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Synthesis and evaluation of new Furanyl and Thiophenyl azoles as antileishmanial agents

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Abstract: A series of benzyloxy furanyl and benzyloxy thiophenyl azoles were synthesized and screened for their *in vitro* antileishmanial activity against *Leishmania donovani*. Among all, 16 compounds have shown more than 90% inhibition against promastigotes at 20 μM while 11 compounds exhibited IC_{50} in the range of 3.04-9.39 μM against amastigotes. Compound **4**, a 3-chlorobenzyloxy furanyl imidazole emerged as the most active compound in the series with IC_{50} value of 3.04 μM and SI value of 19.80, and was several folds more potent than the reference drugs miltefosine and miconazole.

1. Introduction

The discovery and development of essential drugs for neglected diseases such as leishmaniasis is a major concern in the pharmaceutical world. Leishmaniasis [1,2] are a group of tropical diseases caused by parasites of about 20 species of the genus Leishmania, and are transmitted by a group of 50 species and subspecies of phlebotomine insects [3,4]. Official data show that there are 20 million infected people around the world, 400 million at risk of acquiring the disease, and 1.5 to 2 million that will be infected annually [5,6]. The protozoa of the genus *Leishmania*, which are distributed throughout the world, are the cause of various clinical syndromes. Visceral leishmaniasis (VL), commonly known as kala azar is caused by *Leishmania donovani* and is most lethal, if left untreated [7]. Cutaneous leishmaniasis (CL) can be associated with significant morbidity and occasional deforming scars. Leishmaniasis showed a complex and diverse clinical manifestation and epidemiology [8].The conventional chemotherapy relies on multiple parenteral injections with pentavalent antimonials that are significantly toxic and prone to induce resistance. Second-line drugs, such as Amphotericin B and its lipid formulations, are either too toxic or expensive for routine use. The oral anticancer drug miltefosine is an effective drug, but there are side effects and drawbacks related to treatment. These facts [9] call for safer, cheaper, and more effective new antileishmanial drugs.

The search for safe and efficacious oral therapy has been ongoing for more than 2 decades. The azole antifungals ketoconazole , miconazole and itraconazole have been used to treat cutaneous leishmaniasis with variable success rates [9,10]. There have been conflicting reports of the success and failure of azoles in the treatment of VL. Azoles are essentially sterol biosynthesis inhibitors (SBIs), offer an attractive possibility for the treatment of leishmaniasis [11]. Leishmania resemble fungi in synthesizing 24-substituted sterols such as ergosterol, whereas mammals have just cholesterol. Imidazole and triazole antifungals inhibit C-14 demethylation of lanosterol, which interferes with the production of leishmanial ergosterol, an essential

component of their membrane structure [12]. This results in impaired membrane stability and in growth inhibition of fungi and possibly in Leishmania as well.

In continuation of our efforts to develop azole-based anti-Leishmanial compounds coupled with encouraging results [13,14], we have designed and synthesized a series of furanyl and thiophenyl azoles by applying rational drug design approach (Fig. 1), as modified analogues of the antifungal drug miconazole. The principal structural modifications introduced in the miconazole molecule to give the new derivatives 4–23 are summarized in Figure 1.

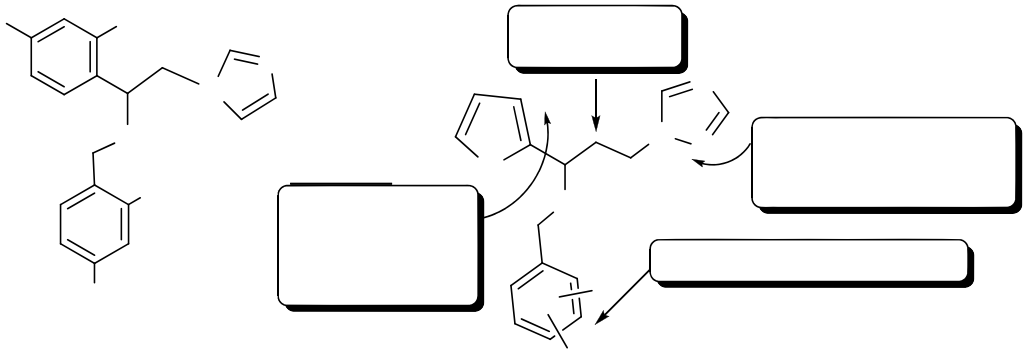
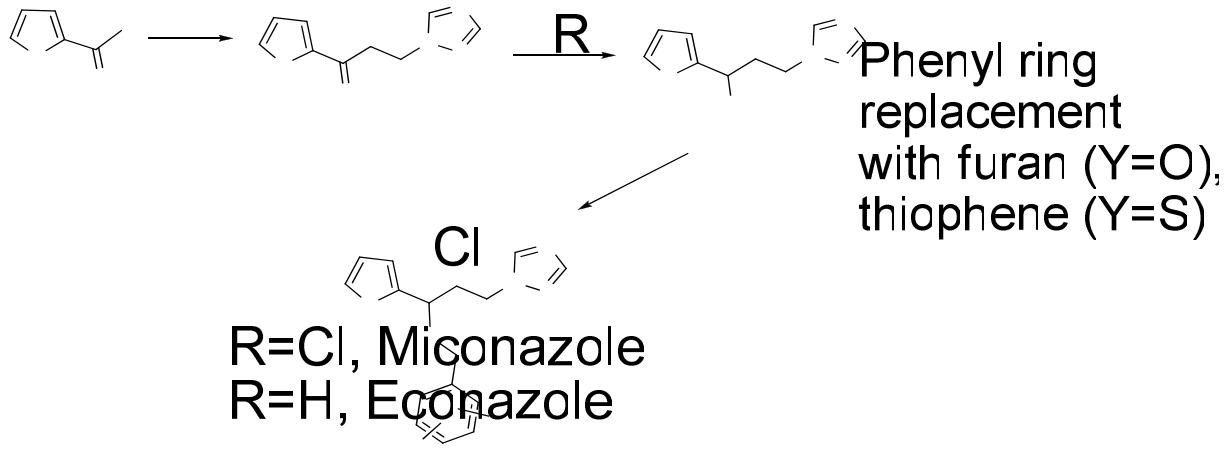


Figure 1. Strucuture of drugs Miconazole, Econazole and general structure of new benzyloxy furanyl, benzyloxy thiophenyl azoles **4-23** for SAR study.

