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Original article

Discovery of target based novel pyrrolyl phenoxy derivatives as antimycobacterial agents: An in *silico* approach

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ABSTRACT

A new series of pyrrolyl phenoxy derivatives bearing alkoxy linker were synthesized and evaluated for anti-tubercular activity (anti-TB) against *Mycobacterium tuberculosis*. Molecular modeling, pharmacophore constructed using GALAHAD to produce an effective alignment of data set and evaluated by Pareto ranking. The pharmacophore features were filtered by Surflex-dock study using enoyl ACP reductase from *M. tuberculosis*, which is one of the key enzymes involved in type II fatty acid biosynthesis pathway of *M. tuberculosis*. Compound **6a27** showed the H-bond with NAD^+, whereas compound **6a26** showed H-bonds with Tyr158, Thr196, Met199 and NAD^+ that fitted well into the binding pocket of target InhA. The alkoxy linker bridge and acceptor groups with benzene ring were advantageous for anti-TB activity, which merit further investigation.

1. Introduction

Tuberculosis (TB) is caused by various strains of mycobacteria, mainly by *Mycobacterium tuberculosis* (*M. tuberculosis*) and the disease attacks lungs as well as other parts of the human system. However, the unique structure of cell-wall allows it to be dormant as a latent infection, which is a successful pathogen that overcomes numerous challenges presented by the immune system of the host. Furthermore, increase in immuno-suppressed individuals due to AIDS are more susceptible to TB infection [1,2]. Over the past decades, several anti-tuberculosis (anti-TB) drugs have been developed (Fig. 1), but drug-resistance issue is still increasing. There is thus a demand to develop new anti-TB drugs that are active against both acute and chronic growth phases of mycobacterium. Enoyl ACP reductase (ENR) is an enzyme involved in the synthesis of mycolic acids (MAs), which are essential structural components of the mycobacterial cell-wall. As an anti-TB drug target, *M. tuberculosis*-ENR is InhA that has been well validated. However, complete genome sequence of TB bacteria helped to identify several important drug targets that may have utility in prophylactic and therapeutic interventions [3].

Mycobacteria possess both FAS-I and FAS-II systems; of these, FAS-I for fatty acyl chains up to 16 carbons and FAS-II for the production of long chains up to 56 carbons that are precursors of MAs, indicating that FAS-II system utilizes the products of FAS-I system as the primers to extend fatty acyl chain lengths even further. MAs are long chain α-alkyl-β-hydroxy fatty acids, which are the major components of mycobacterial cell-walls [4,5]. The protein encoded by the *inhA* gene, referred to as InhA, has similar amino acid sequence to the two previously characterized enoyl-ACP reductases, 28% identical to FabI from *Escherichia coli* and 23% identical to ENR1 from *Brassica napus* [6,7]. Further analysis revealed that InhA catalyzes NADH-dependent reduction of trans double bond between the positions C2 and C3 of fatty acyl substrates. In addition, InhA prefers fatty acyl substrates of C16 or even greater, consistent with its being a member of the mycobacterial FAS-II system [8].

The gene named *inhA* is deduced from isoniazid (INH), which is

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0223-5234/

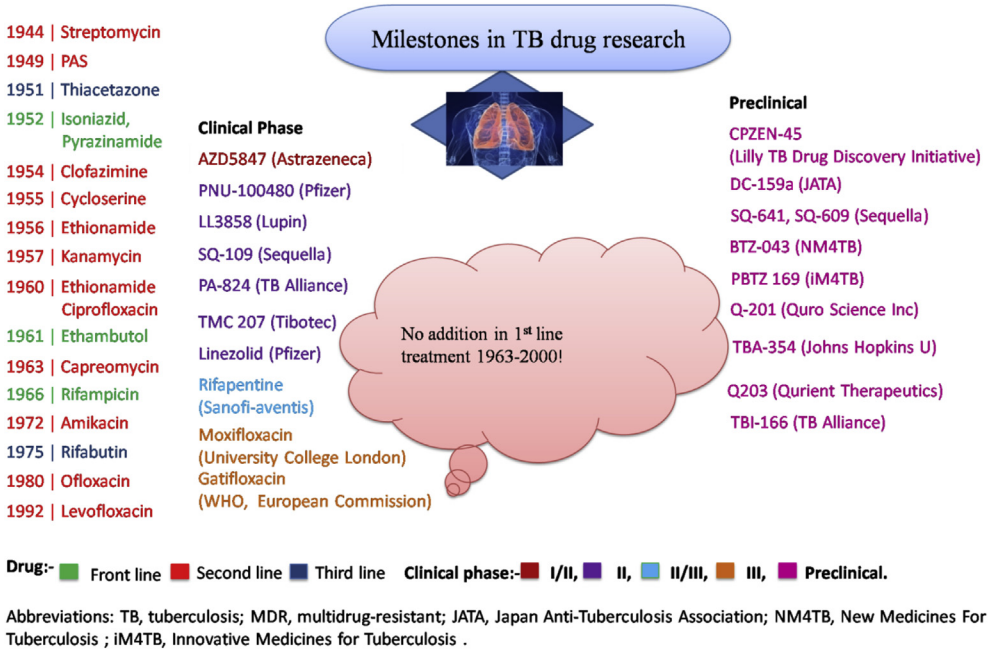


Fig. 1. Milestones in TB drug research.

the first-line antibiotic for the treatment of TB for over 50 years that is known to inhibit mycolic acid biosynthesis [9]. InhA is inhibited by the active adduct of INH (INH-NAD), which is covalently formed between NAD^+ and the reactive acyl radical of INH generated by the activation of catalase-peroxidase (KatG) [10]. More recently, triclosan (TCL) has been shown to inhibit InhA without the requirement for KatG-mediated activation [11]. For modifications in the parent triclosan using structure-based drug design, three lipophilic chlorine atoms of triclosan were removed, and one chlorine atom of ring was replaced by an alkyl chain of varying length, resulting in alkyl diphenyl ethers (5-hexyl-2-(2-methylphenoxy)phenol; PT70) [12,13]. These are more potent than the parent compound TCL.

We have previously described the synthesis of potential inhibitors of InhA bearing pyrrole, aryloxy and –C═N–NHCO– bridge as the core fragments compared to PT70 and TCL [14–16], wherein we have synthesized these along with 2D and 3D-QSAR studies [17–19]. During our studies on *Paal-Knorr* and *Williamson* ether reactions on amine and phenol, we have focused our attention on pyrrole with aryloxy/ethoxy/propoxy fragments as the core structures of the newly designed inhibitors. Molecules containing aryloxy/ethoxy/propoxy and pyrrole as structural fragments have been widely explored in drug design. For instance, TCL and its derivatives, Epiroprim, LL-3858, Br-WR99210 are some of the approved drugs as well as clinical drug candidates (Fig. 2). The pyrrole ring is a part of many natural compounds [20–22] as well as it is biologically active molecule [23]. Earlier, Yale [24] and Gazave [25] have reported *in vitro* anti-TB pyrrole derivatives and later, Cerreto et al. [26,27], reported some 1,5-diaryl-2-methyl-pyrrole derivatives that exhibit potent anti-candida activity against *Candida albicans*. Porretta, Deidda and Biava [28–30] also developed 1,5-diaryl-2-methyl-3-(4-methylpiperazin-1-yl)-methyl-pyrrole (BM212) as a potent anti-TB drug and based on this approach, Lupin Ltd. [31] developed LL-3858 that is currently used in clinical development for the treatment of TB. Additionally, recent reports on other scaffolds as anti-TB agents [32–34], encouraged us for the discovery of new anti-TB agents.

Traditionally, however, it is difficult to select the best chemical moiety that can play an effective role in treating or preventing TB. Recently, TCL and its derivatives are becoming important antitubercular agents against Enoyl ACP reductase. This prompted us to use phenoxy moiety as the core structure by employing computational strategies that include pharmacophore based on an automated computational alignment technique and molecular docking studies to identify Enoyl ACP reductase as a potential target of phenoxy pyrrole derivatives. Using these computational techniques, we have demonstrated a quantitative pharmacophore mapping tool that is valuable to identify physicochemical and structural requirements for ligand binding and biological activity [35] aspects along with the molecular docking investigations on 1-(4-(2/3-aryloxyethoxy/propoxy)phenyl)-1*H*-pyrroles as inhibitors of InhA and *M. tuberculosis*. No previous literature exists on these aspects and hence, the study is novel.

2. Computational details

2.1. General method

The crystal structure of *M. tuberculosis* InhA inhibited by PT70 were obtained from the Brookheaven Protein Databank as entries 2X22 (2.1 Å, R-value 0.174%, R-free 0.216%). The 3D model of ENR from *M. tuberculosis* was constructed previously [14]. In the present case, biopolymer and each molecule in the data set energetically minimized by employing Tripos force field [36], Powell optimization method [37], Amber7FF9902 (biopolymer) and MMFF94 (molecules) charges (NB cut-off 9.0 and dielectric constant 4.0) with a convergence criterion set at 0.001 kcal/mol Å. The pharmacophore models were generated and analyzed using GALAHAD (Genetic Algorithm with Linear Assignment of Hypermolecular Alignment of Datasets) module. All the calculations were performed using the commercially available SYBYL-X 2.0 software package (Tripos Associates, St. Louis, MO, USA) [38].

Modeling protein–ligand interactions is the key step in modern drug designing. If the structure of a binding site is known, then docking studies will provide valuable insights into such interactions and, in favorable cases, tone can identify high-affinity

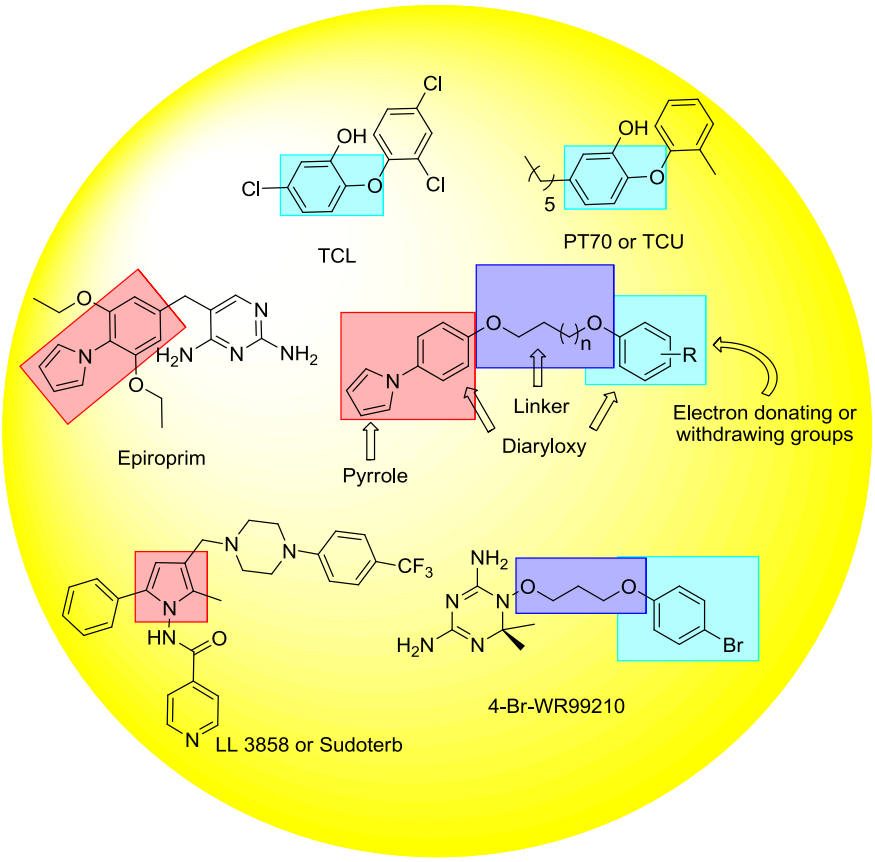


Fig. 2. Design concept for new molecular entities.

ligands by virtual high-throughput screening. The pharmacophore-based 3D searching also proved particularly useful [39]. It is characterized in terms of subgroups of two, three or four features, and arrangement of particular characteristics that are necessary for ligand binding as well as spatial relationship between them, thus providing a fast and flexible tool for carrying out these searches. Genetic Algorithm with Linear Assignment of Hypermolecular Alignment of Database [40] was also utilized in the formulation of pharmacophore hypothesis for the synthesized molecules, which is a unique method as it does not require any template structure such that it allows immediate and effective generation of partial-coverage models with multiple partial match constraints [41].

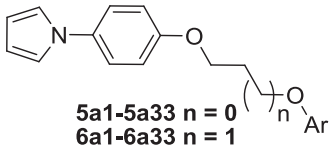
2.2. Alignment and pharmacophore generation

A total of 66 newly synthesized pyrrolyl phenoxy anti-tubercular compounds were used as data set in the identification of a feature-based pharmacophore and docking analysis. The alignment was performed in two steps. In the first step, eight compounds (**5a9**/**6a9**, **5a12**/**6a12**, **5a26**/**6a26**, **5a27**/**6a27** labeled with asterisks as shown in Table 1) were selected to carry out pharmacophore hypothesis; the genetic algorithm was used here to create the conformers for all molecules. The compounds that were selected to generate pharmacophore hypothesis are highly active. All the selected ligands were aligned flexibly by GALAHAD, completely independent of a template, with a population size of 50 and a maximum generation value of 70 with molecular required hitting of 4. Twenty models were generated with default parameters and using all the molecules in this stage to generate flexible alignment that may lead to some features by neglecting the interaction [42]. Using more than four molecules from each series (i.e., >8) led to a reduction in the quality of pharmacophore, while using a single molecule, we could induce a non-specific feature set. The biological activity of each compound was expressed as minimal inhibitory concentration (MIC) against *M. tuberculosis* and the −log(MIC) values were used in pharmacophore analysis.

Using flexible alignment, GALAHAD produced a set of probable hypotheses (Table 3, 20 models). SPECIFICITY is a logarithmic indicator of the expected discrimination for each query. The actual number hit is given in the N_HITS column and the values in FEATS column indicate the total number of features in the model query. The next five columns are model score components from the genetic algorithm. PARETO is a pareto rank of each model, where all the models have a Pareto rank of zero. This means none of the models are superior to any other when using all the four criteria in columns 5–8 (ENERGY, STERICS, H_BOND, and MOL_QRY). ENERGY calculates the total energy of the model; STERICS is a steric overlap for the model; H_BOND, the pharmacophoric concordance and MOL_QRY is an agreement between the query tuplet and pharmacophoric tuplets for the ligands as a group. The last four columns are the scores for individual ligands within each model. Thus, in this case, every cell in each of the last four columns contains a list of eight values.

In the second step, for rigid alignment of the remaining molecules in data set, we need to select one best template model and the selection of the model from obtained 20 models in the first stage based on the model needed to “hit” all the 8 active molecules. The model needed to have high sterics with low energy and pharmacophoric features. We have constructed a scatter plot (ENERGY vs STERICS vs MOL_QRY) to visualize the Pareto surface and selected

Table 1
Anti-tubercular results of compounds **5a1**–**33** and **6a1**–**33** against *Mycobacterium tuberculosis* $H_{37}RV$.



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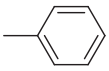
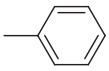
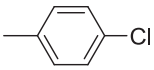
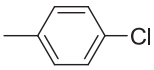
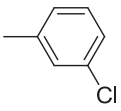
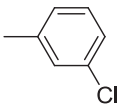
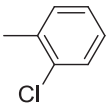
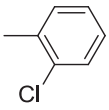
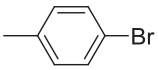
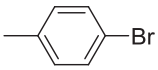
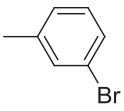
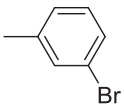
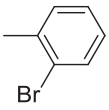
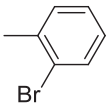
5a1		50	**6a1**		50
5a2		12.5	**6a2**		6.25
5a3		25	**6a3**		50
5a4		25	**6a4**		25
5a5		12.5	**6a5**		6.25
5a6		25	**6a6**		25
5a7		25	**6a7**		25
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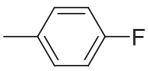
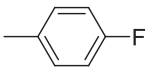
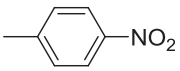
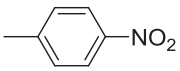
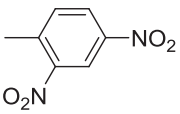
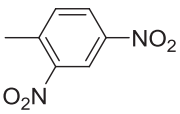
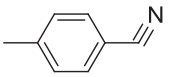
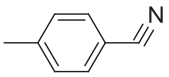
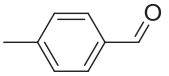
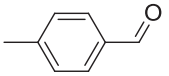
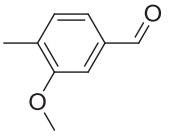
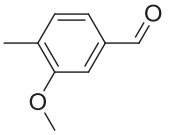
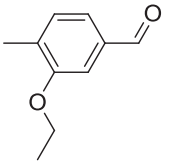
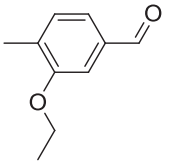
5a9*		6.25	**6a9***		6.25
5a10		50	**6a10**		100
5a11		100	**6a11**		100
5a12*		6.25	**6a12***		6.25
5a13		12.5	**6a13**		12.5
5a14		6.25	**6a14**		3.125
5a15		3.125	**6a15**		3.125

Table 1 (*continued*)

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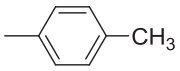
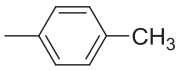
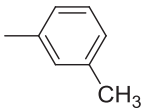
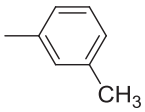
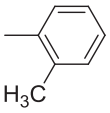
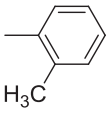
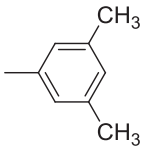
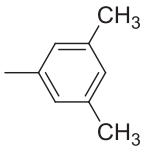
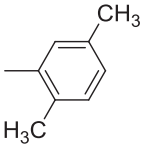
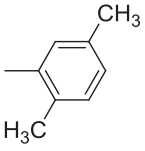
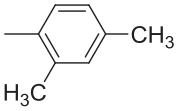
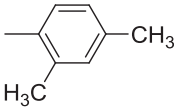
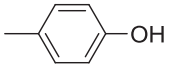
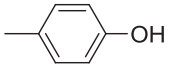
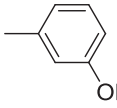
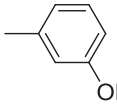
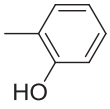
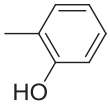
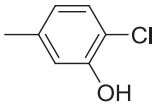
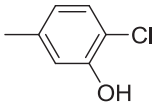
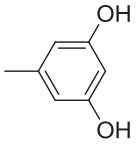
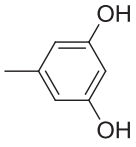
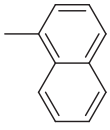
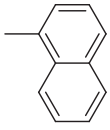
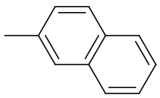
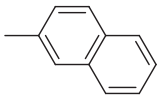
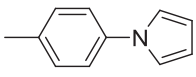
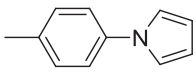
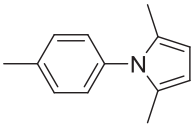
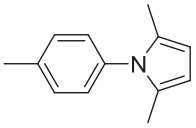
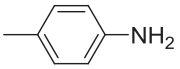
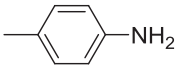
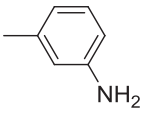
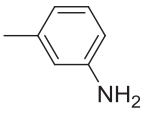
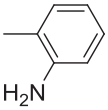
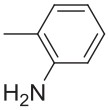
5a16		25	**6a16**		12.5
5a17		25	**6a17**		25
5a18		25	**6a18**		25
5a19		50	**6a19**		25
5a20		25	**6a20**		25
5a21		12.5	**6a21**		25
5a22		12.5	**6a22**		12.5
5a23		6.25	**6a23**		12.5
5a24		12.5	**6a24**		12.5
5a25		6.25	**6a25**		6.25
5a26*		3.125	**6a26***		3.125
5a27*		3.125	**6a27***		1.6
5a28		3.125	**6a28**		3.125
5a29		6.25	**6a29**		6.25

(*continued on next page*)

Table 1 (*continued*)

Compound	Ar	MIC μg/mL	Compound	Ar	MIC μg/mL
5a30		6.25	**6a30**		3.125
5a31		100	**6a31**		50
5a32		100	**6a32**		100
5a33		100	**6a33**		100
Isoniazid	–	0.25	**Triclosan**	–	10

Astringe (*) training set for pharmacophore generation.

the best pharmacophore model (Fig. 3). Considering the ENERGY, STERICS and MOL_QRY criteria, the best model is shown in graph, where the ENERGY is reasonably low and STERICS score is high. Among the considered models, MODEL_04 (represented with a black circle in Fig. 3) has the optimal position because it fulfills all the three criteria and has better Specificity, N_hits and Feats values [40,43,44].

