (10, 25 and 50 μg/ml along with a control set). We took 10 μl of the inoculums on 3rd, 6th and 9th day (from the day of drug addition) and measured the conversion of ADP to ATP using microplate reader.

In brief, the total content of ATP and ADP obtained form 100 μl of inoculums (from 3rd, 6th and 9th day separately) by adding trichloroacetic acid (0.5%). After 5 min it was neutralize by addition of TEA buffer and diluted to 5 fold with the same. Then we used 100 μl of reaction mix (containing 10 μl ATP monitoring enzyme and 90 μl nucleotide releasing buffer) with 10 μl of the solution containing ADP and ATP and incubated for 2 min and take the reading using a plate reader. Thereafter, 10 μl ADP converting enzyme was added and luminescence was recorded using the plate reader. The ATP/ADP ratio was determined according to the manufacturer protocol.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2020.104170.

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