The present paper describes the syntheses, *in vitro* antileishmanial activity and the structure-activity relationship (SAR) studies for a designed series of substituted benzyloxy furanyl and thiophenyl azoles (**4**–**23**).

2. Chemistry

Synthesis of benzyloxy thiophenyl azoles and benzyloxy furanyl azoles has been carried out as outlined in scheme 1.



Reagents and conditions: (i) pyrrolidine, $(HCHO)_n$, isopropanol, 90-95^oC, 6–8 h; (ii) corresponding Mannich salt, imidazole or 1*H*-1,2,4-triazole, ethanol:H_2O (3:2), 90^oC , 5–9 h; (iii) $NaBH_4$/MeOH, 0^oC–rt, 2 h; (iv) K(t-OBu), DMSO, substituted benzyl halides, 5^oC–rt, 2–3 h.

Ketones (2-acetyl thiophene or 2-acetyl furan) **1a**–**1b** was reacted with pyrrolidine and paraformaldehyde under Mannich conditions [14] to give the corresponding Mannich products. Subsequent replacement of the pyrrolidine with imidazole/1*H*-1,2,4-triazole (amine exchange reaction) to give the respective azolyl ketones **2a-2d**, followed by sodium borohydride reduction gave the hydroxyl intermediates **3a**–**3d**. Condensation of the hydroxyl intermediates **3a**–**3d** with substituted benzyl halides furnished the required benzyl ethers **4**–**23**. All the above synthesized compounds were well characterized by spectroscopic methods such as IR, mass, NMR and elemental analyses.

3. Biological activities

3.1. Materials and methods

3.1.1. Antipromastigote activity

The luciferase transfected *L. donovani* (strain MHOM/IN/80/Dd_8) promastigotes are being maintained in this laboratory (Division of Parasitology, C.D.R.I., Lucknow) since 2005 as detailed by Sunduru et al. [15]. The *in vitro* effect of the compounds on the growth of promastigotes was assessed by monitoring the luciferase activity of viable cells after treatment. The transgenic promastigotes of late log phase were seeded at $5x10^5$/100µl medium 199 well in 96-well flat bottomed microtitre (MT) plates (CELLSTAR) and incubated for 72 h in medium alone or in the presence of compounds (20 µM Conc.) in DMSO [16]. Parallel dilutions of DMSO were used as controls. After incubation, an aliquot (50 µL) of promastigote suspension was aspirated from each well of a 96 well plate and mixed with an equal volume of Steady Glo$^{(R)}$ reagent (Promega) and luminescence was measured by a luminometer. The values were expressed as relative luminescence unit (RLU).

$$\text{Percentage Inhibition} = \frac{N-n}{N} \times 100$$

Where N is average relative luminescence unit (RLU) of control wells; n is average RLU of treated wells.

3.1.2. Antiamastigote activity

For assessing the activity of compounds against the amastigote stage of the parasite, mouse macrophage cell line (J-774A.1) infected with promastigotes expressing luciferase firefly reporter gene was used. Cells were seeded in a 96-well plate ($4x10^4$cell/100µL/well) in RPMI-1640 containing 10% foetal calf serum and the plates were incubated at 37°C in a CO_2 incubator. After 24 h, the medium was replaced with fresh medium containing stationary phase promastigotes ($4x10^5$/100µL/well). Promastigotes invade the macrophage and are transformed into amastigotes. The test compounds were added at two fold dilutions up to 7 points in complete medium starting from 40 µM conc. after replacing the previous medium and the plates were incubated at 37^oC in a CO_2 incubator for 72 h. After incubation, the drug containing medium was decanted and 50 µL PBS was added in each well and mixed with an equal volume of Steady Glo reagent. After gentle shaking for 1-2 minute, the reading was taken in a luminometer [16–18]. The values are expressed as relative luminescence units (RLU). Data are transformed into a

graphic program (Excel). IC_{50} of antileishmanial activity was calculated by nonlinear regression analysis of the concentration – response curve using the four parameter Hill equations.

3.1.3. Cytotoxicity assay

The cell viability was determined using the MTT assay [18]. Exponentially growing cells (KB Cell line) (1×10^5cells /100µL/well) were incubated with test drug for 72 hours. The test compounds are added at three fold dilutions up to 7 points in complete medium starting from 400 µM concentration, and were incubated at 37ºC in a humidified mixture of CO_2 and 95% air in an incubator. Podophyllotoxin was used as reference drug. Stock solutions of compounds were initially dissolved in DMSO and further diluted with fresh complete medium. After incubation, 25 µL of MTT reagent (5 mg/mL) in PBS medium, followed by syringe filtration were added to each well and incubated at 37 °C for 2 hours. At the end of the incubation period, the supernatant were removed by tilting plate completely without disturbing cell layer and 150 µL of pure DMSO are added to each well. After 15 min. of shaking the readings were recorded as absorbance at 544 nm on a micro plate reader. The cytotoxic effect were expressed as 50% lethal dose, i.e., as the concentration of a compound which provoked a 50% reduction in cell viability compared to cell in culture medium alone. CC50 values were estimated as previously described [19, 20].

4. Results and discussion

The *in vitro* biological activity of benzyloxy thiophenyl and benzyloxy furanyl azole derivatives (**4-23**) has shown encouraging results against *L. donovani* and clearly suggests that the furanyl azoles are better inhibitors in comparison to thiophenyl azoles and also imidazole derivatives are more active compare to triazole derivatives.

All the compounds were evaluated in vitro against extracellular promastigotes and intracellular amastigotes.

Table 1.