Finally, the associated pharmacophore (MODEL_04) was used as a template to align all the molecules using GALAHAD's Align to template procedure (Table 4). Here, model fitness evaluation starts by applying the corresponding torsions to the specified base configuration of each ligand. Pharmacophore and steric bitmaps were created for each ligand, and (compressed) the count vectors were then generated for the ensemble. Next, the post-processing step in GALAHAD involves taking the genetic algorithm results and producing the final models along with their alignments, scoring of the models, and displaying their rank. In GALAHAD, the needed frame of reference is generated via postprocessing using hypermolecular alignment program LAMDA (Linear Assignment for Molecular Dataset Alignment) [42].

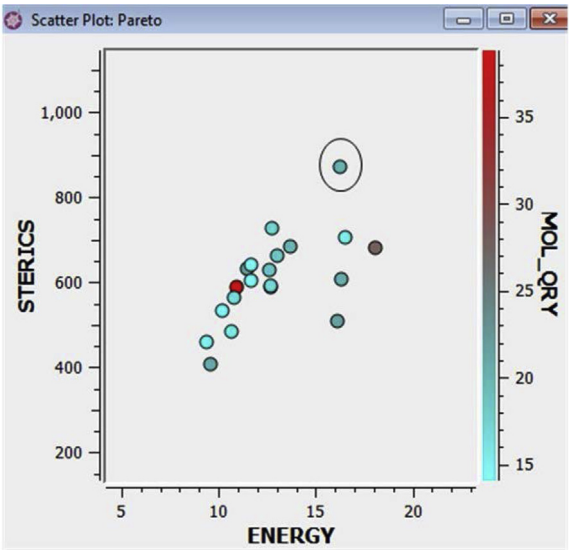


Fig. 3. Pareto scatter plot (energy vs sterics) from 20 models, black circled model_04 was selected for further alignment of all compounds.

2.3. Surflex-docking

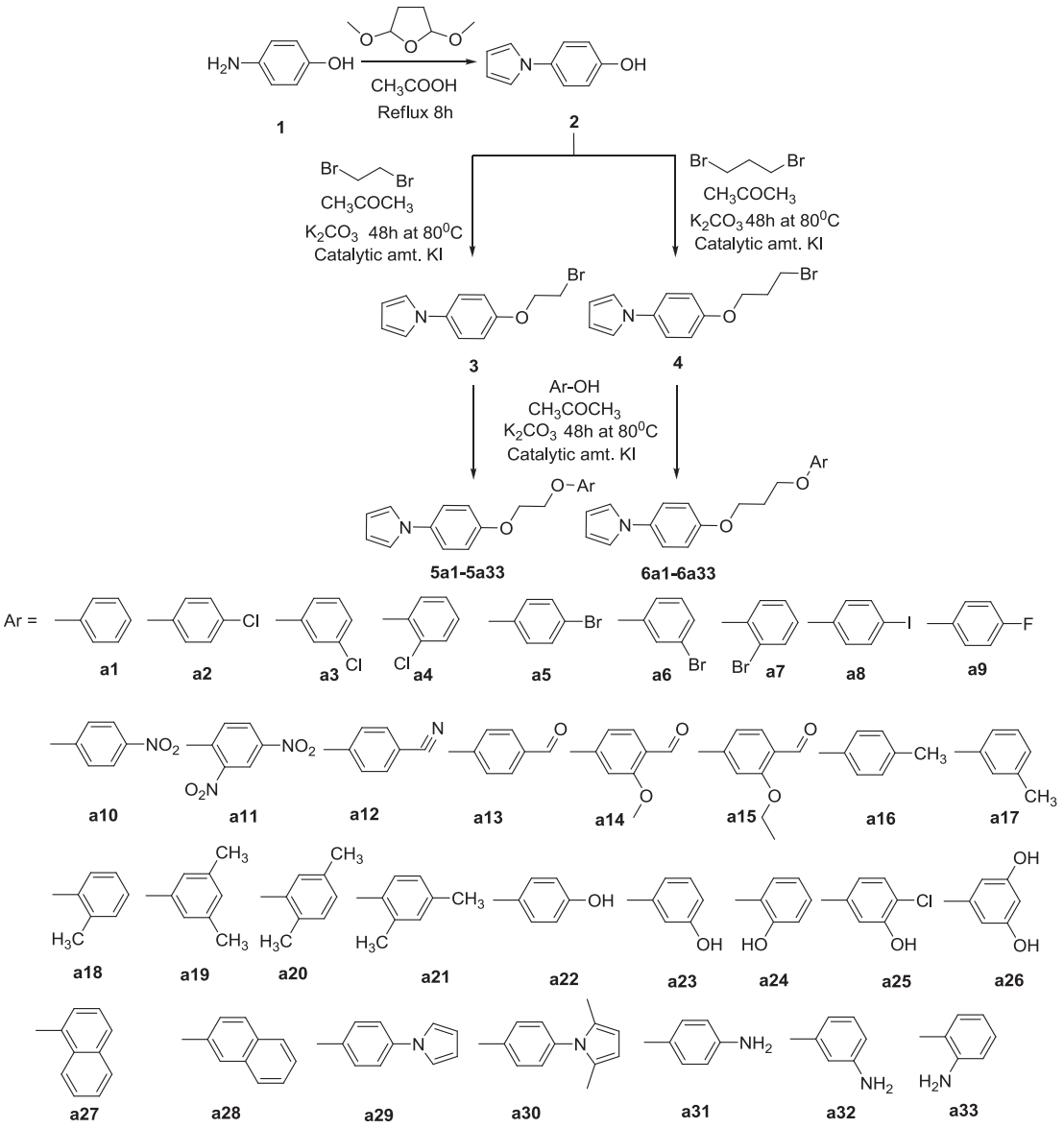
In order to explore the interaction and illustrate accurate binding model for the active site of ENR with ligands, molecular docking was performed using the Surflex-dock module of another advanced version of SYBYL package (X 2.0). This docking approach aligns the ligand to a "protomol" (called also idealized ligand) in the active site of the target. Surflex-dock that adopted an empirical scoring function and a patented search engine [45,46] was employed for molecular docking study of training set as well as test set molecules into the active site of monomeric unit "A" of the crystal structure of ENR catalytic core.

3. Results and discussion

3.1. Chemistry

Compounds **5a1**–**5a33** and **6a1**–**6a33** were synthesized through as per the steps outlined in Scheme 1. The *Paal-Knorr* reaction was performed to synthesize 4-(1*H*-pyrrol-1-yl)phenol (**2**) by condensing 4-aminophenol (**1**) with 2,5-dimethoxytetrahydrofuran. Then, *Williamson* ether synthesis method was used to afford key intermediates viz., 1-(4-(2-bromoethoxy)phenyl)-1*H*-pyrrole (**3**) and 1-(4-(3-bromopropoxy) phenyl)-1*H*-pyrrole (**4**), by reacting 4-(1*H*-pyrrol-1-yl)phenol (**2**) with excessive amounts of dihaloalkanes (1,2-dibromoethane and 1,3-dibromopropane) in the presence of anhydrous K_2CO_3 and a catalytic amount of KI in acetone at 80 °C. Next, different phenols were reacted with intermediate **3** or **4** to get the final desired diphenoxy derivatives **5a1**–**5a33** or **6a1**–**6a33** with good yields. Catalytic amount of KI improved the reaction time and yield. The final step also followed the *Williamson* ether synthesis method. All the new compounds were purified by recrystallization or chromatography and their spectroscopic data confirmed the structures.

All the synthesized compounds were characterized by FTIR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. FTIR spectra of the compounds showed absorption bands at 3143–2875 cm^{-1} due to aromatic C–H stretching and C=C stretching at 1603–1514 cm^{-1}, while the characteristic ether linkage (C–O–C) asymmetric and



Scheme 1. Synthetic route for pyrrolyl phenoxy derivatives.

symmetric stretches appeared in the regions 1260–1231 cm^{-1}, 1073–1058 cm^{-1}, respectively confirming the formation of compounds **5a1**–**5a33** and **6a1**–**6a33**. The ^1H NMR spectra of all the compounds showed typical triplet signal for two protons of pyrrole at C_3 and C_4 positions with the δ values of 6.22–6.36 ppm and aromatic proton signals (doublet, doublet of doublet, doublet of triplet, triplet, triplet of doublet and multiplet) between δ of 6.16 and 8.73 ppm. The $-OC\underline{H}_2-C\underline{H}_2O-$ protons resonated as a triplet between δ of 4.04 and 4.45 ppm. In case of compounds in the 6a series, additional $-C\underline{H}_2-$ observed as a quintet (pentate) at δ of 2.21–2.40 ppm. However, in both the series, multiplets also observed. In the ^{13}C NMR spectra, C_1 carbon resonance frequency for both the aromatic rings (Ar–$\underline{C}_1$–O and O–$\underline{C}_1$–Ar) was observed around δ of 154–158 ppm, while the remaining aromatic carbons appeared around δ of 82–138 ppm and those of $-\underline{C}H_2-$ groups appeared in the at δ rang of 28–70 ppm. Furthermore, structures of all the compounds were confirmed by EI-MS (Electron Impact Ionization) spectra that showed the molecular ion [M+] or [M^++1] and all the spectroscopic measurements confirmed the structures and their high purity.

3.2. Anti-tubercular and cytotoxicity studies

The anti-TB activity of the compounds was studied with *M. tuberculosis* (Table 1). INH and TCL were used as references for inhibitory activity against *M. tuberculosis*. The majority of compounds showed quite moderate to good anti-TB activity. In the first series of compounds viz., **5a9**, **5a12**, **5a14**, **5a15**, **5a23**, **5a25**, **5a26**–**30** showed a better activity with MIC values ranging from 3.125 to 6.25 μg/mL, while those from the second series of compound **6a27** showed the highest activity with MIC value of 1.6 μg/mL. These results demonstrate the presence of an alkoxy group bridge between the two benzene rings bearing one less carbon (in series **5a1**–**5a33**) is little detrimental for biological activity. Certain therapeutic properties are required to be identified if an anti-mycobacterial compound has the potential as a drug. Toxicity is one of these important criteria. Hence, we have investigated the potential toxicity of ten selected pyrrolyl phenoxy derivatives (**5a15**, **5a26**–**28**, **6a14**, **6a15**, **6a26**–**28**, and **6a30**) towards the mammalian Vero cell-lines and A_{549} (lung adenocarcinoma) cell-lines up to concentrations of 62.5 μg/mL. Compounds showed a moderate

cytotoxicity in comparison to the standard INH (see Table 2).

3.3. Pharmacophore results

Total of 20 GALAHAD models were derived using 8 active ligands with the MIC values of 1.6–6.25 μg/mL (PMIC 5.796–5.204) against *M. tuberculosis*. All the models showed Pareto rank 0, which means no one model was superior to any other (Table 3). Amongst the 20 models, MODEL_04 was selected, which showed better steric values, features, hits and reasonably low energy than others. Hence, MODEL_04 was considered for the final rigid alignment of the remaining compounds. Two 5a series of molecules viz., **5a10**, **5a14**, were not aligned by GALAHAD (low H_Bond, Mol_qury values; see Table 4). The final MODEL_04 obtained from GALAHAD is displayed in Fig. 4A and B that is comprised of 8 substructures, one conformer for each molecule from the selected active 8 molecules as the training set. This includes hydrophobes centered on benzene and pyrrole rings as well as one on aliphatic linking chain, but the acceptor atom centers on two oxygen atoms and at one end of the benzene ring (opposite to pyrrole). The pharmacophore model clearly shows the importance of hydrophobic phenyl rings with polar oxygen to exhibit anti-TB activity. The hydrophobic linking chain is also important for activity.

3.4. Molecular modeling: examination of ENR active site

The Ramachandran scatter plot for ENR model indicates that 0% violation (Fig. 5A) and Fig. 5B gives a clear idea of biding site for the ligands (i.e., substrate-binding domain). After successful finding of pharmacophore model and alignment, it is important to understand how these interact with *M. tuberculosis*. Docking studies give a fair idea related to drug–receptor interactions. For this study, ENR has been chosen as it is assumed that the interaction of drug with this enzyme is the important step during fatty acid elongation system FAS-II, which is involved in the biosynthesis of MAs that are the major and specific long-chain fatty acids of the cell envelope of *M. tuberculosis*. The active pocket was considered to be the site where PT70 complexes with enoyl-ACP reductase in 2X22. The PT70 was re-docked to get its interactions and orientation at the active site for comparison with other synthesized molecules. This has shown two H-bond interactions i.e., through oxygen of hydroxy group with the NAD + ribose (1.8 Å), while hydrogen of hydroxy group makes H-bonds with OH of the active site Tyr158 (1.9 Å) (Fig. 6). Three representative compounds viz., **5a23**, **6a26** and **6a27** were chosen for this study. The compounds **5a23** and **6a26** were selected as they have the basic structures of all the compounds of this study and also catechol moiety mimics the standard drug PT70 or TCL and **6a27** was selected since it shows the highest activity among all the compounds reported here.

According to the crystal structure of **6a27** (Fig. 7) with the ENR (PDB ID 2X22, chain A), the ether functionality participates into H-bond with the co-factor NAD of ENR-binding pocket. The compound **6a26** (Fig. 8) contains a phenoxy-3,5-diol group instead of naphthoxy group, the two hydroxyl groups makes six H-bonds, of one which H-bond with Tyr158 (1.95 Å, hydrophilic residue), three with NAD (1.73, 2.15, 2.67 Å, co-factor), one with Thr196 (2.22 Å, hydrophilic residue) and one with Met199 (2.36 Å, hydrophobic/alpha_helix10 residue). The third compound **5a23** (Fig. 9), which contains 2-hydroxy phenoxy moiety makes two H-bonds i.e., one with Tyr158 (1.97 Å, hydrophilic residue) and one with NAD (1.77 Å, co-factor). The orientation and interactions of molecules are identical to PT70 or TCL (Fig. 10A–D). On the other hand, hydrophobic (Ile95, Phe97, Met98, Met103, Ala154, Met155, Pro156, Trp160, Met161, Pro193, Ile194, Leu197, Ala198, Ala201, Ile202, Val203, Leu217, Leu218, Trp222, Trp230) and hydrophilic (Gly96, Gln100, Gly104, Asp148, Asp150, Tyr158, Asn159, Thr162, Lys165, Gly192, Arg195, Thr196, Ser200, Gly204, Gly208, Gln214, Glu219) amino acid residues are surrounded to the representative compound **6a27** (Fig. 11A and B).

The molecules showed consensus score in the range of 8.88–4.36, indicating the summary of all forces of interaction between the ligands and the InhA. Charge and van der Waals interactions between protein and ligands were found to vary from −479.40 to −869.99 of Helmholtz free energies of interactions for protein–ligands atom pairs that range between −20.41 and −77.55 and its H-bonding, complex (ligand-protein), and internal (ligand–ligand) energies range from −124.77 to −264.04, while those ranging from −37.51 to −51.53 indicate the ligands with respect to the reward for H-bonding, lipophilic contact, and rotational entropy, along with the intercept terms. These scores indicate that the molecules preferentially bind to InhA in comparison to reference PT70 or TCL (Table 5).

3.5. Pharmacophore map correlation with the binding site

For a comparison between binding site residues and pharmacophoric features, the docked conformation (Figs. 7–9) was correlated with the identified pharmacophore features. The interactions identified by docking program were quite consistent with the outcome of pharmacophore modeling. The NAD^+ co-factor of the receptor protein is mediating an H-bond with polar oxygen of linker ether (acceptor interaction) of the most active compound **6a27**. The acceptor feature (oxygen, fluorine, nitrile atoms or groups with hydrophobic benzene ring at one end of the molecules) makes a key H-bond with Thr196, Met199 (oxygen atom), and these amino acid residues were well conserved in the ENR family, also called substrate-binding site. Fluorine makes H-bond with Thr196, while that of nitrile functionality makes H-bond with Gly104. This key interaction was found to coherent with the outcome of pharmacophoric mapping because the same region of the ligand has occupied favorable H-bond acceptor features. The hydrophobic features of benzene and pyrrole ring helps the molecule for penetration, but the crash score negative values indicate the extent of penetration (Table 5; Crash score).

Table 2
Cytotoxicity activity of selected pyrrolyl phenoxy derivatives.

Compound	IC_{50} (μM)[a]	
	MV cell-lines[b]	A_{549}[c]
5a15	211 ± 0.2	217 ± 0.2
5a26	231 ± 0.3	237 ± 0.2
5a27	220 ± 0.3	215 ± 0.2
5a28	231 ± 0.3	233 ± 0.2
6a14	212 ± 0.2	210 ± 0.3
6a15	215 ± 0.4	223 ± 0.3
6a26	220 ± 0.3	227 ± 0.2
6a27	240 ± 0.3	243 ± 0.2
6a28	238 ± 0.4	235 ± 0.3
6a30	235 ± 0.3	237 ± 0.2
Isoniazid	>450	>450
Cisplatin	1.29	9.90

[a] Cytotoxicity is expressed as IC_{50} which is the concentration of compound reduced by 50% of the optical density of treated cells with respect to untreated cells using MTT assay. Values are the means ± SEM of three independent experiments.
[b] Mammalian Vero cell-lines.
[c] A_{549} (lung adenocarcinoma) cell-lines.

4. Experimental section

All the chemicals were commercially available and used without further purification unless otherwise stated. Melting points were

Table 3
Different pharmacophore models proposed by GALAHAD.