In vitro antileishmanial activity and cytotoxicity of synthesized azoles

Comp. No.	Antipromastigote activity % inhibition at 20µM	Antiamastigote activity IC_{50}(µM) (against MQ amastigotes)	Cytotoxicity against J774A.1 cell lines CC_{50} (µM)	SI (selectivity index) CC_{50}/IC_{50}
4	100	3.04	60.21	19.80
5	91.83	5.15	56.16	10.90
6	95.97	4.03	37.55	7.15
7	95.47	4.20	28.84	6.86
8	98.99	5.35	30.91	5.77
9	97.50	7.36	18.56	3.17

10	97.79	NI	ND	NA
11	94.45	9.39	28.92	3.08
12	90.50	NI	ND	NA
13	98.50	NI	ND	NA
14	100	5.14	45.95	8.93
15	87.83	5.26	29.71	5.65
16	85.90	6.75	18.02	2.66
17	90.56	7.81	34.41	4.40
18	86.83	7.35	15.12	2.05
19	80.62	8.04	15.58	1.93
20	97.13	NI	ND	NA
21	97.29	NI	ND	NA
22	91.97	NI	ND	NA
23	94.75	NI	ND	NA
miltefosine	99.90	13.40	3.23	0.24
miconazole	100	6.00	9.93	1.66

NI: no inhibition at 40 μM; ND: not done; NA; not available.

Table1.Displays the percentage inhibition of these compounds against promastigotes. Interestingly, all the 20 compounds exhibited high inhibition of 80–100% at 20 μM concentration against promastigotes. These compounds were further screened against amastigote model and their IC50, CC50 and selectivity index (SI) are given in Table 1. All the 10 compounds in the furanyl series (4–13) exhibited more than 90% inhibition against promastigote form of parasite, while 6 compounds in the thiophenyl series (14, 17, 20–23) showed the same percentage of inhibition against promastigotes. However, on further screening, the triazoles were not selective against amastigote model and most of the triazolyl compounds were found to be inactive. The IC50 and SI values for amastigotes of the furanyl azoles (4–13) indicate that these compounds exhibited high activity against L. donavani (IC50 = 3.04–9.39 μM), better than the reference drug miltefosine (IC50 = 13.40 μM) except the triazolyl compounds 10, 12 & 13 which were found to be inactive. Two compounds 4 and 5 produced an interesting selective amastigote activity (SI >10). Further, the compound 4, with a 3-chlorobenzyloxy moiety was found to be the most potent among all, with an IC50 of 3.04 μM and a SI of 19.80. It was also found to be the least toxic with a CC50 of 60.21μM and was several folds more selective than the standard drugs miltefosine (SI = 0.24) and miconazole (SI = 1.66).

Among the thiophenyl azoles (1**4**–**23**) all the imidazole analogs appeared active exerting a strong inhibitory effect on the amastigote form of parasite with IC_{50} in the range of 5.14 to 7.81 μM,

while all the triazoles (**20**–**23**) except that of **19** were found inactive against amastigote model (no inhibition at 40 μM).

The overall activity profile of the test compounds demonstrated that the biological activity was highly influenced by the azole moiety. Compounds (**4**–**8** and 1**4**–**18**) consisting an imidazole moiety showed the lowest IC_{50} (3.04–5.65 and 5.14–7.81 μM) and the maximum SI values, whereas compounds with a triazolyl moiety (**9**–**13** and 1**9**–**23**) showed either low inhibition or were found inactive. Thus it is apparent from the activity results (Table 1) that the imidazole ring is crucial for the activity as on replacement of this with triazoles the antiamastigote activity decreased several folds leading to inactive compounds.

Further, the antiamastigote activity was also noticeably influenced by the type of substituent attached at the benzyloxy nucleus. Compounds (4, 9, 14 and 19) consisting a 3-chlorobenzyloxy group showed the lowest IC50 (3.04, 7.36, 5.14 and 8.04 μM) and the maximum SI values in both the series. It is interesting to note that while the chloro- group at position-2,5 (6, and 16) renders the molecule moderately active, the same group at position-2,4 enhances the activity in compounds 5 and 15 and in addition, the presence of same Cl atom at position-3 further confers maximum selectivity (4 and 14). Moreover, the replacement of chlorine atom with fluorine (7, 8, 22 & 23) resulted in decreased selectivity. This finding indicates that benzyloxy moiety with 3-chloro- substituent should be investigated for the development of highly selective antileishmanial compounds.

5. Conclusions

In conclusion, this study has identified benzyloxy furanyl and benzyloxy thiophenyl imidazoles as a new structural class of azoles with antileishmanial activity. The tested compounds were found several folds less toxic (CC_{50} values 15–60 μM) than the reference drug miltefosine (CC_{50} =3.23μM) and also with miconazole (CC50 =9.93μM). They have also shown better selectivity index in comparison to miltefosine (SI= 0.24) and miconazole (SI= 1.66) indicating the clean potential of these compounds in treating leishmaniasis. The potent activity and simple synthesis of these azoles suggest that they are potential candidates for the development of more efficacious antileishmanial agents.

6. Experimental

IR spectra were recorded on Perkin Elmer 881 and FTIR 8210 PC, Schimadzu spectrophotometers either on KBr discs or in neat. Nuclear magnetic resonance (NMR) spectra were recorded on Bruker Avance DRX-300 MHz spectrometers using TMS as an internal reference. All shifts are given in ppm and signals were abbreviated as s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet. EI mass spectra were recorded on JEOL JMS-D-300 spectrometer with the ionization potential of 70 eV and ES mass spectra on Quantro-II, micro mass. Purity of all tested compounds was ascertained on the basis of their elemental analysis and was carried out on Carlo-Erba-1108 instrument. The melting points were recorded on an electrically heated melting point apparatus and are uncorrected.

*6.1. General procedure for synthesis of compounds **2a**–**2d***

To a stirred mixture of 1-(furan-2-yl)ethanone (**1a**) or 1-(thiophen-2-yl)ethanone **(1b)** (10 mmol), pyrrolidine hydrochloride (10 mmol) and $1/5^{th}$ of paraformaldehyde (10 mmol) in isopropanol (10 mL) was added conc. HCl dropwise to adjust the pH of the solution to 4. The reaction mixture was then heated in an oil bath at 90-95 ^{0}C for 30 minutes with stirring. Other four

portion of the paraformaldehyde were added at 15 minutes interval. The reaction mixture was further refluxed for 6-8 h. The solvent was distilled off. The residue obtained was washed with hexane (2x5 mL). The Mannich base of pyrrolidine obtained as a HCl salt were used further without purification.

A mixture of above Mannich salt (10 mmol) and imidazole/ 1*H*-1, 2, 4-triazole (12 mmol) in 10 mL ethanol : water (3:2) was heated for 5-9 h at 90 ^{o}C. The organic solvent was distilled off and the compound was extracted with dichloromethane (2x5 mL). The combined organic layer was dried over sodium sulphate and concentrated to give the crude product which was purified by column chromatography using methanol: chloroform (1: 99) as an eluant to provide the required compounds (**2a**–**2d**).