	SPECIFICITY	N_HITS	FEATS	PARETO	ENERGY	STERICS	H_BOND	MOL_QRY
MODEL_01	4.867	7	7	0	10.94	587.80	49.70	38.82
MODEL_02	3.208	7	5	0	10.80	564.80	46.80	16.96
MODEL_03	5.265	6	6	0	12.69	588.20	44.40	21.08
MODEL_04	**4.725**	**8**	**8**	**0**	**16.25**	**873.50**	**37.70**	**20.53**
MODEL_05	4.873	8	7	0	11.44	633.40	33.00	22.09
MODEL_06	5.188	5	6	0	18.11	680.20	41.80	27.80
MODEL_07	4.871	5	7	0	16.33	608.80	57.30	20.87
MODEL_08	5.228	6	6	0	11.65	641.00	39.00	14.56
MODEL_09	5.292	7	6	0	11.69	604.10	43.90	14.08
MODEL_10	4.923	5	7	0	12.78	729.10	34.60	17.68
MODEL_11	3.497	7	7	0	9.56	406.30	36.00	20.98
MODEL_12	4.844	7	7	0	13.05	662.20	34.70	18.78
MODEL_13	5.256	7	6	0	10.63	485.30	40.70	15.93
MODEL_14	4.871	8	7	0	12.60	628.30	33.70	18.98
MODEL_15	4.649	8	8	0	16.15	510.50	53.90	21.70
MODEL_16	5.195	8	6	0	12.66	592.60	39.20	17.34
MODEL_17	4.179	4	5	0	16.53	707.50	40.70	15.56
MODEL_18	5.213	4	6	0	10.16	535.00	35.00	14.45
MODEL_19	5.178	8	6	0	9.35	460.80	36.10	15.32
MODEL_20	3.087	8	9	0	13.67	685.50	31.40	20.35
	IND_ENERGY				IND_STERICS			
MODEL_01	9.59	9.39	14.83	11.16	20,019.33	19,976.33	12,771.50	16,656.33
	1.50	9.26	12.51	9.27	12,473.50	16,048.83	19,080.67	13,015.17
MODEL_02	9.86	9.92	14.75	11.15	16,958.00	19,844.00	12,832.00	15,204.33
	9.05	9.28	11.45	10.95	16,802.67	17,526.33	19,408.67	14,098.33
MODEL_03	12.29	11.40	14.22	12.16	16,503.67	19,525.33	14,234.17	18,565.67
	9.68	8.57	14.77	18.42	17,026.33	14,823.17	18,306.00	14,373.17
MODEL_04	**9.60**	**13.27**	**25.75**	**26.58**	**24,456.67**	**27,122.33**	**13,686.83**	**22,907.67**
	9.25	**10.98**	**24.50**	**10.09**	**29,708.83**	**32,553.83**	**36,105.33**	**29,740.00**
MODEL_05	10.06	9.26	19.02	9.88	20,615.17	23,867.17	13,093.67	19,065.17
	9.31	10.82	12.73	10.46	17,680.33	20,275.83	18,547.33	14,776.00
MODEL_06	9.88	13.11	14.95	21.15	19,661.50	20,650.83	16,651.33	12,010.83
	8.82	9.00	12.20	55.81	22,507.83	22,540.33	20,959.83	18,993.83
MODEL_07	14.70	11.00	15.05	36.51	16,906.50	18,854.33	14,191.83	16,283.00
	9.01	13.40	11.89	19.09	25,921.33	25,360.83	15,583.50	16,845.33
MODEL_08	13.38	11.61	12.21	11.65	26,882.83	27,800.17	16,146.33	24,948.83
	8.75	12.24	11.49	11.86	12,390.33	8273.17	21,642.83	19,080.83
MODEL_09	10.97	11.61	14.23	10.62	23,084.33	23,861.17	14,950.33	17,396.67
	4.49	8.57	14.74	18.32	11,995.33	14,308.33	16,200.33	13,447.83
MODEL_10	13.96	17.08	16.04	9.06	19,089.33	9958.50	13,876.50	22,683.00
	9.14	10.98	16.58	9.44	27,021.17	25,655.00	31,631.17	24,205.67
MODEL_11	10.16	10.08	8.75	9.66	12,182.67	7949.50	9970.00	10,965.33
	5.02	8.97	12.96	10.86	17,491.83	16,392.33	15,607.67	12,477.83
MODEL_12	9.78	9.27	16.12	25.69	25,200.17	26,205.83	15,738.00	20,186.50
	9.16	10.99	13.46	9.95	19,875.83	22,396.83	17,742.83	14,891.33
MODEL_13	12.95	9.61	13.09	9.02	8842.17	14,404.33	13,931.50	15,245.67
	2.65	8.86	16.09	12.77	19,041.50	18,823.00	18,195.67	13,008.50
MODEL_14	10.06	9.97	12.10	20.92	19,100.50	19,828.67	15,757.17	11,617.33
	8.82	8.83	12.27	17.82	23,024.00	23,652.50	19,560.83	17,695.00
MODEL_15	9.89	18.18	15.07	36.52	17,148.33	17,977.83	12,383.83	15,685.00
	10.08	13.00	12.52	13.98	16,263.83	17,004.50	15,425.50	16,009.33
MODEL_16	12.40	11.72	12.07	14.54	14,338.00	15,656.17	12,478.83	12,913.83
	9.14	11.08	11.55	18.76	25,090.00	25,670.17	17,618.67	15,801.83
MODEL_17	12.14	37.88	12.18	25.91	23,495.17	25,461.17	16,938.83	18,967.50
	10.16	11.07	12.69	10.22	22 701.00	24,912.17	22,186.67	16,311.17
MODEL_18	8.27	9.41	15.30	11.17	13,267.83	15,502.83	10,659.83	16,547.83
	7.72	8.53	11.37	9.55	17,988.00	18,453.50	21,734.00	15,354.67
MODEL_19	11.93	10.48	5.73	9.18	12,513.83	14,580.00	13,005.67	14,509.00
	4.95	9.24	12.47	10.85	13,423.00	16,011.67	15,926.50	15,326.83
MODEL_20	13.93	10.11	13.93	22.50	14,906.67	18,149.83	13,621.83	14,431.17
	14.24	9.13	17.05	8.45	25,812.33	26,985.50	23,447.00	20,695.17
	IND_H_BOND				IND_MOL_QRY			
MODEL_01	1730.67	1997.33	1843.33	1358.67	−4.30	−4.30	−4.00	−4.30
	2431.33	2698.00	2759.33	2131.33	−3.60	−3.60	−3.50	−3.60
MODEL_02	868.67	982.00	1667.67	1028.67	−0.50	−0.50	−0.30	−0.30
	1791.67	1905.00	2570.33	1827.67	−0.60	−0.60	−0.60	−0.60
MODEL_03	1275.33	1504.67	2081.33	1327.33	−1.30	−1.30	−1.00	−1.30
	482.00	1719.00	2209.67	1282.33	−1.40	−0.60	−0.50	−0.50
MODEL_04	**572.00**	**616.00**	**991.00**	**694.00**	**−4.30**	**−4.50**	**−4.40**	**−4.00**
	1513.00	**1525.00**	**1930.33**	**1518.33**	**−3.80**	**−3.80**	**−3.80**	**−3.80**
MODEL_05	592.00	705.33	516.33	956.67	−1.40	−1.40	−1.50	−0.80

(*continued on next page*)

Table 3 (*continued*)

	SPECIFICITY	N_HITS	FEATS	PARETO	ENERGY	STERICS	H_BOND	MOL_QRY
	1594.00	1707.33	1358.33	1615.33	−0.30	−0.30	−0.70	−0.30
MODEL_06	1334.67	1601.33	701.33	305.33	−0.80	−0.80	−1.50	−1.50
	1812.00	2078.67	2201.33	1685.33	−0.30	−0.30	−0.30	−0.20
MODEL_07	1345.67	1090.67	2857.00	573.33	−2.60	−2.80	−2.50	−2.70
	1966.00	2195.33	3294.00	1124.67	−2.40	−2.40	−2.40	−2.30
MODEL_08	929.33	941.33	1635.00	1104.00	−1.20	−1.20	−1.20	−1.20
	687.33	382.67	1676.33	1171.00	−1.60	−1.70	−1.40	−1.30
MODEL_09	1158.67	1388.00	1964.67	1328.00	−2.50	−2.50	−2.20	−2.10
	493.33	1847.33	2338.00	1394.67	−2.40	−1.90	−1.80	−1.50
MODEL_10	427.33	202.67	799.67	624.33	−3.20	−2.90	−3.00	−2.90
	1540.00	1552.00	1921.33	1545.33	−2.10	−2.10	−2.10	−2.10
MODEL_11	1245.67	182.67	1706.00	529.33	−0.80	−1.10	−0.80	−1.00
	1885.33	1897.33	1801.67	1905.33	−0.20	−0.20	−0.20	−0.20
MODEL_12	658.67	764.00	1305.67	727.00	−2.20	−2.20	−2.10	−2.00
	1195.67	1309.00	1507.33	452.33	−1.20	−1.20	−1.50	−2.10
MODEL_13	178.67	190.67	1658.00	1159.00	−1.70	−1.70	−1.50	−1.20
	1891.67	1903.67	2551.67	1927.67	−0.90	−0.90	−0.90	−0.80
MODEL_14	755.33	868.67	1008.67	284.33	−1.30	−1.30	−1.30	−1.40
	1553.00	1666.33	1779.67	1453.67	−0.60	−0.60	−0.60	−0.40
MODEL_15	1203.00	1017.33	2646.33	537.33	−2.20	−2.40	−1.90	−2.30
	1788.33	2017.67	2536.67	1161.67	−1.80	−1.80	−2.10	−1.80
MODEL_16	274.33	286.33	1845.00	684.33	−1.70	−1.70	−1.30	−1.50
	1624.67	1636.67	2376.67	1179.00	−0.60	−0.60	−0.60	−0.70
MODEL_17	558.67	672.00	1856.67	868.33	−1.60	−1.60	−1.60	−1.30
	1327.67	1441.00	1966.33	399.00	−1.00	−1.00	−0.90	−1.60
MODEL_18	397.33	1230.67	1198.00	879.00	−1.70	−1.30	−1.20	−1.20
	1207.33	1764.67	850.67	1362.33	−1.00	−1.10	−1.50	−1.00
MODEL_19	662.67	570.67	1581.67	564.00	−1.30	−1.60	−1.00	−1.60
	1303.00	589.33	1557.33	1478.67	−0.90	−1.40	−1.20	−0.90
MODEL_20	660.00	762.67	931.00	342.67	−6.70	−6.80	−6.60	−7.20
	1177.00	1189.00	1505.00	1141.67	−6.50	−6.50	−6.50	−6.10

MODEL_04 given in bold was considered for the final rigid alignment of the remaining compounds.

Table 4
GALAHAD score for all aligned molecules using MODEL_04.

Compd	PMIC	ENERGY	STERICS	H_BOND	MOL_QRY	Compd	PMIC	ENERGY	STERICS	H_BOND	MOL_QRY
5a01	4.301	2.79	456.70	3.70	1.71	**6a01**	4.301	8.54	940.90	48.80	22.35
5a02	4.903	4.55	1056.50	3.70	1.71	**6a02**	5.204	8.82	1535.20	48.80	22.35
5a03	4.602	2.72	565.30	3.70	1.71	**6a03**	4.301	1.91	849.30	48.80	22.35
5a04	4.602	2.18	537.90	3.70	1.71	**6a04**	4.602	6.95	940.90	48.80	22.35
5a05	4.903	2.72	1175.50	3.70	1.71	**6a05**	5.204	3.41	1595.10	48.80	22.35
5a06	4.602	8.78	386.40	3.70	1.71	**6a06**	4.602	1.79	849.30	48.80	22.35
5a07	4.602	1.44	456.70	3.70	1.71	**6a07**	4.602	2.60	940.90	48.80	22.35
5a08	4.903	1.66	1056.50	3.70	1.71	**6a08**	4.903	2.53	1595.10	48.80	22.35
5a09	5.204	2.13	1056.50	3.70	1.71	**6a09**	5.204	13.49	1625.70	48.80	22.35
5a10	4.301	22.42	815.00	0.20	0.00	**6a10**	4.000	7.54	1982.30	68.00	22.35
5a11	4.000	4.94	1713.70	5.10	1.71	**6a11**	4.000	4.65	2389.70	73.40	22.35
5a12	5.204	9.86	1845.00	16.10	1.71	**6a12**	5.204	6.06	2647.80	156.70	22.35
5a13	4.903	8.64	1444.80	5.10	1.71	**6a13**	4.903	8.87	2041.20	68.00	22.35
5a14	5.204	14.14	236.30	0.30	0.00	**6a14**	5.505	8.33	1903.40	68.00	22.35
5a15	5.505	9.02	1387.90	5.10	1.71	**6a15**	5.505	5.45	2134.10	68.00	22.35
5a16	4.602	3.33	528.10	3.70	1.71	**6a16**	4.903	4.98	1091.30	48.80	22.35
5a17	4.602	3.35	1038.10	3.70	1.71	**6a17**	4.602	2.27	1684.90	48.80	22.35
5a18	4.602	4.11	488.50	3.70	1.71	**6a18**	4.602	1.94	1016.30	48.80	22.35
5a19	4.301	12.70	1013.00	3.70	1.71	**6a19**	4.602	9.55	3065.50	48.80	22.35
5a20	4.602	8.79	1057.70	3.70	1.71	**6a20**	4.602	6.54	1207.10	48.80	22.35
5a21	4.903	2.20	562.60	3.70	1.71	**6a21**	4.602	8.02	1310.90	48.80	22.35
5a22	4.903	9.19	702.70	4.50	1.71	**6a22**	4.903	10.49	1108.50	129.80	22.35
5a23	5.204	5.34	1389.40	63.70	1.71	**6a23**	4.903	9.23	1734.70	378.10	22.35
5a24	4.903	8.83	505.50	3.70	1.71	**6a24**	4.903	7.81	1291.00	53.30	22.35
5a25	5.204	10.51	1258.30	63.70	1.71	**6a25**	5.204	12.24	1792.40	378.10	22.35
5a26	5.505	7.80	1795.70	452.40	1.71	**6a26**	5.505	4.15	3198.50	732.20	22.35
5a27	5.505	2.42	1261.80	19.20	1.71	**6a27**	5.796	3.34	3534.80	133.20	22.35
5a28	5.505	2.73	1761.90	5.00	1.71	**6a28**	5.505	6.05	1812.10	48.80	22.35
5a29	5.204	19.73	2095.70	8.00	1.71	**6a29**	5.204	8.37	1823.50	48.80	22.35
5a30	5.204	15.91	2608.80	8.00	1.71	**6a30**	5.505	17.25	2980.30	48.80	22.35
5a31	4.000	11.42	865.60	4.50	1.71	**6a31**	4.301	5.27	1362.20	129.80	22.35
5a32	4.000	3.77	1259.20	63.70	1.71	**6a32**	4.000	5.25	994.50	378.10	22.35
5a33	4.000	3.10	589.40	3.70	1.71	**6a33**	4.000	2.98	1299.70	53.30	22.35

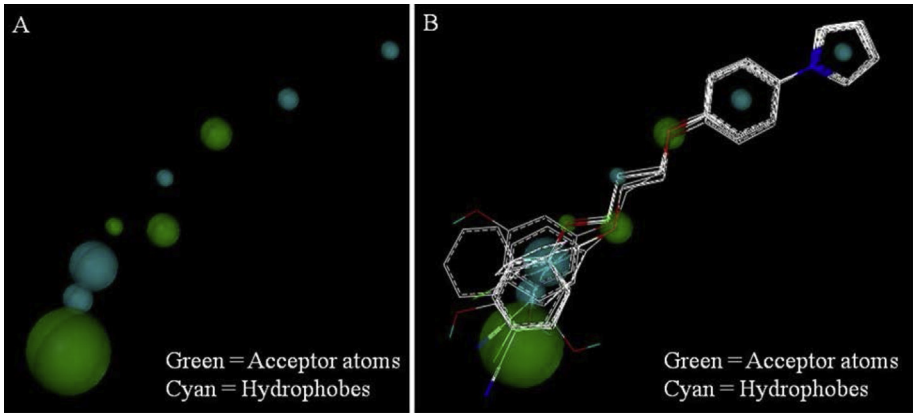


Fig. 4. A) Final selected pharmacophore model and B) molecular alignment for InhA receptor ligands (total of 8 compounds), containing acceptor atoms (green) and hydrophobes (cyan). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

determined with capillary melting point apparatus (Shital-digital) and are uncorrected. FTIR spectra were obtained on a Bruker FTIR spectrophotometer in KBr disks. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE II 400 (400 and 100 MHz, respectively) in $CDCl_3$ and DMSO-d_6 using TMS as the internal standard. The abbreviations used to describe the peak patterns are: (b) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (p) pentet and (m) multiplet. Mass spectra (MS) were recorded on a JEOL GCMATE II GC-Mass spectrometer. Elemental analysis data (performed on Leco Tru Spec CHNS Analyzer) for C, H, and N were within ±0.4% of the theoretical values. Analytical thin-layer chromatography (TLC) was performed on the pre-coated TLC sheets of silica gel 60 F_{254} (Merck, Darmstadt, Germany) visualized by long- and short-wavelength ultraviolet (UV) lamps. Chromatographic purifications were performed on Merck silica gel (70–230 mesh).

4.1. Synthesis of 4-(1H-pyrrol-1-yl)phenol (**2**)

4-Aminophenol (1.0 eq.) was added to warm glacial acetic acid (25 mL). After 15 min, 2,5-dimethoxytetrahydrofuran (1.2 eq.) was added to the mixture, refluxed for 8 h, cooled, the reaction mixture poured into ice-cold water (500 mL) and basified with Na_2CO_3 solution. The precipitated solid was filtered, washed with water, dried and recrystallized using cyclohexane (200 mL) to afford pure white crystals.

(Yield 60%). mp 116–118 °C; FTIR (KBr): 3393 (OH), 3142, 2923 (Ar–H), 1520 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 6.19 (t, 2H, J = 2.12, pyrrole-C_3 and C_4–H), 6.83, 6.85 (td, 2H, J = 2.08, 2.08, Ph-C_2 and C_6–H), 7.00 (t, 2H, J = 2.08, pyrrole-C_2 and C_5–H), 7.19, 7.22 (td, 2H, J = 2.12, 2.08, Ph-C_3 and C_5–H), 9.29 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 109.92, 116.17, 119.80, 122.46, 134.71, 153.55; MS (EI): m/z = found 159.07 [M^+]; calcd. 159.07. Anal. Calcd. For $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.01; H, 5.68; N, 8.81.

4.2. General procedure for the synthesis of 1-(4-(2 or 3-bromoethoxy/propoxy)phenyl)-1H-pyrroles (**3** or **4**)

A round-bottom flask was charged with 4-(1*H*-pyrrol-1-yl) phenol (**2**) (1.0 eq.), anhydrous K_2CO_3 (3.0 eq.) and catalytic amount

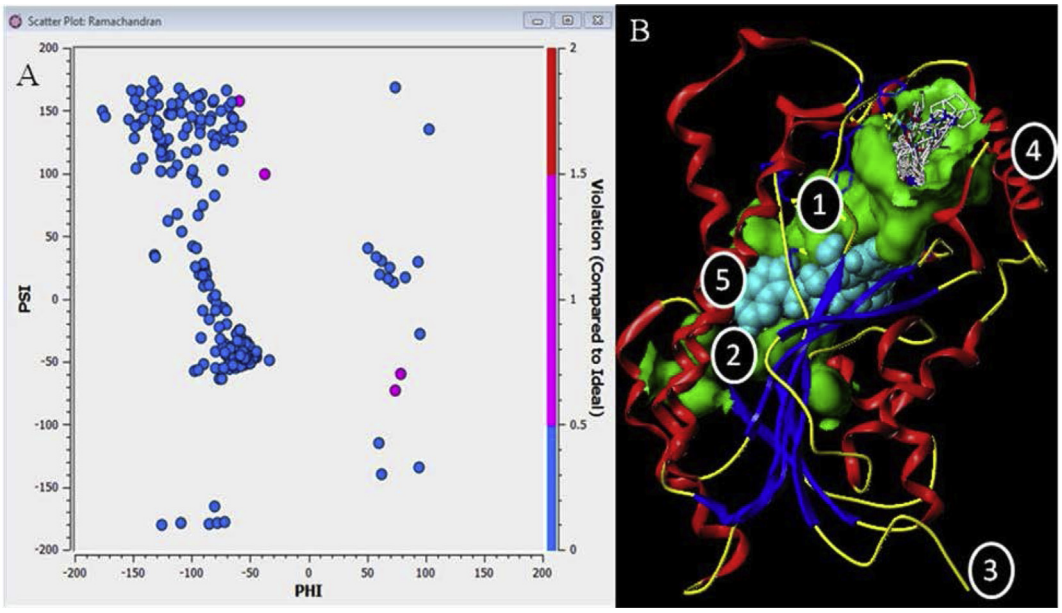


Fig. 5. A: Ramachandran scatter plot (PHI vs PSI) of ENR model; 92% of the residues were found in the most favored region; 7.5% were found in the additional allowed regions; 0.5% were found in the generously allowed regions and 0% were found in the disallowed regions; B: The X-ray crystal of InhA (PDB: 2X22, Chain A). The protein is represented by ribbon model with 1, substrate-binding domain; 2, NAD-binding domain; 3, N-terminus; 4, C-terminus; 5, the coenzyme NADH is shown in space filled model.

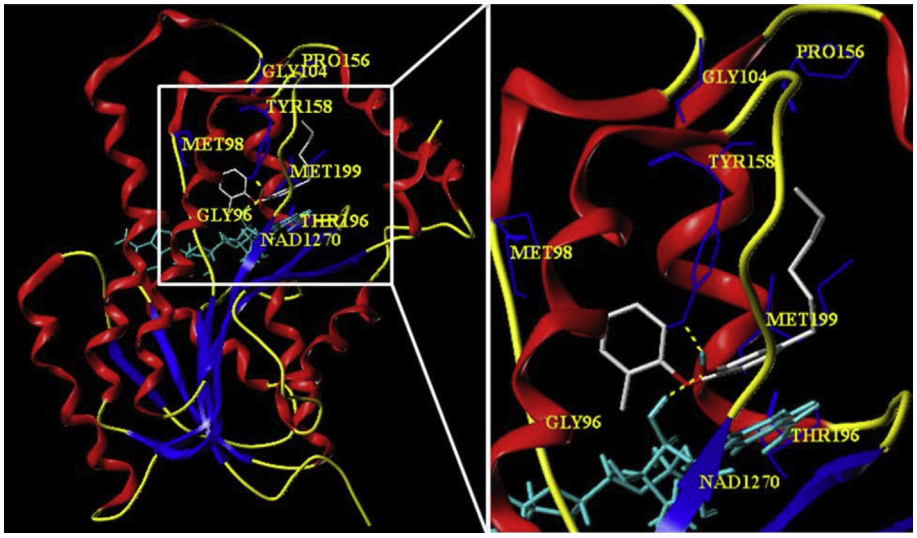


Fig. 6. Crystal structure of PT70 in a complex with InhA and H-bonds are indicated by a dashed yellow line. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of KI; the mixture were stirred for 20 min in dry acetone (25 mL) to which 1,2-dibromoethane or 1,3-dibromopropane (1.2 eq.) was added and stirred for 48 h at 80 °C and the reaction was monitored using TLC. After cooling to ambient temperature, acetone was filtered over a pad of celite and further rinsed with acetone (60 mL). The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with diethyl ether/petroleum ether (1:9) as eluent to afford the corresponding ethoxy (**3**) or propoxy (**4**) derivatives in high purity with good yields.