*6.1.1. 1-(*Furan-2-yl)-3-(1H-imidazol-1-yl) propan-1-one (2a)

from 1-(furan-2-yl)-3-(pyrrolidin-1-yl)propan-1-one hydrochloride and 1H-imidazole; Yield: 78%; oil; MS (ESI) m/z: 191 (100) $[M+1]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.31 (t, 2H, *J*=6.4 Hz), 4.39 (t, 2H, *J*=6.4 Hz), 6.53-6.55 (m, 1H), 6.96 (s, 1H, *imidazole H*), 7.01 (s, 1H, *imidazole H*), 7.19-7.21 (m, 1H, Ar*H*), 7.53 (s, 1H, *imidazole H*), 7.58-7.59 (m, 1H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): 39.5, 40.9, 112.5, 117.7, 119.1, 129.4, 137.3, 146.9, 152.0, 185.5; IR (Neat cm^{-1}): 3020, 2963, 2364, 1682, 1512, 1217, 1012, 769.

6.1.2. 1-(Furan-2-yl)-3-(1H-1, 2, 4-triazol-1-yl)propan-1-one (2b)

from 1-(furan-2-yl)-3-(pyrrolidin-1-yl)propan-1-one hydrochloride and 1*H*-1,2,4-triazole; Yield: 64%; oil; MS (ESI) m/z: 192 (100) $[M+1]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.45 (t, 2H, *J*=6.2 Hz), 4.61 (t, 2H, *J*=6.2 Hz), 6.53-6.55 (m, 1H), 7.20-7.22 (m, 1H), 7.59-7.60 (m, 1H), 7.90 (s, 1H, tri*azole H*), 8.19 (s, 1H, tri*azole H*); ^{13}C NMR (75 MHz, $CDCl_3$): 39.9, 41.2, 112.8, 118.1, 119.8, 131.1, 149.1, 154.4, 185.7; IR (Neat cm^{-1}): 3101, 2961, 1685, 1271, 782, 677.

6.1.3. 3-(1H-imidazol-1-yl)-1-(thiophen-2-yl) propan-1-one ***(2c)***

from 3-(pyrrolidin-1-yl)-1-(thiophen-2-yl)propan-1-one hydrochloride and 1*H*-imidazole; Yield: 81%; oil; MS (ESI) m/z: 207 (100) $[M+1]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.37 (t, 2H, *J*=6.5 Hz), 4.42 (t, 2H, *J*=6.4 Hz), 6.95-6.96 (m, 1H), 6.97 (s, 1H, *imidazole H*), 7.03 (s, 1H, *imidazole H*), 7.11-7.14 (m, 1H), 7.54 (s, 1H, *imidazole H*), 7.66-7.68 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 40.4, 41.3, 119.1, 128.3, 129.6, 132.3, 134.5, 137.4, 143.2, 189.3 ; IR (Neat cm^{-1}): 3019, *2967, 1678, 1259, 763, 689.*

6.1.4. 1-(Thiophen-2-yl)-3-(1H-1, 2, 4-triazol-1-yl) propan-1-one (2d)

from 3-(pyrrolidin-1-yl)-1-(thiophen-2-yl)propan-1-one hydrochloride and 1*H*-1,2,4-triazole; Yield: 67%; oil; MS (ESI) m/z: 208 (100) $[M+1]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.53 (t, 2H, *J*=6.2 Hz), 4.63 (t, 2H, *J*=6.1 Hz), 7.11-7.14 (m, 1H), 7.66-7.68 (m, 2H), 7.70-7.72 (m, IH), 7.90 (s, 1H, *triazole H*), 8.20 (s, 1H, tri*azole H*); ^{13}C NMR (75 MHz, $CDCl_3$): 40.6, 41.7, 119.8, 129.1, 129.8, 133.6, 149.6, 154.8, 190.2; IR (Neat cm^{-1}): 3020, 2958, 1679, 1217, 1076, 767, 669.

*6.2. General procedure for synthesis of compounds **3a-3d*:**

Sodium borohydride (30 mmol) was added in portions to a stirred and cooled solution of **2a**–**2d** (10 mmol) in methanol (10 mL) over a period of 30 minutes. The reaction mixture was further stirred at room temperature for 2 h. Methanol was distilled under reduced pressure. The residue was triturated with water (15 mL) and extracted with dichloromethane (3x10 mL). The combined organic layer was dried over sodium sulphate and concentrated to give the crude product which was purified by column chromatography using methanol: chloroform (2:98) as an eluant to *provide the hydroxy compound (3a–3d).*

6.2.1. 1-(Furan-2-yl)-3-(1H-imidazol-1-yl)propan-1-ol (3a)

from **2a**; Yield: 91%; oil; MS (ESI) m/z: 193 (100) $[M+1]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17-2.26 (m, 2H), 3.98-4.06 (m, 1H), 4.15-4.25 (m, 1H), 4.48 (dd, 1H, *J*=2.4, 5.6 Hz), 6.19 (d, 1H, *J*=3.2 Hz), 6.29-6.30 (m, 1H), 6.90 (s, 1H, *imidazole H*), 6.93 (s, 1H, *imidazole H*), 7.93-7.33 (m, 1H), 7.39 (s, 1H, *imidazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): 36.4, 43.3, 63.3, 105.7, 110.1, 118.9, 128.7, 137.2, 141.8, 151.7; IR (Neat cm^{-1}): 3512, 3018, 1512, 1237, 1071, 728.

6.2.2. 1-(Furan-2-yl)-3-(1H-1, 2, 4-triazol-1-yl) propan-1-ol (3b)

from **2b**; Yield: 94%; oil; MS (ESI) m/z: 194 (100) $[M+1]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35-2.42 (m, 2H), 4.26-4.47(m, 2H), 4.60 (dd, 1H, *J*=2.3, 5.4 Hz), 6.23 (d, 1H, *J*=3.2 Hz), 6.31-6.33 (m, 1H), 7.35-7.36 (m, 1H), 7.91 (s, 1H, tr*iazole H*), 8.06 (s, 1H, tr*iazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): 34.9, 45.9, 63.8, 106.1, 110.2, 142.1, 143.3, 151.8, 155.8; IR (Neat cm^{-1}): 3518, 3010, 1518, 1212, 1076, 784.