*4.2.1. 1-(4-(2-Bromoethoxy)phenyl)-1H-pyrrole (**3**)*

(Yield 85%). mp 72–74 °C; FTIR (KBr): 3129, 2926 (Ar–H), 1518 (C=C), 1255 (C–O–C^{asym}), 1071 (C–O–C^{sym}), 739 (C–Br) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 3.64 (t, 2H, $BrCH_2$), 4.29 (t, 2H, OCH_2), 6.32 (t, 2H, $J = 2.12$, pyrrole-C_3 and C_4–H), 6.94, 6.96 (td, 2H, $J = 2.16$, 3.44, Ph-C_2 and C_6–H), 6.99 (t, 2H, $J = 2.16$, pyrrole-C_2 and C_5–H), 7.29, 7.31 (td, 2H, $J = 2.20$, 3.44, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.08, 68.27, 110.03, 115.64, 119.65, 122.20, 135.12, 156.12; MS (EI): *m/z* = found 266.13 [M^++1]; calcd. 265.01. Anal. Calcd. For $C_{12}H_{12}BrNO$: C, 54.16; H, 4.54; N, 5.26. Found: C, 53.94; H, 4.56; N, 5.28.

*4.2.2. 1-(4-(3-Bromopropoxy)phenyl)-1H-pyrrole (**4**)*

(Yield 70%). mp 68–70 °C; FTIR (KBr): 3140, 2921 (Ar–H), 1520 (C=C), 1250 (C–O–C^{asym}), 1023 (C–O–C^{sym}), 721 (C–Br) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.31 (p, 2H, $-CH_2-$), 3.59 (t, 2H, $J = 6.44$, $BrCH_2$), 4.09 (t, 2H, $J = 5.80$, OCH_2), 6.30, 6.31 (dd, 2H, $J = 1.96$, 2.08, pyrrole-C_3 and C_4–H), 6.91–6.97 (m, 2H, Ph-C_2 and C_6–H), 6.98 (t, 2H, $J = 2.16$, pyrrole-C_2 and C_5–H), 7.26–7.30 (m, 2H, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 30.12, 32.99, 67.72, 110.06, 115.60, 117.93, 119.71, 122.18, 134.74, 156.80; MS (EI): *m/z* = found 280.23 [M^++1]; calcd. 279.03. Anal. Calcd. For $C_{13}H_{14}BrNO$: C, 55.73; H, 5.04; N, 5.00. Found: C, 55.51; H, 5.06; N, 4.98.

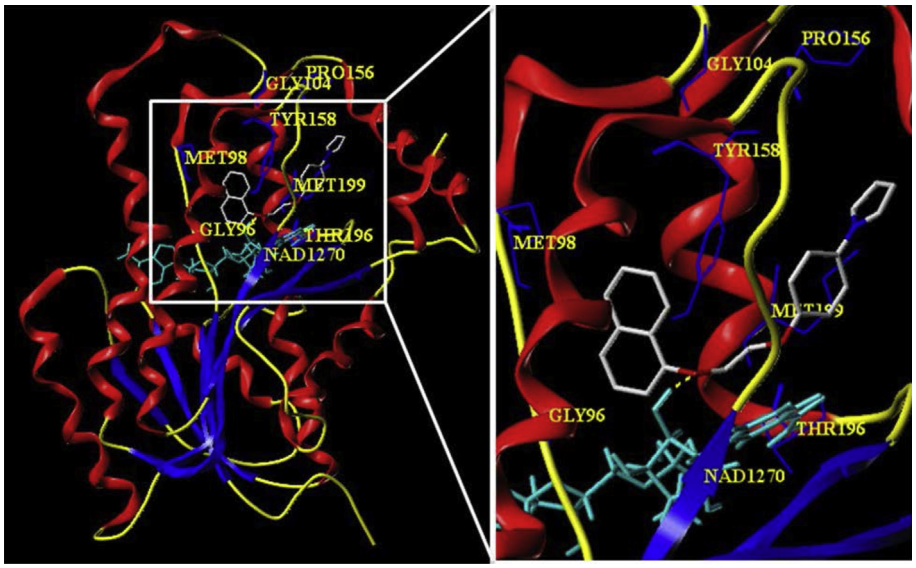


Fig. 7. Crystal structure of **6a27** in a complex with InhA and H-bond is indicated by a dashed yellow line. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

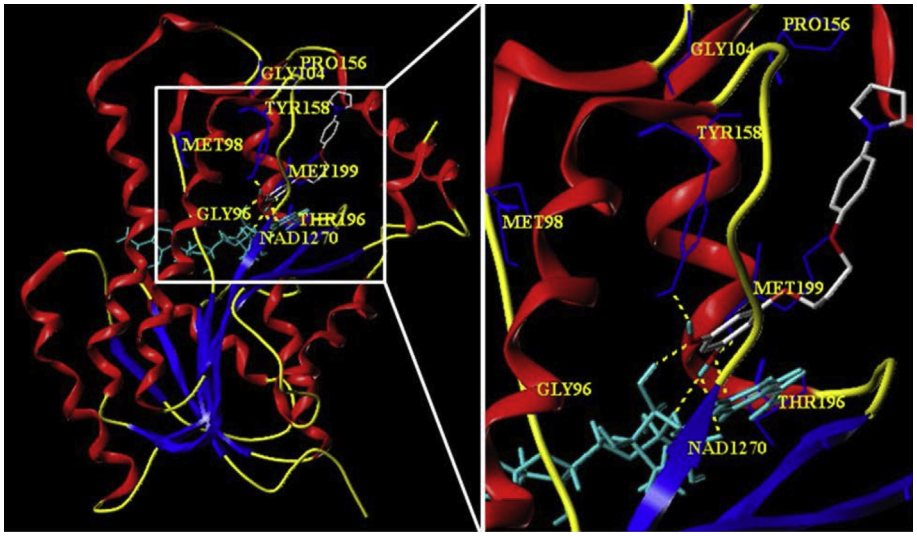


Fig. 8. Crystal structure of **6a26** in a complex with InhA and H-bonds are indicated by a dashed yellow line. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

*4.3. General procedure for the synthesis of 1-(4-(2-aryloxyethoxy) phenyl)-1H-pyrroles (**5a1**–**5a33**) or 1-(4-(3-aryloxypropoxy) phenyl)-1H-pyrroles (**6a1**–**6a33**)*

A round-bottom flask was charged with appropriate phenols (1.0 eq.), anhydrous K_2CO_3 (3.0 eq.) and a catalytic amount of KI and the mixture were stirred for 20 min in dry acetone (25 mL). To this, 1-(4-(2-bromoethoxy)phenyl)-1*H*-pyrrole (**3**) or 1-(4-(3-bromopropoxy)phenyl)-1*H*-pyrrole **(4)** (1.0 eq.) was added and stirred for 48 h at 80 °C, the reaction was monitored using TLC. After cooling to ambient temperature, acetone was filtered over a pad of celite and further rinsed with acetone (60 mL). The solvent was removed under reduced pressure and the residue was recrystallized with ethyl acetate and diethyl ether mixture (7:3) or cyclohexane to afford the corresponding diaryloxy derivatives in varying yields.

*4.3.1. 1-(4-(2-Phenoxyethoxy)phenyl)-1H-pyrrole (**5a1**)*

(Yield 87%). mp 156–158 °C; FTIR (KBr): 3143, 2931 (Ar–H), 1524 (C=C), 1238 (C–O–C^{asym}), 1068 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 4.33, 4.35 (td, 4H, J = 4.52, 4.44, $2OCH_2$), 6.26 (t, 2H, J = 2.12, pyrrole-C_3 and C_4–H), 6.93–6.97 (m, 3H, Ph-C_2, C_6–H and Ph-C_4), 7.00–7.03 (m, 4H, Ph-C_2, C_6–H at pyrrole and pyrrole-C_2 and C_5–H), 7.27–7.35 (m, 4H, Ph-C_3, C_5–H and Ph-C_3, C_5–H at pyrrole); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 66.06, 66.58, 109.76, 114.27, 115.23, 118.87, 120.60, 120.98, 129.28, 133.83, 156.02, 158.18; MS (EI): m/z = found 279.25 [M^+]; calcd. 279.13. Anal. Calcd. For $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.71; H, 6.11; N, 4.99.

*4.3.2. 1-(4-(2-(4-Chlorophenoxy)ethoxy)phenyl)-1H-pyrrole (**5a2**)*

(Yield 79%). mp 140–142 °C; FTIR (KBr): 3141, 2928 (Ar–H), 1525 (C=C), 1237 (C–O–C^{asym}), 1070 (C–O–C^{sym}), 825 (C–Cl) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.28–4.35 (m, 4H, $2OCH_2$), 6.32 (t, 2H, J = 2.12, pyrrole-C_3 and C_4–H), 6.87, 6.89 (td, 2H, J = 2.12, 3.36, Ph-C_2 and C_6–H), 6.96–7.00 (m, 4H, chloroPh-C_2, C_6–H and pyrrole-C_2 and C_5–H), 7.22–7.26 (m, 2H, chloroPh-C_3 and C_5–H) 7.30, 7.32 (td, 2H, J = 2.28, 3.00, Ph-C_3, C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$)

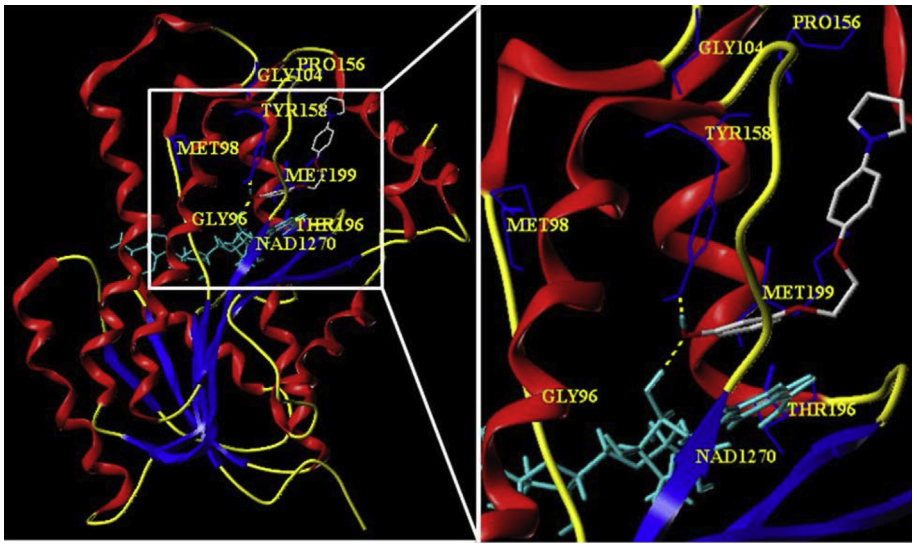


Fig. 9. Crystal structure of **5a23** in a complex with InhA and H-bonds are indicated by a dashed yellow line. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

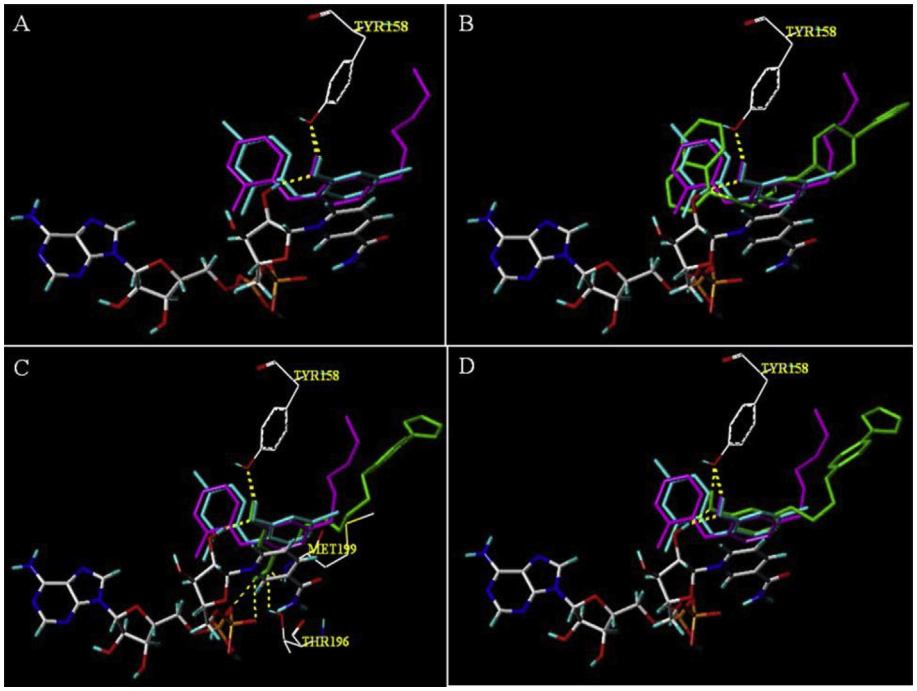


Fig. 10. Superposition of the A) PT70 (magenta), TCL (cyan) with B) **6a27**, C) **6a26**, D) **5a23** (green) at active site of InhA. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

δ ppm: 66.85, 109.97, 115.50, 116.00, 119.65, 122.15, 126.10, 129.42, 134.92, 156.60, 157.22; MS (EI): *m/z* = found 313.75 [M^+]; calcd. 313.09. Anal. Calcd. For $C_{18}H_{16}ClNO_2$: C, 68.90; H, 5.14; N, 4.46. Found: C, 69.18; H, 5.12; N, 4.48.

*4.3.3. 1-(4-(2-(3-Chlorophenoxy)ethoxy)phenyl)-1H-pyrrole (**5a3**)*

(Yield 77%). mp 138–140 °C; FTIR (KBr): 3141, 2875 (Ar–H), 1524 (C=C), 1240 (C–O–C^{asym}), 1071 (C–O–C^{sym}), 719 (C–Cl) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.35 (p, 4H, $2OCH_2$), 6.36 (t, 2H, J = 2.04, pyrrole-C_3 and C_4–H), 6.87–6.89 (m, 1H, chloroPh-C_6-H), 6.99–7.04 (m, 6H, Ph-C_2, C_6–H, chloroPh-C_2, C_6–H and pyrrole-C_2 and C_5–H), 7.28 (q, 1H, chloroPh-C_5-H) 7.34, 7.36 (dd, 2H, J = 2.08, 2.16, Ph-C_3, C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 66.76, 66.80, 109.98, 113.25, 115.12, 115.52, 119.66, 121.39, 122.16, 130.32, 134.95, 156.59, 159.33; MS (EI): *m/z* = found 313.15 [M^+]; calcd. 313.09. Anal. Calcd. For $C_{18}H_{16}ClNO_2$: C, 68.90; H, 5.14; N, 4.46. Found: C, 68.62; H, 5.16; N, 4.48.

*4.3.4. 1-(4-(2-(2-Chlorophenoxy)ethoxy)phenyl)-1H-pyrrole (**5a4**)*

(Yield 77%). mp 145–147 °C; FTIR (KBr): 3137, 2941 (Ar–H), 1516 (C=C), 1239 (C–O–C^{asym}), 1070 (C–O–C^{sym}), 733 (C–Cl) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 4.40 (s, 4H, $2OCH_2$), 6.27 (d, 2H, J = 1.44, pyrrole-C_3 and C_4–H), 6.94 (t, 1H, J = 7.64, chloroPh-C_4), 7.03–7.07 (m, 5H, chloroPh-C_6, ph-C_2, C_6–H and pyrrole-C_2, C_5–H), 7.25 (t, 1H, chloroPh-C_5) 7.32–7.37 (m, 3H, chloroPh-C_3 and Ph-C_3, C_5–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 66.59, 67.43, 109.72, 113.80, 115.36, 118.84, 121.04, 121.51, 121.87, 127.82, 129.81, 133.95, 153.69, 156.06; MS (EI): *m/z* = found 313.78 [M^+]; calcd. 313.09. Anal. Calcd. For $C_{18}H_{16}ClNO_2$: C, 68.90; H, 5.14; N, 4.46. Found: C, 68.79; H, 5.16; N, 4.47.

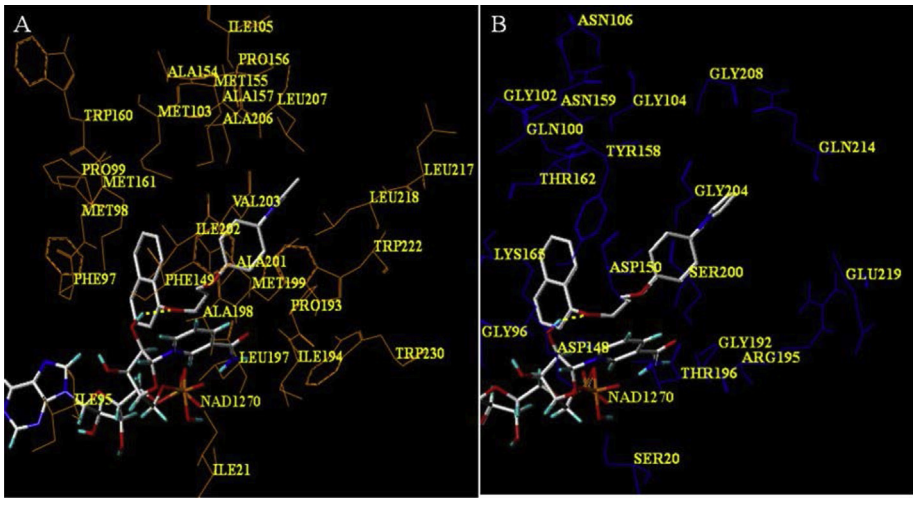


Fig. 11. A) Hydrophobic and B) hydrophilic amino acid residues of active site surrounded to **6a27**.

Table 5
Surflex-dock scores (kcal/mol) of pyrrolyl phenoxy derivatives.

Compd	C score[a]	Crash score[b]	Polar score[c]	D score[d]	PMF score[e]	G score[f]	Chem score[g]
PT70	13.54	−0.55	2.20	−356.647	−36.975	−225.068	−48.052
6a26	8.88	−1.89	2.85	−687.186	−40.517	−151.376	−43.022
6a27	8.59	−1.48	0.09	−501.676	−23.835	−211.838	−50.009
5a23	8.45	−0.84	2.12	−593.566	−50.667	−128.347	−41.474
6a20	8.27	−1.31	0.06	−515.999	−19.971	−208.209	−45.521
6a15	8.24	−1.17	0.05	−712.488	−43.748	−219.403	−45.452
6a30	8.20	−1.21	0.00	−638.570	−51.347	−219.866	−51.530
5a27	8.15	−1.34	0.01	−476.605	−27.067	−211.658	−46.745
5a26	8.02	−0.96	2.14	−685.785	−50.726	−132.902	−39.705
5a30	7.96	−1.28	0.00	−641.980	−57.915	−216.269	−50.924
5a20	7.89	−1.37	0.00	−509.127	−41.371	−218.670	−46.141
6a12	7.61	−1.08	1.13	−575.951	−47.755	−173.728	−46.704
6a29	6.88	−1.06	0.00	−588.935	−49.913	−217.666	−43.627
6a14	6.55	−1.40	0.50	−781.271	−28.345	−185.190	−47.471
5a12	6.54	−1.39	1.05	−562.662	−52.324	−208.465	−42.231
5a25	6.53	−0.82	2.18	−598.044	−38.592	−153.925	−41.917
6a21	6.48	−2.65	0.00	−541.399	−30.313	−264.035	−47.073
6a9	6.46	−1.38	0.00	−543.901	−20.407	−162.225	−37.511
6a33	6.41	−1.11	0.38	−602.340	−53.812	−236.516	−46.580
5a19	6.35	−0.35	0.00	−529.494	−74.240	−166.448	−46.385
6a31	6.34	−0.59	1.16	−628.213	−67.107	−171.774	−45.742
6a7	6.33	−1.40	0.00	−534.955	−54.635	−218.778	−45.924
6a19	6.32	−0.54	0.00	−524.786	−53.962	−183.780	−43.438
6a32	6.21	−1.25	1.30	−583.773	−40.209	−169.459	−42.910
TCL	6.17	−1.20	2.22	−322.294	−32.830	−176.909	−40.209
5a31	6.12	−1.04	1.14	−591.019	−71.675	−198.380	−41.671
6a16	6.11	−0.53	0.00	−515.080	−45.026	−160.744	−42.828
5a17	6.05	−0.31	0.00	−524.736	−75.613	−184.828	−45.101
5a9	6.04	−0.46	0.00	−571.843	−68.084	−169.150	−42.651
5a33	6.02	−1.32	0.71	−582.961	−66.871	−209.940	−41.382
5a32	6.01	−0.29	1.03	−633.877	−75.913	−145.350	−44.176
6a28	5.99	−0.66	0.00	−528.537	−44.359	−193.164	−48.946
5a22	5.97	−0.46	1.14	−624.742	−68.484	−179.632	−43.354
6a23	5.95	−0.97	2.25	−613.798	−36.762	−124.769	−42.582
5a29	5.92	−0.44	0.00	−607.934	−58.273	−192.958	−47.357
6a18	5.91	−1.59	0.77	−507.481	−35.324	−201.677	−47.386
6a24	5.88	−0.91	0.01	−602.931	−46.330	−195.100	−42.308
6a17	5.81	−1.13	0.00	−517.930	−57.358	−186.273	−40.368
5a18	5.80	−0.67	0.00	−524.262	−63.727	−185.178	−45.513
6a13	5.79	−0.97	0.47	−639.352	−31.631	−168.660	−46.314
6a25	5.79	−1.63	1.09	−636.041	−64.313	−195.096	−43.151
5a24	5.77	−1.99	0.55	−553.070	−34.522	−213.528	−44.696
5a13	5.73	−1.97	0.00	−611.893	−54.981	−214.155	−43.511
5a6	5.68	−0.54	0.00	−519.420	−65.270	−191.935	−45.480
6a22	5.66	−0.66	2.19	−586.362	−52.702	−159.829	−41.234
6a3	5.64	−0.58	0.89	−561.066	−68.694	−167.052	−45.700
6a8	5.61	−0.35	0.00	−520.905	−50.905	−161.246	−43.011
6a2	5.60	−0.80	0.70	−555.662	−49.023	−166.760	−44.122
6a5	5.59	−0.38	0.00	−517.349	−47.449	−154.983	−42.815
5a1	5.57	−0.88	0.00	−517.214	−63.274	−209.723	−40.947
6a1	5.55	−0.66	0.00	−539.315	−59.403	−180.297	−45.238
5a4	5.48	−0.47	0.08	−509.237	−65.939	−180.018	−45.187
5a28	5.45	−0.89	0.00	−479.396	−47.470	−186.385	−42.192
5a3	5.45	−0.33	0.88	−547.037	−67.034	−157.940	−44.181
5a7	5.44	−0.72	0.00	−522.813	−60.907	−196.414	−44.172
5a14	5.40	−0.82	0.01	−707.284	−49.284	−174.374	−44.590
5a15	5.39	−1.51	0.00	−751.595	−63.420	−217.026	−44.415
5a5	5.33	−1.32	0.00	−500.591	−44.065	−185.046	−39.806
5a16	5.30	−0.35	0.00	−525.192	−66.242	−172.742	−43.306
5a21	5.28	−0.66	0.00	−524.734	−75.319	−180.856	−47.034
6a6	5.26	−0.58	0.00	−548.686	−55.624	−173.063	−44.561
6a4	5.22	−1.01	0.01	−525.253	−53.910	−199.952	−46.135
5a2	5.22	−0.94	0.89	−519.826	−65.246	−188.962	−40.234
5a10	5.12	−1.12	2.16	−718.086	−52.312	−136.104	−40.377
6a10	4.99	−2.78	0.86	−713.447	−36.150	−212.885	−43.696
5a8	4.99	−0.66	0.00	−530.053	−67.575	−185.943	−44.787
6a11	4.77	−0.48	0.00	−869.990	−70.763	−180.450	−41.241
5a11	4.36	−0.512	0.00	−860.936	−77.545	−170.835	−41.003

[a] CScore (Consensus Score) integrates a number of popular scoring functions for ranking the affinity of ligands bound to the active site of a receptor and reports the output of total score.
[b] Crash-score revealing the inappropriate penetration into the binding site. Crash scores close to 0 are favorable. Negative numbers indicate penetration.

*4.3.5. 1-(4-(2-(4-Bromophenoxy)ethoxy)phenyl)-1H-pyrrole (**5a5**)*

(Yield 80%). mp 168–170 °C; FTIR (KBr): 3141, 2929 (Ar–H), 1525 (C=C), 1237 (C–O–C^{asym}), 1070 (C–O–C^{sym}), 824 (C–Br) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 4.31–4.36 (m, 4H, $2OCH_2$), 6.22 (t, 2H, J = 2.12, pyrrole-C_3 and C_4–H), 6.93, 6.94, (dd, 2H, J = 2.16, 2.16, bromoPh-C_2 and C_6–H), 7.03, 7.04 (dd, 2H, J = 2.16, 2.12, Ph-C_2 and C_6–H), 7.13 (t, 2H, J = 2.16, pyrrole-C_2 and C_5–H), 7.40–7.43 (m, 4H, bromoPh-C_3, C_5–H and Ph-C_3, C_5–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 66.43, 109.70, 112.33, 115.16, 116.33, 118.81, 121.07, 131.84, 133.94, 155.99, 157.41; MS (EI): m/z = found 358.22 [M^++1]; calcd. 357.04. Anal. Calcd. For $C_{18}H_{16}BrNO_2$: C, 60.35; H, 4.50; N, 3.91. Found: C, 60.59; H, 4.52; N, 3.89.

*4.3.6. 1-(4-(2-(3-Bromophenoxy)ethoxy)phenyl)-1H-pyrrole (**5a6**)*

(Yield 80%). mp 142–144 °C; FTIR (KBr): 3141, 2928 (Ar–H), 1524 (C=C), 1238 (C–O–C^{asym}), 1071 (C–O–C^{sym}), 719 (C–Br) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.33–4.38 (m, 4H, $2OCH_2$), 6.35 (t, 2H, J = 2.12, pyrrole-C_3 and C_4–H), 6.91–6.93 (m, 1H, bromoPh-C_6-H), 7.01–7.04 (m, 4H, Ph-C_2,C_6–H and pyrrole-C_2, C_5–H), 7.13–7.21 (m, 3H, bromoPh-C_2, C_4 and C_5–H), 7.34, 7.36 (dd, 2H, J = 2.20, 2.16, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 66.76, 66.78, 109.99, 113.76, 115.51, 117.99, 119.66, 122.16, 122.87, 124.32, 130.66, 134.93, 156.58, 159.38; MS (EI): m/z = found 358.24 [M^++1]; calcd. 357.04. Anal. Calcd. For $C_{18}H_{16}BrNO_2$: C, 60.35; H, 4.50; N, 3.91. Found: C, 60.59; H, 4.48; N, 3.89.

*4.3.7. 1-(4-(2-(2-Bromophenoxy)ethoxy)phenyl)-1H-pyrrole (**5a7**)*

(Yield 79%). mp 133–135 °C; FTIR (KBr): 3131, 2937 (Ar–H), 1515 (C=C), 1241 (C–O–C^{asym}), 1068 (C–O–C^{sym}), 732 (C–Br) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.35–4.40 (m, 4H, $2OCH_2$), 6.30–6.32 (m, 2H, pyrrole-C_3 and C_4–H), 6.85, 6.87, 6.89 (dt, 1H, J = 1.40, 0.92, 1.36, bromoPh-C_6-H), 6.96–7.04 (m, 5H, bromoPh-C_4-H, Ph-C_2,C_6–H and pyrrole-C_2, C_5–H), 7.23–7.33 (m, 3H, bromoPh-C_5 and Ph-C_3, C_5–H), 7.54, 7.56 (dd, 1H, J = 1.60, 1.52, bromoPh-C_3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 67.00, 68.03, 109.87, 109.96, 110.00, 112.65, 114.08, 115.56, 115.76, 116.13, 119.69, 122.17, 122.40, 122.58, 128.52, 133.57, 134.95, 155.18, 156.72; MS (EI): m/z = found 358.22 [M^++1]; calcd. 357.04. Anal. Calcd. For $C_{18}H_{16}BrNO_2$: C, 60.35; H, 4.50; N, 3.91. Found: C, 60.43; H, 4.48; N, 3.93.

*4.3.8. 1-(4-(2-(4-Iodophenoxy)ethoxy)phenyl)-1H-pyrrole (**5a8**)*

(Yield 67%). mp 173–175 °C; FTIR (KBr): 3141, 2929 (Ar–H), 1522 (C=C), 1238 (C–O–C^{asym}), 1069 (C–O–C^{sym}), 719 (C–I) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 4.30–4.41 (m, 4H, $2OCH_2$), 6.22 (t, 2H, J = 1.84, pyrrole-C_3 and C_4–H), 6.80–6.83 (m, 2H, iodoPh-C_2 and C_6–H), 7.01–7.07 (m, 2H, Ph-C_2 and C_6–H), 7.09–7.15 (m, 2H, pyrrole-C_2 and C_5–H), 7.37–7.41 (m, 2H, Ph-C_3 and C_5–H), 7.56–7.58 (dd, 2H, J = 1.96, 1.92, iodoPh-C_3 and C_5–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 66.36, 66.46, 82.83, 109.34, 109.72, 115.22, 117.00, 118.83, 121.05, 121.24, 134.60, 137.78, 156.85, 158.70; MS (EI): m/z = found 405.02 [M^+]; calcd. 405.02. Anal. Calcd. For $C_{18}H_{16}INO_2$: C, 53.35; H, 3.98; N, 3.46. Found: C, 53.56; H, 4.00; N, 3.47.

[c] Polar indicating the contribution of polar interactions to the total score.
[d] D-score for charge and van der Waals interactions between the protein and the ligand (work of Kuntz) [50].
[e] PMF-score indicating Helmholtz free energies of interactions for protein–ligand atom pairs (Potential of Mean Force, PMF) (work of Muegge and Martin) [51].
[f] G-score showing hydrogen bonding, complex (ligand-protein), and internal (ligand–ligand) energies (work of Willett's group) [52].
[g] Chem-score points for H-bonding, lipophilic contact, and rotational entropy, along with an intercept term (work of Eldridge, Murray, Auton, Paolini, and Mee) [53].

*4.3.9. 1-(4-(2-(4-Fluorophenoxy)ethoxy)phenyl)-1H-pyrrole (**5a9**)*

(Yield 70%). mp 139–141 °C; FTIR (KBr): 3142, 2929 (Ar–H), 1514 (C=C), 1231 (C–O–C^{asym}), 1071 (C–O–C^{sym}), 828 (C–F) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 4.30 (q, 4H, $2OCH_2$), 6.20 (t, 2H, $J = 2.12$, pyrrole-C_3 and C_4–H), 6.91–6.95 (m, 2H, Ph-C_2 and C_6–H), 6.99–7.03 (m, 4H, fluoroPh-C_2, C_3, C_5 and C_6–H), 7.08 (t, 2H, $J = 2.08$, pyrrole-C_2 and C_5–H), 7.35, 7.38 (dd, 2H, $J = 3.32, 1.84$, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 66.57, 66.81, 109.75, 115.22, 115.43, 115.49, 115.57, 115.66, 118.85, 121.01, 133.88, 154.49, 155.45, 156.02, 157.80; MS (EI): *m/z* = found 297.25 [M^+]; calcd. 297.12. Anal. Calcd. For $C_{18}H_{16}FNO_2$: C, 72.71; H, 5.42; N, 4.71. Found: C, 72.42; H, 5.44; N, 4.73.

*4.3.10. 1-(4-(2-(4-Nitrophenoxy)ethoxy)phenyl)-1H-pyrrole (**5a10**)*

(Yield 65%). mp 98–100 °C; FTIR (KBr): 3107, 2929 (Ar–H), 1594 (NO_2^{asym}), 1515 (C=C), 1332 (NO_2^{sym}), 1249 (C–O–C^{asym}), 1067 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.38–4.46 (m, 4H, $2OCH_2$), 6.37 (t, 2H, $J = 2.00$, pyrrole-C_3 and C_4–H), 6.94–7.06 (m, 6H, Ph-C_2, C_6–H, nitroPh-C_2, C_6–H and pyrrole-C_2 and C_5–H), 7.32–7.42 (m, 2H, Ph-C_3 and C_5–H), 8.23, 8.25 (td, 2H, $J = 3.40, 3.40$, nitroPh-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 66.59, 66.99, 110.83, 115.36, 115.45, 115.52, 115.69, 118.89, 122.31, 125.98, 126.19, 134.22, 141.85, 156.65, 163.65; MS (EI): *m/z* = found 324.51 [M^+]; calcd. 324.11. Anal. Calcd. For $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.39; H, 4.99; N, 8.61.

*4.3.11. 1-(4-(2-(2,4-Dinitrophenoxy)ethoxy)phenyl)-1H-pyrrole (**5a11**)*

(Yield 65%). mp 104–106 °C; FTIR (KBr): 3143, 2918 (Ar–H), 1559 (NO_2^{asym}), 1523 (C=C), 1330 (NO_2^{sym}), 1246 (C–O–C^{asym}), 1069 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 4.35–4.45 (m, 4H, $2OCH_2$), 6.33 (t, 2H, $J = 2.04$, pyrrole-C_3 and C_4–H), 6.93–6.97 (m, 2H, Ph-C_2 and C_6–H), 6.98 (t, 2H, $J = 2.12$, pyrrole-C_2 and C_5–H), 7.20–724 (m, 1H, nitroph-C_6-H), 7.27–7.33 (m, 2H, ph-C_3 and C_5–H), 8.35–8.64 (m, 2H, nitroPh-C_3 and C_5–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 66.55, 66.89, 110.81, 114.23, 115.43, 115.50, 115.63, 118.72, 122.34, 126.03, 132.18, 139.50, 141.85, 156.65, 158.23; MS (EI): *m/z* = found 369.36 [M^+]; calcd. 369.10. Anal. Calcd. For $C_{18}H_{15}N_3O_6$: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.31; H, 4.07; N, 11.33.

*4.3.12. 4-(2-(4-(1H-Pyrrol-1-yl)phenoxy)ethoxy)benzonitrile (**5a12**)*

(Yield 75%). mp 108–110 °C; FTIR (KBr): 3139, 2945 (Ar–H), 2221 (CN), 1603 (C=C), 1252 (C–O–C^{asym}), 1068 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.24–4.34 (m, 4H, $2OCH_2$), 6.23 (t, 2H, $J = 2.04$, pyrrole-C_3 and C_4–H), 6.87–6.95 (m, 6H, Ph-C_2, C_6–H, nitrileph-C_2, C_6–H and pyrrole-C_2, C_5–H) 7.20–7.25 (m, 2H, ph-C_3 and C_5–H), 7.49, 7.50 (dd, 2H, $J = 2.60, 1.84$, nitrile Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 66.62, 66.86, 104.32, 109.83, 115.42, 115.61, 119.16, 121.75, 134.11, 134.21, 156.43, 161.96; MS (EI): *m/z* = found 304.23 [M^+]; calcd. 304.12. Anal. Calcd. For $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.68; H, 5.28; N, 9.24.

*4.3.13. 4-(2-(4-(1H-Pyrrol-1-yl)phenoxy)ethoxy)benzaldehyde (**5a13**)*

(Yield 60%). mp 146–148 °C; FTIR (KBr): 3142, 2923 (Ar–H), 1678 (C=O), 1523 (C=C), 1243 (C–O–C^{asym}), 1070 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.32–4.43 (m, 4H, $2OCH_2$), 6.32 (t, $J = 1.96$, 2H, pyrrole-C_3 and C_4–H), 6.92–7.08 (m, 6H, Ph-C_2, C_6–H, pyrrole-C_2, C_5–H and aldehyde ph-C_2, C_6–H), 7.30–7.33 (m, 2H, ph-C_3 and C_5–H), 7.50–7.52 (d, 2H, $J = 8.68$, aldehyde Ph-C_3 and C_5–H), 9.90 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 66.45, 66.83, 109.77, 114.81, 115.25, 118.88, 120.96, 126.12, 129.97, 131.25, 132.52, 156.51, 168.33, 190.12; MS (EI): *m/z* = found 307.52 [M^+]; calcd. 307.12. Anal. Calcd. For $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.55; H, 5.60; N, 4.58.

*4.3.14. 4-(2-(4-(1H-Pyrrol-1-yl)phenoxy)ethoxy)-3-methoxybenzaldehyde (**5a14**)*

(Yield 60%). mp 152–154 °C; FTIR (KBr): 3143, 2925 (Ar–H), 1680 (C=O), 1522 (C=C), 1260 (C–O–C^{asym}), 1070 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 3.87 (s, 3H, OCH_3), 4.36–4.47 (m, 4H, $2OCH_2$), 6.23, 6.22 (dd, 2H, $J = 2.68, 2.16$, pyrrole-C_3 and C_4–H), 7.04–7.21 (m, 6H, Ph-C_2, C_6–H, pyrrole-C_2, C_5–H and aldehyde ph-C_3, C_6–H), 7.39–7.42 (m, 2H, ph-C_3 and C_5–H), 7.51–7.54 (m, 1H, aldehyde Ph-C_5-H), 9.84 (s, 1H, CHO); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 56.10, 66.40, 66.73, 109.29, 109.32, 109.40, 112.37, 115.57, 115.63, 118.77, 118.89, 124.03, 126.56, 126.26, 129.96, 133.00, 151.67, 155.33, 156.69, 190.10; MS (EI): *m/z* = found 337.52 [M^+]; calcd. 337.13. Anal. Calcd. For $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.48; H, 5.70; N, 4.17.

*4.3.15. 4-(2-(4-(1H-Pyrrol-1-yl)phenoxy)ethoxy)-3-ethoxybenzaldehyde (**5a15**)*

(Yield 58%). mp 148–150 °C; FTIR (KBr): 2922 (Ar–H), 1601 (C=O), 1522 (C=C), 1243 (C–O–C^{asym}), 1070 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 1.67 (s, 3H, $OCH_2\underline{CH}_3$), 3.24–3.25 (m, 2H, $O\underline{CH}_2CH_3$), 4.09–4.42 (m, 4H, $2OCH_2$), 6.22, 6.23 (dd, 2H, $J = 2.16, \underline{2}.12$, pyrrole-$C_3$ and C_4–H), 6.83–7.28 (m, 6H, Ph-C_2, C_6–H, pyrrole-C_2, C_5–H and aldehyde ph-C_3, C_6–H), 7.43–7.55 (m, 3H, ph-C_3, C_5–H and aldehyde Ph-C_5-H), 9.82 (s, 1H, CHO); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 15.18, 64.91, 67.43, 68.52, 109.83, 110.56, 112.35, 113.58, 115.16, 115.89, 118.35, 118.89, 122.51, 126.26, 126.37, 129.95, 133.08, 150.20, 155.65, 156.74, 190.09; MS (EI): *m/z* = found 351.33 [M^+]; calcd. 351.15. Anal. Calcd. For $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.49; H, 6.04; N, 3.97.

*4.3.16. 1-(4-(2-(4-Tolyloxy)ethoxy)phenyl)-1H-pyrrole (**5a16**)*

(Yield 83%). mp 176–178 °C; FTIR (KBr): 3143, 2927 (Ar–H), 1519 (C=C), 1235 (C–O–C^{asym}), 1072 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.29 (s, 3H, CH_3), 4.29–4.36 (m, 4H, $2OCH_2$), 6.32 (t, 2H, $J = 2.00$, pyrrole-C_3 and C_4–H), 6.87, (d, 2H, $J = 8.56$, methylPh-C_2 and C_6–H), 6.98–7.00 (m, 4H, Ph-C_2, C_6–H and pyrrole-C_2, C_5–H), 7.10 (d, 2H, $J = 8.20$, methylPh-C_3 and C_5–H) 7.30–7.33 (m, 2H, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 20.06, 66.14, 66.62, 109.73, 114.11, 115.20, 118.85, 121.00, 129.35, 129.62, 133.84, 156.06; MS (EI): *m/z* = found 293.35 [M^+]; calcd. 293.14. Anal. Calcd. For $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.48; H, 6.50; N, 4.75.

*4.3.17. 1-(4-(2-(3-Tolyloxy)ethoxy)phenyl)-1H-pyrrole (**5a17**)*

(Yield 80%). mp 151–153 °C; FTIR (KBr): 3142, 2928 (Ar–H), 1525 (C=C), 1244 (C–O–C^{asym}), 1070 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.33 (s, 3H, CH_3), 4.30–4.34 (m, 4H, $2OCH_2$), 6.32 (t, 2H, $J = 2.20$, pyrrole-C_3 and C_4–H), 6.75–6.80 (m, 3H, methylPh-C_2, C_4 and C_6–H), 6.97–7.01 (m, 4H, Ph-C_2, C_6–H and pyrrole-C_2, C_5–H), 7.18 (t, 1H, $J = 7.56$, methylPh-C_5-H), 7.28–7.33 (m, 2H, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 21.11, 65.98, 66.61, 109.77, 111.28, 114.97, 115.24, 118.88, 120.96, 121.39, 129.03, 133.82, 138.86, 156.02, 158.20; MS (EI): *m/z* = found 293.35 [M^+]; calcd. 293.14. Anal. Calcd. For $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 78.10; H, 6.50; N, 4.79.