*6.2.3. 3-(1H-imidazol-1-yl)-1-(thiophen-2-yl) propan-1-ol **(3c)***

from **2c**; Yield: 89%; oil; MS (ESI) m/z: 209(100) $[M+1]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.15-2.34 (m, 2H), 4.00-4.09 (m, 1H), 4.20-4.29 (m, 1H), 4.53 (dd, 1H, *J*=4.8, 8.7 Hz), 6.92-6.94 (m, 2H), 6.96-6.99 (m, 2H), 7.23-7.26 (m, 1H), 7.43 (s, 1H, *imidazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): 36.7, 44.1, 63.8, 105.7, 110.7, 119.2, 129.1, 137.9, 141.1, 153.6; IR (Neat cm^{-1}): 3521, 3023, 1519, 1226, 1078, 798.

6.2.4. 1-(Thiophen-2-yl)-3-(1H-1, 2, 4-triazol-1-yl)propan-1-ol (3d)

from **2d**; Yield: 82%; oil; MS (ESI) m/z: 210(100) $[M+1]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17-2.33 (m, 2H), 4.03-4.08 (m, 1H), 4.25-4.38 (m, 1H), 4.56 (dd, 1H, *J*=4.8, 8.7 Hz), 7.01-7.04 (m, 2H), 7.22-7.28 (m, 1H), 7.91 (s, 1H, tr*iazole H*), 8.06 (s, 1H, tr*iazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): 38.4, 47.2, 65.2, 106.1, 110.8, 122.9, 129.7, 151.8, 159.7; IR (Neat cm^{-1}): 3512, 3015, 1521, 1217, 1072, 792.

*6.3. General procedure for synthesis of compounds **4–23:***

To a stirred suspension of **3a**–**3d** (1 mmol)) in dimethylsulfoxide (DMSO) (3 mL) at 5-10°C was added potassium *t*-butoxide (1.2 mmol) in small portions within a period of 10 min. After stirring 30 min. appropriate benzyl halide (1 mmol) was added and then stirring was continued at room temperature for 2-3 h. The reaction mixture was quenched with ice cold (5 mL) water and

extracted with ethyl acetate (3×5 mL), the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude product which was purified by column *chromatography by using silica gel (60-120 mesh) to give the desired compounds 4–23* .

6.3.1. 1-(3-(3-Chlorobenzyloxy)-3-(furan-2-yl) propyl)-1H-imidazole (4)

from **3a** and 3-chlorobenzylchloride; Yield: 68%; oil; MS (ESI) m/z: 317 (100) $[M+1]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.17-2.50 (m, 2H), 4.02-4.12 (m, 2H), 4.21-4.32 (m, 2H), 4.41-4.49 (m, 1H), 6.30-6.40 (m, 2H, Ar*H*), 6.86 (s, 1H, *imidazole H*), 7.06 (s, 1H, *imidazole H*), 7.15-7.16 (m, 1H, Ar*H*), 7.28-7.30 (m, 4H, Ar*H*), 7.43 (s, 1H, *imidazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ *35.6, 43.2, 69.6, 70.9, 109.0, 110.2, 118.7, 125.7, 127.7, 127.9, 129.6, 129.7, 134.3, 137.1, 139.8, 142.9, 152.6; IR (Neat cm-1): 3020, 2983, 1602, 1509, 1217, 767; Anal. Calcd. for C17H17ClN2O2 : C, 64.46; H, 5.41; N, 8.84; Found C, 64.43; H, 5.48; N, 8.91.*

6.3.2. 1-(3-(2,4-Dichlorobenzyloxy)-3-(furan-2-yl)propyl)-1H-imidazole (5)

from **3a** and 2,4-dichlorobenzylchloride; Yield: 71%; oil; MS (ESI) m/z: 351 (100) $[M+1]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.21-2.52 (m, 2H), 4.03-4.16 (m, 2H), 4.27-4.31 (m, 1H), 4.38-4.49 (m, 2H), 6.33-6.37 (m, 2H, Ar*H*), 6.88 (s, 1H, *imidazole H*), 7.06 (s, 1H, *imidazole H*), 7.23-7.28 (m, 1H, Ar*H*), 7.33-7.37 (m, 3H, Ar*H*), 7.43 (s, 1H, *imidazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.5, 43.2, 67.1, 71.3, 109.0, 110.2, 118.7, 127.1, 129.1, 129.6, 130.2, 133.7, 134.0, 134.1, 137.1, 142.9, 152.5; IR (Neat cm^{-1}): 3023, 2962, 1579, 1487, 1231,786; Anal. Calcd. for $C_{17}H_{16}Cl_2N_2O_2$: C*, 58.13; H, 4.59; N, 7.98; Found C, 58.19; H, 4.62; N, 8.01.*

6.3.3. 1-(3-(2, 5-Dichlorobenzyloxy)-3-(furan-2-yl) propyl)-1H-imidazole (6)

from **3a** and 2,5-dichlorobenzylbromide; Yield: 69%; oil; MS (ESI) m/z: 351 (100) $[M+1]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.20-2.57 (m, 2H), 4.01-4.20 (m, 2H), 4.25-4.30 (m, 1H), 4.37-4.47 (m, 2H), 6.33-6.37 (m, 2H, Ar*H*), 6.89 (s, 1H, *imidazole H*), 7.06 (s, 1H, *imidazole H*), 7.17-7.28 (m, 2H, Ar*H*), 7.40-7.43 (m, 3H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.5, 43.2, 67.2, 71.4, 109.2, 110.2, 118.8, 128.7, 128.9, 129.6, 130.3, 130.9, 132.7, 137.2, 137.3, 143.0, 152.2; IR (Neat cm^{-1}): 3013, 2957, 1635, 1508, 1231, 1021, 767; Anal. Calcd. for $C_{17}H_{16}Cl_2N_2O_2$: C, *58.13; H, 4.59; N, 7.98; Found C, 58.15; H, 4.67; N, 8.07.*