*4.3.18. 1-(4-(2-(2-Tolyloxy)ethoxy)phenyl)-1H-pyrrole (**5a18**)*

(Yield 80%). mp 123–125 °C; FTIR (KBr): 3142, 2936 (Ar–H), 1517 (C=C), 1235 (C–O–C^{asym}), 1071 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.22 (s, 3H, CH_3), 4.32–4.38 (m, 4H,

2OCH$_2$), 6.32 (t, 2H, J = 2.12, pyrrole-C$_3$ and C$_4$–H), 6.89 (t, 2H, J = 7.52, methylPh-C$_5$ and C$_6$–H), 6.99–7.03 (m, 4H, Ph-C$_2$, C$_6$–H and pyrrole-C$_2$, C$_5$–H), 7.16 (t, 2H, J = 8.16, methylPh-C$_3$ and C$_4$–H), 7.30, 7.32 (td, 2H, J = 3.40, 3.28, Ph-C$_3$ and C$_5$–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 15.87 66.45, 66.71, 109.69, 111.17, 115.26, 118.83, 120.36, 121.08, 126.56, 130.26, 133.89, 156.21, 156.27; MS (EI): m/z = found 293.35 [M$^+$]; calcd. 293.14. Anal. Calcd. For $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 78.10; H, 6.56; N, 4.79.

4.3.19. 1-(4-(2-(3,5-Dimethylphenoxy)ethoxy)phenyl)-1H-pyrrole (**5a19**)

(Yield 72%). mp 140–142 °C; FTIR (KBr): 2921 (Ar–H), 1514 (C=C), 1239 (C–O–C^{asym}), 1071 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 2.20–2.25 (m, 6H, 2CH$_3$), 4.09–4.17 (m, 4H, 2OCH$_2$), 6.31 (t, 2H, J = 2.16, pyrrole-C$_3$ and C$_4$–H), 6.53 (s, 2H, methylPh-C$_2$ and C$_6$–H), 6.57 (s, 1H, methylph-C$_4$-H), 6.91–6.95 (m, 2H, ph-C$_2$ and C$_6$–H), 6.97 (t, 2H, J = 2.12, pyrrole-C$_2$ and C$_5$–H), 7.25–7.28 (m, 2H, Ph-C$_3$ and C$_5$–H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 21.40, 67.09, 67.89, 109.27, 112.55, 115.28, 119.57, 122.14, 122.49, 134.51, 139.09, 156.89, 158.90; MS (EI): m/z = found 307.51 [M$^+$]; calcd. 307.16. Anal. Calcd. For $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.46; H, 6.92; N, 4.58.

4.3.20. 1-(4-(2-(2,5-Dimethylphenoxy)ethoxy)phenyl)-1H-pyrrole (**5a20**)

(Yield 75%). mp 141–143 °C; FTIR (KBr): 3142, 2925 (Ar–H), 1521 (C=C), 1260 (C–O–C^{asym}), 1073 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 2.17 (s, 3H, CH$_3$ at C$_2$ position), 2.32 (s, 3H, CH$_3$ at C$_5$ position), 4.33–4.36 (m, 4H, 2OCH$_2$), 6.32, 6.33 (dd, 2H, J = 1.44, 2.08, pyrrole-C$_3$ and C$_4$–H), 6.69–6.71 (m, 2H, methylPh-C$_4$ and C$_6$–H), 7.00–7.03 (m, 5H, ph-C$_2$, C$_4$–H, pyrrole-C$_2$, C$_5$–H and methylph-C$_3$-H), 7.30–7.33 (m, 2H, Ph-C$_3$ and C$_5$–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 15.84, 21.41, 66.83, 67.20, 109.93, 112.58, 115.61, 119.70, 121.49, 122.18, 124.04, 130.58, 134.83, 136.59, 156.66, 156.90; MS (EI): m/z = found 307.15 [M$^+$]; calcd. 307.16. Anal. Calcd. For $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.46; H, 6.92; N, 4.54.

4.3.21. 1-(4-(2-(2,4-Dimethylphenoxy)ethoxy)phenyl)-1H-pyrrole (**5a21**)

(Yield 70%). mp 98–100 °C; FTIR (KBr): 3132, 2924 (Ar–H), 1515 (C=C), 1245 (C–O–C^{asym}), 1072 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.12 (s, 3H, CH$_3$ at C$_2$ position), 2.21 (s, 3H, CH$_3$ at C$_4$ position), 4.26–4.35 (m, 4H, 2OCH$_2$), 6.21 (t, 2H, J = 2.08, pyrrole-C$_3$ and C$_4$–H), 6.83 (d, 1H, J = 8.76, methylPh-C$_6$-H), 6.93 (d, 2H, J = 5.52, methylph-C$_3$ and C$_5$–H), 7.03–7.07 (m, 2H, ph-C$_2$ and C$_6$–H), 7.15 (t, 2H, J = 2.36, pyrrole-C$_2$ and C$_5$–H), 7.40–7.43 (m, 2H, Ph-C$_3$ and C$_5$–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 16.17, 20.48, 67.15, 67.22, 109.91, 109.98, 111.76, 115.55, 115.60, 119.69, 122.17, 126.98, 127.06, 130.23, 131.68, 134.81, 154.69, 156.90; MS (EI): m/z = found 307.10 [M$^+$]; calcd. 307.16. Anal. Calcd. For $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.84; H, 6.86; N, 4.54.

4.3.22. 4-(2-(4-(1H-Pyrrol-1-yl)phenoxy)ethoxy)phenol (**5a22**)

(Yield 65%). mp 148–150 °C; FTIR (KBr): 3423 (OH), 3143, 2927 (Ar–H), 1520 (C=C), 1239 (C–O–C^{asym}), 1070 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 4.27–4.49 (m, 4H, 2OCH$_2$), 5.76 (s, 1H, OH), 6.33–6.37 (m, 2H, pyrrole-C$_3$ and C$_4$–H), 6.78–7.09 (m, 8H, Phenol-C$_2$, C$_3$, C$_5$, C$_6$–H, Ph-C$_2$, C$_6$–H and pyrrole-C$_2$, C$_5$–H), 7.31–7.38 (m, 2H, Ph-C$_3$ and C$_5$–H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 68.65, 69.10, 109.88, 110.00, 110.48, 113.23, 115.56, 116.29, 119.63, 119.69, 121.82, 122.45, 132.00, 155.67, 156.01, 156.67; MS (EI): m/z = found 295.10 [M$^+$]; calcd. 295.12. Anal. Calcd. For $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.91; H, 5.78; N, 4.76.

4.3.23. 3-(2-(4-(1H-Pyrrol-1-yl)phenoxy)ethoxy)phenol (**5a23**)

(Yield 60%). mp 146–148 °C; FTIR (KBr): 3311 (OH), 2930 (Ar–H), 1601 (C=C), 1245 (C–O–C^{asym}), 1070 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 4.22–4.35 (m, 4H, 2OCH$_2$), 6.31 (t, 2H, J = 2.16, pyrrole-C$_3$ and C$_4$–H), 6.37–7.26 (m, 8H, Phenol-C$_2$, C$_4$, C$_5$, C$_6$–H, Ph-C$_2$, C$_6$–H and pyrrole-C$_2$, C$_5$–H), 7.35–7.37 (m, 2H, Ph-C$_3$ and C$_5$–H), 9.04 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 66.00, 66.58, 102.50, 106.17, 108.11, 109.80, 110.00, 110.17, 113.21, 115.23, 115.85, 120.90, 121.21, 129.44, 130.14, 133.83, 156.04, 158.31, 159.40; MS (EI): m/z = found 295.17 [M$^+$]; calcd. 295.12. Anal. Calcd. For $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.49; H, 5.82; N, 4.76.

4.3.24. 2-(2-(4-(1H-Pyrrol-1-yl)phenoxy)ethoxy)phenol (**5a24**)

(Yield 65%). mp 153–155 °C; FTIR (KBr): 3425 (OH), 3142, 2926 (Ar–H), 1521 (C=C), 1240 (C–O–C^{asym}), 1070 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 4.23–4.36 (m, 4H, 2OCH$_2$), 5.75 (s, 1H, OH), 6.32 (t, 2H, J = 2.12, pyrrole-C$_3$ and C$_4$–H), 6.96–7.02 (m, 8H, Phenol-C$_3$, C$_4$, C$_5$, C$_6$–H, Ph-C$_2$, C$_6$–H and pyrrole-C$_2$, C$_5$–H), 7.26–7.33 (m, 2H, Ph-C$_3$ and C$_5$–H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 65.68, 67.89, 109.08, 113.84, 114.47, 116.2, 117.53, 118.08, 119.89, 120.19, 120.38, 131.79, 133.20, 144.72, 145.43, 147.43, 155.13; MS (EI): m/z = found 295.21 [M$^+$]; calcd. 295.12. Anal. Calcd. For $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.49; H, 5.82; N, 4.76.

4.3.25. 5-(2-(4-(1H-Pyrrol-1-yl)phenoxy)ethoxy)-2-chlorophenol (**5a25**)

(Yield 60%). mp 92–94 °C; FTIR (KBr): 3320 (OH), 2930 (Ar–H), 1601 (C=C), 1243 (C–O–C^{asym}), 1070 (C–O–C^{sym}), 721 (C–Cl) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 4.31–4.39 (m, 4H, 2OCH$_2$), 6.32, 6.33 (dd, 2H, J = 2.28, 2.20, pyrrole-C$_3$ and C$_4$–H), 6.51–7.25 (m, 7H, Phenol-C$_2$, C$_5$, C$_6$–H, Ph-C$_2$, C$_6$–H and pyrrole-C$_2$, C$_5$–H), 7.25–7.33 (m, 2H, Ph-C$_3$ and C$_5$–H), 9.54 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 66.48, 66.60, 102.00, 109.39, 110.13, 113.56, 115.81, 117.62, 118.53, 120.58, 121.22, 129.75, 132.35, 154.24, 155.27, 156.08; MS (EI): m/z = found 329.11 [M$^+$]; calcd. 329.08. Anal. Calcd. For $C_{18}H_{16}ClNO_3$: C, 65.56; H, 4.89; N, 4.25. Found: C, 65.82; H, 4.91; N, 4.23.

4.3.26. 5-(2-(4-(1H-Pyrrol-1-yl)phenoxy)ethoxy)benzene-1,3-diol (**5a26**)

(Yield 60%). mp 138–140 °C; FTIR (KBr): 3429 (OH), 3143, 2930 (Ar–H), 1518 (C=C), 1241 (C–O–C^{asym}), 1069 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 4.27–4.49 (m, 4H, 2OCH$_2$), 6.10 (s, 2H, 2OH), 6.16 (s, 1H, phenol-C$_4$-H), 6.27–6.31 (m, 2H, pyrrole-C$_3$ and C$_4$–H), 6.87–6.95 (m, 3H, Ph-C$_2$, C$_6$–H and phenol-C$_2$-H), 6.99–7.02 (m, 2H, pyrrole-C$_2$ and C$_5$–H), 7.21–7.34 (m, 3H, Ph-C$_3$, C$_5$–H and phenol-C$_6$-H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 68.65, 69.10, 90.03, 92.11, 97.21, 107.23, 113.15, 113.88, 118.01, 118.26, 119.54, 119.91, 132.01, 154.26, 154.49, 155.55, 158.03; MS (EI): m/z = found 311.25 [M$^+$]; calcd. 311.12. Anal. Calcd. For $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.16; H, 5.48; N, 4.48.

4.3.27. 1-(4-(2-(Naphthalen-1-yloxy)ethoxy)phenyl)-1H-pyrrole (**5a27**)

(Yield 65%). mp 140–142 °C; FTIR (KBr): 3143, 2945 (Ar–H), 1523 (C=C), 1262 (C–O–C^{asym}), 1072 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 4.46–4.51 (m, 4H, 2OCH$_2$), 6.32, 6.33 (dd, 2H, J = 1.96, 2.16, pyrrole-C$_3$ and C$_4$–H), 6.87 (d, 1H, J = 6.88, naphthyl-C$_2$-H), 6.97–7.05 (m, 4H, Ph-C$_2$, C$_6$–H and pyrrole-C$_2$, C$_5$–H), 7.30–7.50 (m, 6H, Ph-C$_3$, C$_5$–H and naphthyl-C$_3$, C$_4$,C$_6$,

C_7–H), 7.80 (d, 1H, J = 7.36, naphthyl-C_5-H), 8.27 (d, 1H, J = 7.16, naphthyl-C_8-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 66.94, 67.08, 105.06, 109.96, 110.47, 115.55, 115.67, 119.60, 119.70, 120.83, 122.11, 122.16, 122.22, 125.31, 125.72, 126.53, 127.47, 134.58, 134.92, 154.43, 156.87; MS (EI): m/z = found 329.14 [M^+]; calcd. 329.14. Anal. Calcd. For $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 79.90; H, 5.79; N, 4.27.

4.3.28. 1-(4-(2-(Naphthalen-2-yloxy)ethoxy)phenyl)-1H-pyrrole (**5a28**)

(Yield 65%). mp 143–145 °C; FTIR (KBr): 2920 (Ar–H), 1517 (C=C), 1253 (C–O–C^{asym}), 1070 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.36–4.53 (m, 4H, 2OCH_2), 6.32 (t, 2H, J = 2.04, pyrrole-C_3 and C_4–H), 6.92–7.05 (m, 4H, Ph-C_2, C_6–H and pyrrole-C_2, C_5–H), 7.19–7.25 (m, 2H, naphthyl-C_3 and C_5–H), 7.31–7.37 (m, 3H, Ph-C_3, C_5–H and naphthyl-C_6-H), 7.45 (t, 1H, J = 7.04, naphthyl-C_7-H), 7.73–7.83 (m, 3H, naphthyl-C_4, C_5 and C_8–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 66.91, 67.01, 106.52, 109.79, 115.03, 118.75, 119.72, 122.21, 123.45, 126.27, 126.77, 127.53, 129.00, 129.32, 134.51, 156.77, 156.86; MS (EI): m/z = found 329.17 [M^+]; calcd. 329.14. Anal. Calcd. For $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.54; H, 5.83; N, 4.27.

4.3.29. 1,2-Bis(4-(1H-pyrrol-1-yl)phenoxy)ethane (**5a29**)

(Yield 70%). mp 138–140 °C; FTIR (KBr): 3147, 2923 (Ar–H), 1522 (C=C), 1241 (C–O–C^{asym}), 1070 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.40–4.42 (m, 4H, 2OCH_2), 6.32 (t, 4H, J = 2.12, pyrrole-C_3 and C_4–H), 6.93–7.05 (m, 8H, 2Ph-C_2, C_6–H and pyrrole-C_2, C_5–H), 7.31–7.36 (m, 4H, 2Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 70.26, 109.43, 110.14, 115.20, 115.86, 117.63, 118.86, 121.01, 132.42, 155.31; MS (EI): m/z = found 344.19 [M^+]; calcd. 344.15. Anal. Calcd. For $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 77.03; H, 5.87; N, 8.16.

4.3.30. 1-(4-(2-(4-(1H-Pyrrol-1-yl)phenoxy)ethoxy)phenyl)-2,5-dimethyl-1H-pyrrole (**5a30**)

(Yield 72%). mp 126–128 °C; FTIR (KBr): 3146, 2928 (Ar–H), 1520 (C=C), 1246 (C–O–C^{asym}), 1071 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.01 (s, 6H, 2CH_3), 4.36 (s, 4H, 2OCH_2), 5.88 (s, 2H, Dimethylpyrrole-C_3 and C_4–H), 6.32 (t, 4H, J = 2.08, pyrrole-C_3 and C_4–H), 6.99–7.02 (m, 6H, 2Ph-C_2, C_6–H and pyrrole-C_2, C_5–H), 7.13, 7.14 (dd, 2H, J = 2.16, 1.84, DimethylpyrrolePh-C_3 and C_5–H), 7.31, 7.33 (dd, 2H, J = 2.16, 1.80, Ph-C_3 and C_5–H),; ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 66.76, 66.90, 105.38, 110.01, 114.97, 115.52, 119.67, 122.17, 129.03, 129.34, 132.24, 134.94, 156.66, 157.91; MS (EI): m/z = found 372.45 [M^+]; calcd. 372.18. Anal. Calcd. For $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52. Found: C, 77.08; H, 6.52; N, 7.49.

4.3.31. 4-(2-(4-(1H-Pyrrol-1-yl)phenoxy)ethoxy)aniline (**5a31**)

(Yield 63%). mp 98–100 °C; FTIR (KBr): 3407 (NH_2), 2922 (Ar–H), 1514 (C=C), 1237 (C–O–C^{asym}), 1069 (C–O–C^{sym}) cm^{-1}; MS (EI): m/z = found 294.17 [M^+]; calcd. 294.14.

4.3.32. 3-(2-(4-(1H-Pyrrol-1-yl)phenoxy)ethoxy)aniline (**5a32**)

(Yield 60%). mp 145–147 °C; FTIR (KBr): 3383 (NH_2), 2924 (Ar–H), 1517 (C=C), 1242 (C–O–C^{asym}), 1070 (C–O–C^{sym}) cm^{-1}; MS (EI): m/z = found 294.17 [M^+]; calcd. 294.14.

4.3.33. 2-(2-(4-(1H-Pyrrol-1-yl)phenoxy)ethoxy)aniline (**5a33**)

(Yield 60%). mp 140–142 °C; FTIR (KBr): 3375 (NH_2), 3140, 2932 (Ar–H), 1521 (C=C), 1241 (C–O–C^{asym}), 1071 (C–O–C^{sym}) cm^{-1}; MS (EI): m/z = found 294.17 [M^+]; calcd. 294.14.

4.3.34. 1-(4-(3-Phenoxypropoxy)phenyl)-1H-pyrrole (**6a1**)

(Yield 85%). mp 95–97 °C; FTIR (KBr): 3134, 2929 (Ar–H), 1520 (C=C), 1237 (C–O–C^{asym}), 1064 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.26 (p, 2H, –CH_2–), 4.15, 4.18 (td, 4H, J = 3.00, 3.24, 2OCH_2), 6.31 (t, 2H, J = 2.16, pyrrole-C_3 and C_4–H), 6.89–6.97 (m, 5H, Ph-C_2, C_4, C_6–H and Ph-C_2, C_6–H at pyrrole), 6.98 (t, 2H, J = 2.16, pyrrole-C_2 and C_5–H), 7.25–7.30 (m, 4H, both ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.42, 64.31, 64.93, 109.99, 114.61, 115.35, 119.74, 120.90, 122.20, 129.60, 134.62, 157.04, 158.93; MS (EI): m/z = found 293.14 [M^+]; calcd. 293.14. Anal. Calcd. For $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.48; H, 6.56; N, 4.79.

4.3.35. 1-(4-(3-(4-Chlorophenoxy)propoxy)phenyl)-1H-pyrrole (**6a2**)

(Yield 75%). mp 103–105 °C; FTIR (KBr): 3141, 2926 (Ar–H), 1525 (C=C), 1240 (C–O–C^{asym}), 1063 (C–O–C^{sym}), 823 (C–Cl) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.26 (p, 2H, –CH_2–), 4.15 (p, 4H, 2OCH_2), 6.31 (t, 2H, J = 2.16, pyrrole-C_3 and C_4–H), 6.83, 6.85 (td, 2H, J = 2.12, 3.40, Ph-C_2 and C_6–H), 6.93, 6.95 (td, 2H, J = 2.12, 3.36, chloroPh-C_2 and C_6–H) 6.99 (t, 2H, pyrrole-C_2 and C_5–H), 7.21, 7.23 (td, 2H, chloroPh-C_3 and C_5–H), 7.28, 7.30 (td, 2H, J = 2.08, 3.32, Ph-C_3, C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.26, 64.69, 109.89, 115.26, 115.53, 115.79, 119.68, 122.19, 125.67, 129.35, 134.62, 156.90, 157.47; MS (EI): m/z = found 327.78 [M^+]; calcd. 327.10. Anal. Calcd. For $C_{19}H_{18}ClNO_2$: C, 69.62; H, 5.53; N, 4.27. Found: C, 69.34; H, 5.55; N, 4.25.

4.3.36. 1-(4-(3-(3-Chlorophenoxy)propoxy)phenyl)-1H-pyrrole (**6a3**)

(Yield 75%). mp 113–115 °C; FTIR (KBr): 3143, 2922 (Ar–H), 1521 (C=C), 1241 (C–O–C^{asym}), 1071 (C–O–C^{sym}), 826 (C–Cl) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.27 (p, 2H, –CH_2–), 4.35 (p, 4H, 2OCH_2), 6.32 (t, 2H, J = 2.16, pyrrole-C_3 and C_4–H), 6.85–6.90 (m, 1H, chloroPh-C_6-H), 7.01–7.06 (m, 6H, Ph-C_2, C_6–H, chloroPh-C_2, C_6–H and pyrrole-C_2 and C_5–H), 7.29 (q, 1H, chloroPh-C_5-H), 7.33–7.37 (m, 2H, Ph-C_3, C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.12, 64.77, 109.89, 113.12, 115.34, 115.97, 119.50, 121.38, 122.06, 130.30, 134.76, 156.77, 159.03; MS (EI): m/z = found 327.10 [M^+]; calcd. 327.10. Anal. Calcd. For $C_{19}H_{18}ClNO_2$: C, 69.62; H, 5.53; N, 4.27. Found: C, 69.90; H, 5.51; N, 4.25.