6.3.4. 1-(3-(2, 4-Difluorobenzyloxy)-3-(furan-2-yl)propyl)-1H-imidazole (7)

from **3a** and 2,4-difluorobenzylbromide; Yield: 58%; oil; MS (ESI) m/z: 319 (100) $[M+1]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.13-2.49 (m, 2H), 3.97-4.16 (m, 2H), 4.20-4.25 (m, 1H), 4.33-4.43 (m, 2H), 6.31-6.38 (m, 2H, Ar*H*), 6.77-6.89 (m, 3H, Ar*H*), 7.05 (s, 1H, *imidazole H*), 7.24-7.32 (m, 1H, Ar*H*), 7.41-7.43 (m, 2H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.5, 43.1, 63.9, 70.8, 103.9, 108.9, 110.2, 111.1, 111.4, 118.8, 120.9, 129.5, 131.3, 131.4, 137.2, 142.9, 152.5; IR (Neat cm^{-1}): 3033, 2923, 1619, 1507, 1220, 763; Anal. Calcd. for $C_{17}H_{16}F_2N_2O_2$: C, 64.14; H, 5.07; N, 8.*80; Found C, 64.21; H, 5.13; N, 8.86.*

6.3.5. 1-(3-(2, 5-Difluorobenzyloxy)-3-(furan-2-yl)propyl)-1H-imidazole (8)

from **3a** and 2,5-difluorobenzylbromide; Yield: 56%; oil; MS (ESI) m/z: 319 (100) $[M+1]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.16-2.53 (m, 2H), 4.00-4.19 (m, 2H), 4.19-4.25 (m, 1H), 4.35-4.44

(m, 2H), 6.32-6.37 (m, 2H, Ar*H*), 6.88 (s, 1H, *imidazole H*), 6.94-7.01 (m, 2H, Ar*H*), 7.04-7.09 (m, 2H, Ar*H*), 7.42-7.43 (m, 2H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.7, 43.8, 64.2, 71.7, 102.8, 109.3, 110.8, 111.3, 113.1, 118.7, 123.1, 128.9, 131.6, 132.5, 137.8, 143.7, 153.1; IR (Neat cm^{-1}): 3116, 2935, 1574, 1271, 781, 674; Anal. Calcd. for $C_{17}H_{16}F_2N_2O_2$: C, 64.14; H, 5.07; N*, 8.80; Found C, 64.19; H, 5.11; N, 8.84.*

6.3.6. 1-(3-(3-Chlorobenzyloxy)-3-(furan-2-yl) propyl)-1H-1, 2, 4-triazole (9)

from **3b** and 3-chlorobenzylchloride; Yield: 71%; oil; MS (ESI) m/z: 318 (100) $[M+1]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34-2.59 (m, 2H), 4.21-4.29 (m, 3H), 4.32-4.46 (m, 2H), 6.30-6.37 (m, 2H, Ar*H*), 7.12-7.16 (m, 1H, Ar*H*), 7.25-7.28 (m, 3H, Ar*H*), 7.43 (s, 1H, Ar*H*), 7.92 (s, 1H, *triazole H*), 7.93 (s, 1H, *triazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.8, 43.4, 64.5, 70.8, 104.7, 108.6, 110.4, 111.5, 112.0, 118.8, 120.7, 130.4, 133.2, 137.2, 143.8, 153.5; IR (Neat cm^{-1}): 3023, 2361, 1638, 1216, 764, 671; Anal. Calcd. for $C_{16}H_{16}F_2N_2O_2$: C, 60.47; H, 5.08; N, 13.22; Found C, 60.51; H*, 5.13; N, 13.29.*

6.3.7. 1-(3-(2, 4-Dichlorobenzyloxy)-3-(furan-2-yl)propyl)-1H-1,2,4-triazole (10)

from **3b** and 2,4-dichlorobenzylchloride; Yield: 73%; oil; MS (ESI) m/z: 352 (100) $[M+1]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43-2.56 (m, 2H), 4.25-4.42 (m, 3H), 4.45-4.49 (m, 2H), 6.34-6.35 (m, 2H, Ar*H*), 7.22-7.26 (m, 1H, Ar*H*), 7.32-7.42 (m, 3H, Ar*H*), 7.93 (s, 1H, *triazole H*), 7.97 (s, 1H, *triazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.0, 46.0, 67.2, 71.4, 108.9, 110.2, 127.0, 129.1, 130.3, 133.7, 134.0, 134.1, 142.9, 143.1, 151.9, 152.6; IR (Neat cm^{-1}): 3015, 2984, 1612, 1210, 714, 698; Anal. Calcd. for $C_{16}H_{15}Cl_2N_3O_2$: C, 54.56; H, 4.29; N, 11.93; Found C, 54.61; H, 4.32; *N, 12.02.*

6.3.8. 1-(3-(2, 5-Dichlorobenzyloxy)-3-(furan-2-yl)propyl)-1H-1,2,4-triazole (11)

from **3b** and 2,5-dichlorobenzylbromide; Yield: 68%; oil; MS (ESI) m/z: 352 (100) $[M+1]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.38-2.64 (m, 2H), 4.24-4.38 (m, 3H), 4.44-4.48 (m, 2H), 6.34-6.37 (m, 2H, Ar*H*), 7.20-7.27 (m, 2H, Ar*H*), 7.41-7.42 (m, 2H, Ar*H*), 7.95 (s, 1H, triazole *H*), 7.99 (s, 1H, *triazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.0, 45.9, 67.2, 71.6, 109.0, 110.2, 128.7, 129.0, *130.3, 130.9, 132.7, 137.3, 142.9, 143.2, 152.1, 152.3; IR (Neat cm-1): 3021, 1615, 1221, 785, 682; Anal.Calcd.for C16H15Cl2N3O2 : C, 54.56; H, 4.29; N, 11.93; Found C, 54.59; H, 4.37; N, 11.97.*

6.3.9. 1-(3-(2, 4-Difluorobenzyloxy)-3-(furan-2-yl)propyl)-1H-1,2,4-triazole (12)

from **3b** and 2,4-difluorobenzylbromide; Yield 51%; oil; MS (ESI) m/z: 320 (100) $[M+1]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33-2.56 (m, 2H), 4.20-4.30 (m, 2H), 4.33-4.35 (m, 1H), 4.37-4.45 (m, 2H), 6.31-6.37 (m, 2H, Ar*H*), 6.77-6.88 (m, 2H, Ar*H*), 7.25-7.32 (m, 1H, Ar*H*), 7.41-7.42 (m, 1H, Ar*H*), 7.93 (s, 1H, *triazole H*), 7.96 (s, 1H, *triazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.0, 45.8, 63.9, 71.0, 103.5, 104.2, 108.8, 110.2, 111.1, 111.4, 120.9, 131.2, 131.4, 142.8, 143.2, 152.6; IR (Neat cm^{-1}): 3100, 3024, 1528, 1224, 743, 618; Anal. Calcd. for $C_{16}H_{15}F_2N3O_2$: C, 60.18; H, 4.73; N, 13.16; Found C, 60.22; H, 4.79; N, 13.19.