4.3.37. 1-(4-(3-(2-Chlorophenoxy)propoxy)phenyl)-1H-pyrrole (**6a4**)

(Yield 73%). mp 136–138 °C; FTIR (KBr): 3129, 2931 (Ar–H), 1521 (C=C), 1245 (C–O–C^{asym}), 1065 (C–O–C^{sym}), 729 (C–Cl) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.31 (p, 2H, –CH_2–), 4.20, 4.22, 4.23 (dt, 4H, J = 1.28, 1.48, 1.64, 2OCH_2), 6.31 (t, 2H, J = 2.16, pyrrole-C_3 and C_4–H), 6.86, 6.88, 6.90 (dt, 2H, J = 1.40, 1.32, 1.36, chloroPh-C_4-H), 6.92–6.99 (m, 5H, Ph-C_2, C_6–H, chloroPh-C_6-H and pyrrole-C_2, C_5–H), 7.17, 7.19, 7.21 (dt, 1H, J = 1.60, 1.44, 1.56, chloroPh-C_5-H), 7.27, 7.29 (td, 2H, J = 3.40, 2.24, Ph-C_3, C_5–H), 7.34, 7.36 (dd, 1H, J = 1.64, 1.60, chloroPh-C_3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.28, 64.69, 65.47, 109.91, 113.53, 115.53, 115.33, 119.71, 121.55, 122.19, 123.03, 127.78, 130.35, 134.59, 154.39, 156.96; MS (EI): m/z = found 327.10 [M^+]; calcd. 327.10. Anal. Calcd. For $C_{19}H_{18}ClNO_2$: C, 69.62; H, 5.53; N, 4.27. Found: C, 69.90; H, 5.51; N, 4.29.

4.3.38. 1-(4-(3-(4-Bromophenoxy)propoxy)phenyl)-1H-pyrrole (**6a5**)

(Yield 77%). mp 101–103 °C; FTIR (KBr): 3140, 2944 (Ar–H), 1524 (C=C), 1241 (C–O–C^{asym}), 1063 (C–O–C^{sym}), 820 (C–Br) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.26 (p, 2H, –CH_2–), 4.14 (p, 4H, 2OCH_2), 6.31 (t, 2H, J = 2.16, pyrrole-C_3 and C_4–H), 6.78, 6.80

(td, 2H, J = 2.04, 3.36, bromoPh-C_2 and C_6–H), 6.93, 6.95 (td, 2H, J = 2.12, 3.48, Ph-C_2 and C_6–H), 6.99 (t, 2H, J = 2.12, pyrrole-C_2 and C_5–H), 7.28, 7.30 (td, 2H, J = 2.12, 3.28, bromoPh-C_3 and C_5–H), 7.35, 7.37 (td, 2H, J = 2.08, 3.40, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.21, 64.60, 64.64, 109.86, 112.93, 115.22, 115.22, 115.50, 116.29, 119.67, 122.18, 132.27, 134.60, 156.87, 157.94; MS (EI): m/z = found 372.25 [M^++1]; calcd. 371.05. Anal. Calcd. For $C_{19}H_{18}BrNO_2$: C, 61.30; H, 4.87; N, 3.76. Found: C, 61.05; H, 4.89; N, 3.78.

4.3.39. 1-(4-(3-(3-Bromophenoxy)propoxy)phenyl)-1H-pyrrole (**6a6**)

(Yield 72%). mp 126–128 °C; FTIR (KBr): 3140, 2944 (Ar–H), 1523 (C=C), 1249 (C–O–C^{asym}), 1065 (C–O–C^{sym}), 718 (C–Br) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.25 (p, 2H, $-CH_2-$), 4.14 (p, 4H, J = $2OCH_2$), 6.31 (t, 2H, J = 2.16, pyrrole-C_3 and C_4–H), 6.81–6.84 (m, 1H, bromoPh-C_6-H), 6.92, 6.93 (td, 2H, J = 2.20, 2.24, Ph-C_2 and C_6–H), 6.98 (t, 2H, J = 2.12, pyrrole-C_2 and C_5–H), 7.05–7.13 (m, 3H, bromoPh-C_2, C_4, C_5–H), 7.27, 7.29 (td, 2H, J = 2.16, 2.16, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.27, 64.70, 64.92, 109.85, 112.56, 115.45, 115.65, 116.57, 119.70, 122.20, 132.87, 134.56, 156.80, 158.03; MS (EI): m/z = found 372.25 [M^++1]; calcd. 371.05. Anal. Calcd. For $C_{19}H_{18}BrNO_2$: C, 61.30; H, 4.87; N, 3.76. Found: C, 61.05; H, 4.89; N, 3.74.

4.3.40. 1-(4-(3-(2-Bromophenoxy)propoxy)phenyl)-1H-pyrrole (**6a7**)

(Yield 70%). mp 138–140 °C; FTIR (KBr): 3129, 2929 (Ar–H), 1520 (C=C), 1249 (C–O–C^{asym}), 1064 (C–O–C^{sym}), 729 (C–Br) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.28 (p, 2H, $-CH_2-$), 4.19 (p, 4H, $2OCH_2$), 6.30 (t, 2H, J = 1.96, pyrrole-C_3 and C_4–H), 6.80 (t, 1H, J = 7.52, bromoPh-C_6-H), 6.89 (d, 1H, J = 8.20, bromoPh-C_4-H), 6.93, 6.95 (dd, 2H, J = 1.80, 1.76, Ph-C_2 and C_6–H), 6.97 (t, 2H, J = 2.00, pyrrole-C_2 and C_5–H), 7.19–7.28 (m, 3H, bromoPh-C_5-H and Ph-C_3, C_5–H), 7.50, 7.52 (dd, 1H, J = 1.36, 1.28, bromoPh-C_3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.26, 29.76, 64.72, 65.48, 109.89, 112.34, 113.33, 115.33, 119.71, 122.03, 122.19, 128.53, 133.40, 134.58, 155.20, 156.96; MS (EI): m/z = found 371.05 [M^+]; calcd. 371.05. Anal. Calcd. For $C_{19}H_{18}BrNO_2$: C, 61.30; H, 4.87; N, 3.76. Found: C, 61.55; H, 4.85; N, 3.74.

4.3.41. 1-(4-(3-(4-Iodophenoxy)propoxy)phenyl)-1H-pyrrole (**6a8**)

(Yield 65%). mp 113–115 °C; FTIR (KBr): 3141, 2951 (Ar–H), 1521 (C=C), 1245 (C–O–C^{asym}), 1065 (C–O–C^{sym}), 719 (C–I) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.24 (p, 2H, $-CH_2-$), 4.12 (p, 4H, $2OCH_2$), 6.31 (t, 2H, J = 2.04, pyrrole-C_3 and C_4–H), 6.66, 6.69 (td, 2H, J = 3.04, 3.08, iodoPh-C_2 and C_6–H), 6.91, 6.94 (td, 2H, J = 3.40, 3.32, Ph-C_2 and C_6–H), 6.98 (t, 2H, J = 2.08, pyrrole-C_2 and C_5–H), 7.26, 7.29 (td, 2H, J = 3.40, 3.32, Ph-C_3 and C_5–H), 7.52, 7.54 (td, 2H, J = 2.96, 3.08, iodoPh-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.23, 64.51, 64.68, 82.86, 109.92, 115.27, 116.96, 119.69, 122.19, 134.62, 138.27, 156.89, 158.75; MS (EI): m/z = found 419.04 [M^+]; calcd. 419.04. Anal. Calcd. For $C_{19}H_{18}INO_2$: C, 54.43; H, 4.33; N, 3.34. Found: C, 54.65; H, 4.31; N, 3.33.

4.3.42. 1-(4-(3-(4-Fluorophenoxy)propoxy)phenyl)-1H-pyrrole (**6a9**)

(Yield 68%). mp 116–118 °C; FTIR (KBr): 3122, 2939 (Ar–H), 1514 (C=C), 1243 (C–O–C^{asym}), 1062 (C–O–C^{sym}), 825 (C–F) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.25 (p, 2H, $-CH_2-$), 4.11, 4.14, 4.17 (dt, 4H, J = 6.08, 6.12, $2OCH_2$), 6.31 (t, 2H, J = 2.12, pyrrole-C_3 and C_4–H), 6.82–6.86 (m, 2H, Ph-C_2 and C_6–H), 6.92–6.99 (m, 6H, fluoroPh-C_2, C_6–H, pyrrole-C_2, C_5–H and ph-C_3 and C_5–H), 7.27, 7.30 (td, 2H, J = 2.16, 3.44, fluoroPh-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.38, 64.80, 65.03, 109.97, 115.31, 115.49, 115.57, 115.77, 115.99, 119.70, 122.18, 134.63, 155.03, 155.05, 156.15, 156.97, 158.52; MS (EI): m/z = found 311.13 [M^+]; calcd. 311.13. Anal. Calcd. For $C_{19}H_{18}FNO_2$: C, 73.29; H, 5.83; N, 4.50. Found: C, 73.58; H, 5.81; N, 4.48.

4.3.43. 1-(4-(3-(4-Nitrophenoxy)propoxy)phenyl)-1H-pyrrole (**6a10**)

(Yield 62%). mp 138–140 °C; FTIR (KBr): 3076, 2934 (Ar–H), 1592 (NO_2^{asym}), 1518 (C=C), 1338 (NO_2^{sym}), 1255 (C–O–C^{asym}), 1059 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.23 (p, 2H, $-CH_2-$), 4.19 (t, 2H, J = 5.92, OCH_2 near to pyrrole), 4.27 (t, 2H, J = 6.12, OCH_2 near to nitro ph), 6.31 (t, 2H, J = 2.16, pyrrole-C_3 and C_4–H), 6.92–6.99 (m, 6H, Ph-C_2, C_6–H, nitroph-C_2, C_6–H and pyrrole-C_2, C_5–H) 7.29, 7.31 (td, 2H, J = 3.36, 3.48, ph-C_3 and C_5–H), 8.18, 8.20 (td, 2H, J = 3.40, 3.32, nitroPh-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.07, 64.33, 65.27, 109.88, 109.95, 114.47, 115.22, 119.65, 122.19, 125.96, 134.73, 141.58, 156.73, 163.89; MS (EI): m/z = found 338.13 [M^+]; calcd. 338.13. Anal. Calcd. For $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.71; H, 5.34; N, 8.31.

4.3.44. 1-(4-(3-(2,4-Dinitrophenoxy)propoxy)phenyl)-1H-pyrrole (**6a11**)

(Yield 60%). mp 58–60 °C; FTIR (KBr): 3141, 2951 (Ar–H), 1607 (NO_2^{asym}), 1522 (C=C), 1343 (NO_2^{sym}), 1253 (C–O–C^{asym}), 1067 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.27 (p, 2H, $-CH_2-$), 3.37 (t, 2H, J = 6.80, OCH_2), 4.04 (t, 2H, J = 5.80, OCH_2), 6.31 (t, 2H, J = 1.80, pyrrole-C_3 and C_4–H), 6.92–6.95 (m, 2H, Ph-C_2 and C_6–H), 6.97–6.99 (m, 2H, pyrrole-C_2 and C_5–H), 7.21 (t, 1H, J = 8.76, nitroph-C_6-H), 7.28, 7.30 (dd, 2H, J = 7.12, 3.20, ph-C_3 and C_5–H), 8.38, 8.40 (dd, 1H, J = 2.40, 2.60, nitroPh-C_5-H), 8.73 (d, 1H, J = 2.56, nitroPh-C_3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.02, 64.66, 65.23, 110.76, 114.20, 115.35, 115.49, 115.61, 118.65, 122.42, 126.01, 132.17, 139.53, 141.87, 156.60, 158.20; MS (EI): m/z = found 383.15 [M^+]; calcd. 383.11. Anal. Calcd. For $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.47; N, 10.96. Found: C, 59.29; H, 4.49; N, 11.00.

4.3.45. 4-(3-(4-(1H-Pyrrol-1-yl)phenoxy)propoxy)benzonitrile (**6a12**)

(Yield 72%). mp 122–124 °C; FTIR (KBr): 3138, 2922 (Ar–H), 2222 (CN), 1525 (C=C), 1258 (C–O–C^{asym}), 1061 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.30 (p, 2H, $-CH_2-$), 4.17 (t, 2H, J = 5.96, OCH_2 near to pyrrole), 4.22 (t, 2H, J = 6.08, OCH_2 near to nitrile ph), 6.31 (t, 2H, J = 2.12, pyrrole-C_3 and C_4–H), 6.93–6.99 (m, 6H, Ph-C_2, C_6–H, nitrileph-C_2, C_6–H and pyrrole-C_2, C_5–H) 7.28, 7.30 (td, 2H, J = 3.44, 3.44, ph-C_3 and C_5–H), 7.56, 7.58 (td, 2H, J = 2.64, 2.68, nitrile Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 28.41, 64.25, 64.73, 102.95, 109.76, 115.19, 115.37, 118.92, 120.94, 133.69, 133.94, 156.12, 161.86; MS (EI): m/z = found 318.14 [M^+]; calcd. 318.14. Anal. Calcd. For $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.15; H, 5.72; N, 8.76.

4.3.46. 4-(3-(4-(1H-Pyrrol-1-yl)phenoxy)propoxy)benzaldehyde (**6a13**)

(Yield 60%). mp 74–76 °C; FTIR (KBr): 3142, 2940 (Ar–H), 1666 (C=O), 1521 (C=C), 1245 (C–O–C^{asym}), 1062 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.18–2.34 (m, 2H, $-CH_2-$), 4.14–4.27 (m, 4H, $2OCH_2$), 6.30–6.31 (m, 2H, pyrrole-C_3 and C_4–H), 6.88–7.02 (m, 6H, Ph-C_2, C_6–H, pyrrole-C_2, C_5–H and aldehyde ph-C_2, C_6–H) 7.24–7.30 (m, 2H, ph-C_3 and C_5–H), 7.45–7.49 (m, 2H, aldehyde Ph-C_3 and C_5–H), 9.87 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.02, 64.56, 65.03, 109.70, 114.80, 115.22, 118.56, 120.59, 126.00, 129.58, 131.05, 132.26, 156.50, 168.31, 190.10; MS (EI): m/z = found 321.09 [M^+]; calcd. 321.14. Anal. Calcd. For $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.45; H, 5.98; N,

4.38.

*4.3.47. 4-(3-(4-(1H-Pyrrol-1-yl)phenoxy)propoxy)-3-methoxybenzaldehyde (**6a14**)*

(Yield 60%). mp 86–88 °C; FTIR (KBr): 3133, 2932 (Ar–H), 1689 (C=O), 1518 (C=C), 1261 (C–O–C^{asym}), 1064 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.29–2.38 (m, 2H, $-CH_2-$), 3.88 (t, 3H, J = 11.44, OCH_3), 4.17–4.22 (m, 2H, OCH_2), 4.24–4.33 (m, 2H, OCH_2), 6.31 (t, 2H, J = 2.12, pyrrole-C_3 and C_4–H), 6.85–7.02 (m, 5H, Ph-C_2, C_6–H, pyrrole-C_2, C_5–H and aldehyde ph-C_6-H), 7.06–7.10 (m, 1H, aldehyde ph-C_3-H), 7.27–7.31 (m, 2H, ph-C_3 and C_5–H), 7.40–7.47 (m, 1H, aldehyde Ph-C_5-H), 9.84 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 28.60, 29.03, 56.12, 64.63, 65.13, 109.15, 109.23, 109.25, 112.40, 115.01, 115.07, 118.63, 118.72, 124.29, 126.17, 126.23, 130.02, 132.96, 151.69, 155.26, 156.68, 190.25; MS (EI): m/z = found 351.15 [M^+]; calcd. 351.15. Anal. Calcd. For $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.49; H, 6.04; N, 3.97.

*4.3.48. 4-(3-(4-(1H-Pyrrol-1-yl)phenoxy)propoxy)-3-ethoxybenzaldehyde (**6a15**)*

(Yield 60%). mp 84–86 °C; FTIR (KBr): 3141, 2946 (Ar–H), 1676 (C=O), 1521 (C=C), 1247 (C–O–C^{asym}), 1065 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.72 (s, 3H, $OCH_2\underline{CH_3}$), 2.24–2.31 (m, 2H, $-CH_2-$), 3.23–3.24 (m, 2H, $O\underline{CH_2}CH_3$), 4.13–4.26 (m, 4H, $2OCH_2$), 6.31 (t, 2H, J = 2.08, pyrrole-$\underline{C_3}$ and C_4–H), 6.87–7.02 (m, 6H, Ph-C_2, C_6–H, pyrrole-C_2, C_5–H and aldehyde ph-C_3, C_6–H), 7.24–7.30 (m, 2H, ph-C_3 and C_5–H), 7.44–7.49 (m, 1H, aldehyde Ph-C_5-H), 9.86 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 15.16, 28.64, 29.36, 64.90, 65.33, 66.52, 109.34, 110.23, 112.26, 113.77, 115.02, 115.77, 118.56, 118.88, 122.52, 126.06, 126.15, 129.23, 133.11, 150.12, 155.67, 156.69, 190.12; MS (EI): m/z = found 365.20 [M^+]; calcd. 365.16. Anal. Calcd. For $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.60; H, 6.31; N, 3.81.

*4.3.49. 1-(4-(3-(4-Tolyloxy)propoxy)phenyl)-1H-pyrrole (**6a16**)*

(Yield 75%). mp 100–102 °C; FTIR (KBr): 3126, 2923 (Ar–H), 1517 (C=C), 1248 (C–O–C^{asym}), 1066 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.22–2.27 (m, 5H, $-CH_2-$ and CH_3), 4.14 (p, 4H, $2OCH_2$), 6.31 (t, 2H, J = 2.20, pyrrole-C_3 and C_4–H), 6.80, 6.82 (dd, 2H, J = 2.00, 2.08, methylPh-C_2 and C_6–H), 6.93, 6.95 (dd, 2H, J = 2.16, 2.24, ph-C_2 and C_6–H), 6.98 (t, 2H, J = 2.12, pyrrole-C_2 and C_5–H), 7.08 (d, 2H, J = 8.24, methylph-C_3 and C_5–H), 7.27, 7.29 (dd, 2H, J = 2.20, 2.20, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 20.49, 29.39, 29.74, 64.42, 64.92, 109.85, 114.40, 115.28, 119.70, 122.18, 129.95, 130.04, 134.54, 156.74, 157.01; MS (EI): m/z = found 307.16 [M^+]; calcd. 307.16. Anal. Calcd. For $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.46; H, 6.86; N, 4.58.

*4.3.50. 1-(4-(3-(3-Tolyloxy)propoxy)phenyl)-1H-pyrrole (**6a17**)*

(Yield 73%). mp 88–90 °C; FTIR (KBr): 3137, 2935 (Ar–H), 1523 (C=C), 1254 (C–O–C^{asym}), 1064 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.24 (p, 2H, $-CH_2-$), 2.31 (s, 3H, CH_3), 4.13, 4.16 (dd, 4H, J = 5.88, 6.00, $2OCH_2$), 6.30 (t, 2H, J = 2.12, pyrrole-C_3 and C_4–H), 6.70–6.76 (m, 3H, methylPh-C_2, C_4 and C_6–H), 6.91, 6.93 (td, 2H, J = 2.20, 2.16, ph-C_2 and C_6–H), 6.97 (t, 2H, J = 2.12, pyrrole-C_2 and C_5–H), 7.15 (t, 1H, J = 7.68, methylph-C_5-H), 7.26, 7.28 (td, 2H, J = 2.16, 2.12, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 21.09, 28.73, 63.71, 64.36, 109.69, 111.17, 114.89, 115.06, 118.84, 121.03, 121.13, 128.91, 133.67, 138.76, 156.26, 158.40; MS (EI): m/z = found 307.16 [M^+]; calcd. 307.16. Anal. Calcd. For $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.84; H, 6.92; N, 4.58.

*4.3.51. 1-(4-(3-(2-Tolyloxy)propoxy)phenyl)-1H-pyrrole (**6a18**)*

(Yield 73%). mp 116–118 °C; FTIR (KBr): 3125, 2930 (Ar–H), 1518 (C=C), 1245 (C–O–C^{asym}), 1061 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.22 (s, 3H, CH_3), 2.29 (p, 2H, $-CH_2-$), 4.14-, 4.21 (m, 4H, $2OCH_2$), 6.31 (t, 2H, J = 2.12, pyrrole-C_3 and C_4–H), 6.82–6.87 (m, 2H, methylPh-C_5 and C_6–H), 6.93, 6.95 (td, 2H, J = 2.12, 2.20, ph-C_2 and C_6–H), 6.98 (t, 2H, J = 2.16, pyrrole-C_2 and C_5–H), 7.14 (t, 2H, J = 7.52, methylph-C_3 and C_4–H), 7.7, 7.29 (dd, 2H, J = 2.16, 2.12, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 16.32, 29.48, 64.26, 65.00, 109.91, 110.99, 115.29, 119.73, 120.49, 122.21, 126.81, 126.87, 130.73, 134.58, 156.97, 157.03; MS (EI): m/z = found 307.16 [M^+]; calcd. 307.16. Anal. Calcd. For $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.84; H, 6.92; N, 4.54.

*4.3.52. 1-(4-(3-(3,5-Dimethylphenoxy)propoxy)phenyl)-1H-pyrrole (**6a19**)*

(Yield 68%). mp 96–98 °C; FTIR (KBr): 3138, 2926 (Ar–H), 1520 (C=C), 1250 (C–O–C^{asym}), 1067 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.21–2.27 (m, 8H, $2CH_3$, $-CH_2-$), 4.11–4.16 (dt, 4H, J = 6.08, 6.12, $2OCH_2$), 6.31 (t, 2H, J = 2.12, pyrrole-C_3 and C_4–H), 6.54 (s, 2H, methylPh-C_2 and C_6–H), 6.59 (s, 1H, methylph-C_4-H), 6.93, 6.94 (dd, 2H, J = 2.12, 2.12, ph-C_2 and C_6–H), 6.98 (t, 2H, J = 2.16, pyrrole-C_2 and C_5–H), 7.27, 7.29 (dd, 2H, J = 2.08, 2.16, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 21.46, 29.41, 64.14, 64.90, 109.84, 112.30, 115.27, 119.70, 122.18, 122.58, 134.53, 139.26, 157.00, 158.92; MS (EI): m/z = found 321.17 [M^+]; calcd. 321.17. Anal. Calcd. For $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.78; H, 7.18; N, 4.34.

*4.3.53. 1-(4-(3-(2,5-Dimethylphenoxy)propoxy)phenyl)-1H-pyrrole (**6a20**)*

(Yield 70%). mp 86–88 °C; FTIR (KBr): 3138, 2928 (Ar–H), 1519 (C=C), 1250 (C–O–C^{asym}), 1061 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.17 (s, 3H, CH_3 at C_2 position), 2.26–2.30 (m, 5H, CH_3 at C_5 position and $-CH_2-$), 4.15 4.18 (dt, 4H, J = 5.96, 6.16, $2OCH_2$), 6.31 (t, 2H, J = 2.00, pyrrole-C_3 and C_4–H), 6.67 (d, 2H, J = 5.92, methylPh-C_4 and C_6–H), 6.92, 6.94 (dd, 2H, J = 3.28, 1.98, ph-C_2 and C_4–H), 6.97–7.01 (m, 3H, pyrrole-C_2, C_5–H and methylph-C_3-H), 7.26, 7.28 (dd, 2H, J = 3.20, 7.00, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 15.91, 21.48, 29.54, 29.80, 64.26, 65.02, 69.20, 109.93, 109.95, 112.09, 115.09, 115.30, 115.58, 117.89, 119.73, 121.01, 122.16, 122.21, 123.61, 130.46, 133.19, 134.58, 136.64, 156.71, 156.86, 157.05; MS (EI): m/z = found 321.18 [M^+]; calcd. 321.17. Anal. Calcd. For $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.78; H, 7.18; N, 4.38.

*4.3.54. 1-(4-(3-(2,4-Dimethylphenoxy)propoxy)phenyl)-1H-pyrrole (**6a21**)*

(Yield 70%). mp 93–95 °C; FTIR (KBr): 3128, 2957 (Ar–H), 1522 (C=C), 1252 (C–O–C^{asym}), 1067 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.27 (s, 3H, CH_3 at C_2 position), 2.31–2.38 (m, 5H, CH_3 at C_4 position and $-CH_2-$), 4.20, 4.26 (dt, 4H, J = 5.96, 6.20, $2OCH_2$), 6.39 (t, 2H, J = 2.16, pyrrole-C_3 and C_4–H), 6.82 (d, 1H, J = 7.92, methylPh-C_6-H), 7.00–7.07 (m, 4H, methylph-C_3, C_5–H and ph-C_2, C_4–H), 7.06 (t, 2H, pyrrole-C_2 and C_5–H), 7.35, 7.38 (td, 2H, J = 2.16, 2.16, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 16.24, 20.51, 29.52, 64.49, 65.03, 109.90, 111.11, 115.28, 119.73, 122.20, 126.58, 127.01, 129.68, 131.58, 134.54, 154.86, 157.05; MS (EI): m/z = found 321.17 [M^+]; calcd. 321.17. Anal. Calcd. For $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.78; H, 7.18; N, 4.34.

*4.3.55. 4-(3-(4-(1H-Pyrrol-1-yl)phenoxy)propoxy)phenol (**6a22**)*

(Yield 68%). mp 101–103 °C; FTIR (KBr): 3416 (OH), 3143, 2927 (Ar–H), 1520 (C=C), 1239 (C–O–C^{asym}), 1070 (C–O–C^{sym}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.21–2.30 (m, 2H, $-CH_2-$),

4.12–4.29 (m, 4H, $2OCH_2$), 5.76 (s, 1H, OH), 6.33 (t, 2H, $J = 2.12$, pyrrole-C_3 and C_4–H), 6.81–7.20 (m, 8H, Phenol-C_2, C_3, C_5, C_6–H, Ph-C_2, C_6–H and pyrrole-C_2, C_5–H), 7.26–7.32 (m, 2H, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 28.76, 28.83, 64.62, 65.10, 109.75, 110.01, 113.40, 115.35, 115.88, 118.80, 119.52, 120.01, 120.28, 122.36, 122.56, 132.03, 155.66, 156.13, 156.48; MS (EI): m/z = found 309.16 [M^+]; calcd. 309.14. Anal. Calcd. For $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 74.07; H, 6.17; N, 4.55.

*4.3.56. 3-(3-(4-(1H-Pyrrol-1-yl)phenoxy)propoxy)phenol (**6a23**)*

(Yield 60%). mp 98–100 °C; FTIR (KBr): 3293 (OH), 2953 (Ar–H), 1522 (C=C), 1249 (C–O–C^{asym}), 1067 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.14–2.20 (m, 2H, $-CH_2-$), 4.04–4.13 (m, 4H, $2OCH_2$), 6.33–6.36 (m, 2H, pyrrole-C_3 and C_4–H), 6.87–7.07 (m, 8H, Phenol-C_2, C_4, C_5, C_6–H, Ph-C_2, C_6–H and pyrrole-C_2, C_5–H), 7.32, 7.35 (dd, 2H, $J = 1.96$, 2.00, Ph-C_3 and C_5–H), 9.00 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 28.69, 29.40, 63.71, 64.39, 101.73, 102.49, 104.90, 106.15, 107.83, 109.73, 115.08, 118.86, 121.01, 129.40, 133.66, 156.25, 158.43, 159.62; MS (EI): m/z = found 293.35 [M^+]; calcd. 309.14. Anal. Calcd. For $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.47; H, 6.21; N, 4.55.

*4.3.57. 2-(3-(4-(1H-Pyrrol-1-yl)phenoxy)propoxy)phenol (**6a24**)*

(Yield 60%). mp 104–106 °C; FTIR (KBr): 3327 (OH), 3141, 2951 (Ar–H), 1521 (C=C), 1245 (C–O–C^{asym}), 1063 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.24–2.31 (m, 2H, $-CH_2-$), 4.11–4.26 (m, 4H, $2OCH_2$), 5.77 (s, 1H, OH), 6.31 (t, 2H, $J = 2.16$, pyrrole-C_3 and C_4–H), 6.80–6.99 (m, 8H, Phenol-C_3, C_4, C_5, C_6–H, Ph-C_2, C_6–H and pyrrole-C_2, C_5–H), 7.27, 7.29 (td, 2H, $J = 2.36$, 3.40, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 28.78, 28.86, 64.43, 65.14, 109.72, 113.40, 114.22, 115.06, 115.15, 115.59, 118.83, 118.89, 119.08, 120.92, 120.99, 121.05, 121.16, 133.63, 146.56, 146.75, 148.50, 156.25, 156.32; MS (EI): m/z = found 309.14 [M^+]; calcd. 309.14. Anal. Calcd. For $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.47; H, 6.21; N, 4.51.

*4.3.58. 5-(3-(4-(1H-Pyrrol-1-yl)phenoxy)propoxy)-2-chlorophenol (**6a25**)*

(Yield 58%). mp 70–72 °C; FTIR (KBr): 3425 (OH), 3110, 2917 (Ar–H), 1531 (C=C), 1253 (C–O–C^{asym}), 1053 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.29–2.36 (m, 2H, $-CH_2-$), 4.17–4.28 (m, 4H, $2OCH_2$), 5.51 (s, 1H, OH), 6.37–6.42 (m, 2H, pyrrole-C_3 and C_4–H), 6.99–7.06 (m, 7H, Phenol-C_2, C_5, C_6–H, Ph-C_2, C_6–H and pyrrole-C_2, C_5–H), 7.32–7.35 (m, 2H, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.15, 29.78, 64.71, 65.38, 101.84, 108.28, 109.94, 113.77, 115.33, 115.59, 117.93, 119.69, 122.09, 130.31, 133.15, 134.64, 155.01, 156.64, 156.91; MS (EI): m/z = found 343.76 [M^+]; calcd. 343.10. Anal. Calcd. For $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; N, 4.07. Found: C, 66.65; H, 5.26; N, 4.05.

*4.3.59. 5-(3-(4-(1H-Pyrrol-1-yl)phenoxy)propoxy)benzene-1,3-diol (**6a26**)*

(Yield 58%). mp 108–110 °C; FTIR (KBr): 3334 (OH), 3140, 2928 (Ar–H), 1521 (C=C), 1256 (C–O–C^{asym}), 1068 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.21–2.28 (m, 2H, $-CH_2-$), 4.13 (p, 4H, $2OCH_2$), 6.11 (s, 2H, 2OH), 6.17 (s, 1H, phenol-C_4-H), 6.29–6.32 (m, 2H, pyrrole-C_3 and C_4–H), 6.89–6.96 (m, 3H, Ph-C_2, C_6–H and phenol-C_2-H), 6.98–7.00 (m, 2H, pyrrole-C_2 and C_5–H), 7.19–7.31 (m, 3H, Ph-C_3, C_5–H and phenol-C_6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 26.87, 27.31, 62.04, 62.38, 89.77, 91.75, 97.58, 107.48, 112.65, 113.12, 117.20, 117.27, 119.68, 119.80, 132.17, 154.35, 154.52, 155.67, 158.36; MS (EI): m/z = found 325.13 [M^+]; calcd. 325.13. Anal. Calcd. For $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.42; H, 5.87; N, 4.33.

*4.3.60. 1-(4-(3-(Naphthalen-1-yloxy)propoxy)phenyl)-1H-pyrrole (**6a27**)*

(Yield 63%). mp 132–134 °C; FTIR (KBr): 3132, 2945 (Ar–H), 1518 (C=C), 1241 (C–O–C^{asym}), 1069 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.40 (p, 2H, $-CH_2-$), 4.25 (t, 2H, $J = 6.20$, OCH_2 near to pyrrole ph), 4.33 (t, 2H, $J = 6.00$, OCH_2 near to naphthyl), 6.30 (t, 2H, $J = 2.16$, pyrrole-C_3 and C_4–H), 6.83 (d, 1H, $J = 6.88$, naphthyl-C_2-H), 6.92–6.98 (m, 4H, Ph-C_2, C_6–H and pyrrole-C_2, C_5–H), 7.26, 7.27 (td, 2H, $J = 2.24$, 2.20, Ph-C_3 and C_5–H), 7.35 (t, 1H, $J = 7.52$, naphthyl-C_3-H), 7.42 (d, 1H, $J = 8.20$, naphthyl-C_4-H), 7.44–7.49 (m, 2H, naphthyl-C_6 and C_7–H), 7.78, 7.79 (dd, 1H, $J = 3.04$, 2.20, naphthyl-C_5-H), 8.26, 8.27 (dd, 1H, $J = 2.36$, 2.64, naphthyl-C_8-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 28.76, 64.35, 64.62, 104.79, 109.71, 115.13, 118.89, 119.81, 121.01, 121.47, 125.94, 126.17, 127.21, 133.68, 133.96, 153.93, 156.25; MS (EI): m/z = found 343.15 [M^+]; calcd. 343.16. Anal. Calcd. For $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.76; H, 6.14; N, 4.10.

*4.3.61. 1-(4-(3-(Naphthalen-2-yloxy)propoxy)phenyl)-1H-pyrrole (**6a28**)*

(Yield 63%). mp 124–126 °C; FTIR (KBr): 3141, 2948 (Ar–H), 1518 (C=C), 1251 (C–O–C^{asym}), 1063 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.30 (p, 2H, $-CH_2-$), 4.17 (t, 2H, $J = 6.12$, OCH_2 near to pyrrole ph), 4.25 (t, 2H, $J = 6.08$, OCH_2 near to Naphthyl), 6.30 (t, 2H, $J = 2.16$, pyrrole-C_3 and C_4–H), 6.92, 6.94 (td, 2H, $J = 2.16$, 3.40, Ph-C_2 and C_6–H), 6.97 (t, 2H, $J = 2.12$, pyrrole-C_2 and C_5–H), 7.12–7.15 (m, 2H, naphthyl-C_3 and C_5–H), 7.25, 7.27 (td, 2H, $J = 2.20$, 3.44, Ph-C_3 and C_5–H), 7.29, 7.31, 7.32 (dt, 1H, $J = 1.12$, 1.12, 1.08, naphthyl-C_6-H), 7.39, 7.41, 7.43 (dt, 1H, $J = 1.20$, 1.24, 1.24, naphthyl-C_7-H), 7.71 (p, 3H, naphthyl-C_4, C_5 and C_8–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.33, 64.42, 64.91, 106.73, 109.86, 115.30, 118.88, 119.70, 122.20, 123.67, 126.41, 126.75, 127.67, 129.02, 129.44, 134.58, 156.82, 156.98; MS (EI): m/z = found 343.14 [M^+]; calcd. 343.16. Anal. Calcd. For $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.76; H, 6.14; N, 4.10.

*4.3.62. 1,3-Bis(4-(1H-pyrrol-1-yl)phenoxy)propane (**6a29**)*

(Yield 65%). mp 140–142 °C; FTIR (KBr): 3141, 2948 (Ar–H), 1523 (C=C), 1254 (C–O–C^{asym}), 1068 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.28 (p, 2H, $-CH_2-$), 4.17 (t, 4H, $J = 6.08$, $2OCH_2$), 6.31 (t, 4H, $J = 2.12$, pyrrole-C_3 and C_4–H), 6.93, 6.96 (td, 4H, $J = 2.12$, 3.40, 2Ph-C_2 and C_6–H), 6.98 (t, 4H, $J = 2.16$, pyrrole-C_2 and C_5–H), 7.28, 7.30 (td, 4H, $J = 2.16$, 3.44, 2Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.34, 64.75, 109.90, 115.28, 119.69, 122.20, 134.62, 156.94; MS (EI): m/z = found 358.17 [M^+]; calcd. 358.17. Anal. Calcd. For $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82. Found: C, 76.76; H, 6.21; N, 7.85.

*4.3.63. 1-(4-(3-(4-(1H-Pyrrol-1-yl)phenoxy)propoxy)phenyl)-2,5-dimethyl-1H-pyrrole (**6a30**)*

(Yield 60%). mp 88–90 °C; FTIR (KBr): 3140, 2943 (Ar–H), 1523 (C=C), 1250 (C–O–C^{asym}), 1066 (C–O–C^{sym}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.11 (s, 6H, $2CH_3$), 2.39 (p, 2H, $-CH_2-$), 4.31 (q, 4H, $2OCH_2$), 5.98 (s, 2H, Dimethylpyrrole-C_3 and C_4–H), 6.41 (t, 4H, $J = 2.12$, pyrrole-C_3 and C_4–H), 7.03–7.09 (m, 6H, 2Ph-C_2, C_6–H and pyrrole-C_2, C_5–H), 7.20, 7.22 (dd, 2H, $J = 2.16$, 2.16, DimethylpyrrolePh-C_3 and C_5–H), 7.38, 7.39 (td, 2H, $J = 2.16$, 2.24, Ph-C_3 and C_5–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 13.08, 29.39, 64.62, 64.75, 105.41, 110.01, 114.82, 115.31, 115.59, 119.72, 122.16, 122.21, 129.06, 129.34, 131.91, 134.64, 156.97, 158.22; MS (EI): m/z = found 386.20 [M^+]; calcd. 386.20. Anal. Calcd. For $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.38; H, 6.81; N, 7.22.

*4.3.64. 4-(3-(4-(1H-Pyrrol-1-yl)phenoxy)propoxy)aniline (**6a31**)*

(Yield 60%). mp 94–96 °C; FTIR (KBr): 3385 (NH_2), 3137, 2924

(Ar–H), 1516 (C=C), 1239 (C–O–C^{asym}), 1067 (C–O–C^{sym}) cm^{-1}; MS (EI): m/z = found 308.17 [M^+]; calcd. 308.15.

*4.3.65. 3-(3-(4-(1H-Pyrrol-1-yl)phenoxy)propoxy)aniline (**6a32**)*

(Yield 58%). mp 107–109 °C; FTIR (KBr): 3366 (NH_2), 3133, 2950 (Ar–H), 1520 (C=C), 1252 (C–O–C^{asym}), 1058 (C–O–C^{sym}) cm^{-1}; MS (EI): m/z = found 308.17 [M^+]; calcd. 308.15.

*4.3.66. 2-(3-(4-(1H-Pyrrol-1-yl)phenoxy)propoxy)aniline (**6a33**)*

(Yield 58%). mp 98–100 °C; FTIR (KBr): 3351 (NH_2), 3137, 2933 (Ar–H), 1520 (C=C), 1240 (C–O–C^{asym}), 1065 (C–O–C^{sym}) cm^{-1}; MS (EI): m/z = found 308.21 [M^+]; calcd. 308.15.

5. Biological activity

5.1. Anti-tubercular studies

All the synthesized compounds were tested for inhibition of *M. tuberculosis* strain $H_{37}RV$ using Microplate Alamar Blue Assay (MABA) as described earlier [47]. The 96 wells plate received 100 μL of Middlebrook 7H9 broth and serial dilution of compounds were made directly on the plate with drug concentrations of 0.2, 0.4, 0.8, 1.6, 3.125, 6.25, 12.5, 25, 50 and 100 μg/mL. Plates were covered and sealed with parafilm and incubated at 37 °C for 5 days. Then, 25 μL of freshly prepared 1:1 mixture of almar blue reagent and 10% Tween 80 was added to the plate and incubated for 24 h. A blue color in the well was interpreted as no bacterial growth and pink color was scored as growth. The MIC was defined as the lowest drug concentration, which prevented color change from blue to pink. Table 1 reveals the anti-tubercular activity (MIC) data.

5.2. MTT-based cytotoxic activity

The cellular conversion of MTT [3-(4,5-dimethylthiazo-2-yl)-2,5-diphenyl-tetrazolium bromide] into a formazan product [48] was used to evaluate cytotoxic activity (IC_{50}) of some of the synthesized compounds against mammalian Vero cell-lines and A_{549} (lung adenocarcinoma) cell-lines up to concentrations of 62.5 μg/mL using the Promega Cell Titer 96 non-radioactive cell proliferation assay [49] and cisplatin was the positive control. The IC_{50} values are the averages ± SEM of three independent experiments, which are presented in Table 2.

6. Conclusions

The novel compounds viz., 1-(4-(2-aryloxyethoxy)phenyl)-1*H*-pyrroles (**5a1**–**5a33**) or 1-(4-(3-aryloxypropoxy)phenyl)-1*H*-pyrroles (**6a1**–**6a33**) were synthesized and identified as the potent InhA inhibitors. The optimized pharmacophore model (MODEL_04) was developed that showed good statistical parameters in the validation process. The pharmacophore delineates important features that are common to phenoxy-based ligands active against *M. tuberculosis*. The corresponding features on linker and benzene acceptor provide the necessary interactions with the binding pockets. Molecular docking studies were performed to improve the reliability and accuracy of the model. The correlation was found to be consistent because the binding site of amino acid residues were in good agreement with the pharmacophoric features. Acceptor atom makes interaction with Try158, Thr196, Met199 amino acids and NAD co-factor. It was found that activity can further be enhanced to extend the distance between acceptor group and aromatic ring, as demonstrated by the 6a series of compounds that are more dominant than the 5a series of compounds. Moreover, introduction of halogen appears to be beneficial for exhibiting anti-TB activity. These compounds will be useful as the lead compounds for developing InhA inhibitors.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.03.013. These data include MOL files and InChiKeys of the most important compounds described in this article.

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