6.3.10. 1-(3-(2, 5-Difluorobenzyloxy)-3-(furan-2-yl)propyl)-1H-1,2,4-triazole (13)

from **3b** and 2,5-difluorobenzylbromide; Yield 54%; oil; MS (ESI) m/z: 320 (100) $[M+1]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.35-2.59 (m, 2H), 4.22-4.31 (m, 2H), 4.33-4.35 (m, 1H), 4.37-4.46 (m, 2H), 6.32-6.37 (m, 2H, Ar*H*), 6.92- 7.00 (m, 2H, Ar*H*), 7.03-7.09 (m, 1H, Ar*H*), 7.42-7.43 (m, 1H, Ar*H*), 7.94 (s, 1H, *triazole H*), 7.97 (s, 1H, *triazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.0, 45.8, 63.9, 71.2, 108.9, 110.2, 115.4, 115.7, 116.5, 126.5, 126.8, 132.5, 133.7, 142.9, 143.2, 152.4; IR (Neat cm^{-1}): 3011, 2961, 1631, 1213, 764, 670; Anal. Calcd. for $C_{16}H_{15}F_2N3O_2$: C, 60.18; H, 4.73; N, 13.16; Found C, 60.25; H, 4.81; N, 13.22.

6.3.11. 1-(3-(3-Chlorobenzyloxy)-3-(thiophen-2-yl)propyl)-1H-imidazole (14)

from 3c and 3-chlorobenzylchloride; Yield 63%; oil; MS (ESI) m/z: 333 (100) [M+1]+; ^1H NMR (300 MHz, $CDCl_3$): δ 2.16-2.47 (m, 2H), 3.99-4.17 (m, 2H), 4.21 (d, 1H, *J*=11.7 Hz), 4.44 (d, 1H, *J*=8.7 Hz), 4.45 (d, 1H, *J*=11.7 Hz), 6.86 (s, 1H, *imidazole H*), 6.96-7.01 (m, 2H, Ar*H*), 7.06 (s, 1H, *imidazole H*), 7.14-7.16 (m, 1H, Ar*H*), 7.27-7.30 (m, 3H, Ar*H*), 7.32-7.34 (m, 1H, Ar*H*), 7.40 (s, 1H, *imidazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.1, 43.8, 70.0, 73.9, 119.1, 126.2, 126.5, 127.1, 128.3, 128.4, 130.0, 130.1, 133.1, 134.8, 137.5, 140.2, 144.6; IR (Neat cm^{-1}): 3021, 2989, 1611, 1215, 779, 682; Anal. Calcd. for $C_{17}H_{17}ClN_2OS$: C, 61.34; H, 5.15; N, 8.42; Found C, 61.27; H, 5.04; N, 8.56.

6.3.12. 1-(3-(2,4-Dichlorobenzyloxy)-3-(thiophen-2-yl)propyl)-1H-imidazole (15)

from **3c** and 2,4-dichlorobenzylchloride; Yield: 59%; oil; MS (ESI) m/z: 367 (100) $[M+1]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.16-2.48 (m, 2H), 4.00-4.19 (m, 2H), 4.35-4.44 (m, 1H), 4.48-4.52 (m, 1H), 4.49-4.52 (m, 1H), 6.88 (s, 1H, *imidazole H*), 6.99-7.01 (m, 2H, Ar*H*), 7.06 (s, 1H, *imidazole H*), 7.23-7.24 (m, 1H, Ar*H*), 7.31-7.36 (m, 2H, Ar*H*), 7.37-7.38 (m, 1H, Ar*H*), 7.43 (s, 1H, *imidazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.8, 43.4, 67.4, 74.6, 118.4, 126.3, 126.1, 126.9, 128.6, 129.3, 129.7, 131.2, 131.9, 133.3, 137.7, 138.1, 144.2; IR (Neat cm^{-1}): 3015, 2972, 1623, 1218, 783, 678; Anal. Calcd. for $C_{17}H_{16}Cl_2N_2OS$: C, 55.59; H, 4.39; N, 7.63; Found C, 55.68; H, 4.44; N, 7.54.

6.3.13. 1-(3-(2,5-Dichlorobenzyloxy)-3-(thiophen-2-yl)propyl)-1H-imidazole (16)

from **3c** and 2,5-dichlorobenzylbromide; Yield 61%; oil; MS(ESI) m/z: 367 (100) $[M+1]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.18-2.52 (m, 2H), 4.01-4.18 (m, 2H), 4.35-4.47 (m, 1H), 4.48-4.52 (m, 1H), 6.89 (s, 1H, *imidazole H*), 6.99-7.02 (m, 2H, Ar*H*), 7.07 (s, 1H, *imidazole H*), 7.19-7.23 (m, 1H, Ar*H*), 7.32-7.34 (m, 2H, Ar*H*), 7.39-7.41(m,1H), 7.42-7.43 (m, 2H, Ar*H* +*imidazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.7, 43.4, 67.1, 74.1, 118.8, 125.9, 126.3, 126.7, 128.8, 129.0, 129.6, 130.4, 131.0, 132.7, 137.2, 137.3, 143.8; IR (Neat cm^{-1}): 3012, 2987, 1615, 1212, 781, 686; Anal. Calcd. for $C_{17}H_{16}Cl_2N_2OS$: C, 55.59; H, 4.39; N, 7.63; Found C, 55.51; H, 4.45; N, 7.69.

*6.3.14. 1-(3-(2,4-Difluorobenzyloxy)-3-(thiophen-2-yl)propyl)-1H-imidazole (17**)***

from **3c** and 2,4-difluorobenzylbromide; Yield: 69%; oil; MS (ESI) m/z: 335 (100) $[M+1]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.12-2.43 (m, 2H), 3.97-4.17 (m, 2H), 4.31-4.48 (m, 3H), 6.78-6.85 (m, 2H, Ar*H*), 6.86 (s, 1H, *imidazole H*), 6.98- 7.01 (m, 2H, Ar*H*), 7.06 (s, 1H, *imidazole H*), 7.28-7.33 (m, 2H, Ar*H*), 7.42 (s, 1H, *imidazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.3, 45.9,

67.2, 74.4, 125.8, 126.3, 126.8, 127.8, 128.8, 130.6, 131.4, 131.9, 134.3, 134.1, 134.9, 142.9, 143.8; IR (Neat cm^{-1}): 3025, 2928, 1611, 1219,1015, 783, 672; Anal. Calcd. for $C_{17}H_{16}F_2N_2OS$: C, 61.06; H, 4.82; N, 8.38; Found C, 61.13; H, 4.73; N, 8.46.

6.3.15. 1-(3-(2,5-Difluorobenzyloxy)-3-(thiophen-2-yl)propyl)-1H-imidazole (18)

from 3c and 2,5-difluorobenzylbromide; Yield : 74%; oil; MS (ESI) m/z: 335 (100) $[M+1]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.15-2.47 (m, 2H), 3.99-4.19 (m, 2H), 4.34-4.49 (m, 3H), 6.88 (s, 1H, *imidazole H*), 6.94-7.01 (m, 4H, Ar*H*), 7.06 (s, 1H, *imidazole H*), 7.07-7.10 (m, 1H, Ar*H*), 7.32-7.34 (m, 1H, Ar*H*), 7.42 (s, 1H, *imidazole H*); ^{13}C NMR (75 MHz, $CDCl_3$ δ 38.3, 46.2, *67.2, 74.3, 125.9, 126.6, 126.9, 127.5, 128.6, 130.7, 131.4, 131.9, 134.7, 134.4, 135.2, 142.7, 143.8; IR (Neat cm-1): 3013, 2922, 1612, 1218, 1012, 789, 698; Anal.Calcd. for C17H16F2N2OS : C, 61.06; H, 4.82; N, 8.38; Found C, 61.09; H, 4.83; N, 8.35.*

6.3.16. 1-(3-(3-Chlorobenzyloxy)-3-(thiophen-2-yl) propyl)-1H-1, 2, 4-triazole ***(19)***

from **3d** and 3-chlorobenzylchloride; Yield :66%; oil; MS (ESI) m/z: 334 (100) $[M+1]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.3-2.47 (m, 2H), 4.21-4.45 (m, 4H), 4.45-4.51 (m, 1H), 6.97-7.01 (m, 2H, Ar*H*), 7.15-7.17 (m, 1H, Ar*H*), 7.27-7.34 (m, 4H, Ar*H*), 7.93 (s, 1H, *triazole H*), 7.95 (s, 1H, *triazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.2, 46.0, 69.6, 73.6, 125.7, 125.8, 126.0, 126.7, 127.9, 128.0, 129.7, 134.3, 139.8, 143.1, 144.2, 152.1; IR (Neat cm^{-1}): 3083, 2982, 1611, 1510, 1210, 1017, 776; Anal. Calcd. for $C_{16}H_{16}ClN_3OS$: C, 57.56; H, 4.83; N, 12.59; Found C, 57.62; H, 4.91; N, 12.47.

6.3.17. 1-(3-(2,4-Dichlorobenzyloxy)-3-(thiophen-2-yl)propyl)-1H-1,2,4-triazole ***(20)***

from **3d** and 2,4-dichlorobenzylchloride; Yield: 53%; oil; MS (ESI) m/z: 368 (100) $[M+1]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.36-2.53 (m, 2H), 4.23-4.50 (m, 4H), 4.54-4.59 (m, 1H), 6.99-7.00 (m, 2H, Ar*H*), 7.22-7.26 (m, 1H, Ar*H*), 7.31-7.36 (m, 2H, Ar*H*), 7.38 (d, 1H, *J*=2.0 Hz, Ar*H*); 7.94 (s, 1H, *triazole H*), 7.97 (s, 1H, *triazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.2, 46.1, 67.2, 74.1, 125.8, 126.1, 126.7, 127.1, ,129.2, 130.4, 133.9, 134.0, 134.7, 143.2, 143.9, 152.1; IR (Neat cm^{-1}): 3022, 1626, 1506, 1214, 1082, 761; Anal. Calcd. for $C_{16}H_{15}Cl_2N_3OS$: C, 52.18; H, 4.11;N, 11.41; Found C, 52.26; H, 4.18; N, 11.46.

6.3.18. 1-(3-(2, 5-Dichlorobenzyloxy)-3-(thiophen-2-yl) propyl)-1H-1, 2, 4-triazole ***(21)***

from **3d** and 2,5-dichlorobenzylbromide; Yield: 64%; oil; MS (ESI) m/z: 368 (100) $[M+1]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.37-2.58 (m, 2H), 4.25-4.49 (m, 4H), 4.54-4.59 (m, 1H), 6.98-7.01 (m, 2H, Ar*H*), 7.19-7.29 (m, 2H, Ar*H*), 7.32-7.34 (m, 1H, Ar*H*), 7.43 (d, 1H, *J*=2.2 Hz, Ar*H*); 7.96 (s, 1H, *triazole H*), 7.99 (s, 1H, *triazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.2, 46.0, 67.2, 74.2, 125.9, 126.2, 126.7, 128.8, 129.1, 130.4, 131.0, 132.7, 137.7, 143.2, 143.8, 152.2; IR (Neat cm^{-1}): 3018, 1627, 1527, 1209, 1012, 796, 686; Anal. Calcd. for $C_{16}H_{15}Cl_2N_3OS$: C, 52.18; H, 4.11;N, 11.41; Found C, 52.26; H, 4.18; N, 11.46.

*6.3.19. 1-(3-(2, 4-*Difluorobenzyloxy*)-3-(thiophen-2-yl) propyl)-1H-1, 2, 4-triazole* ***(22)***

from **3d** and 2,4-difluorobenzylbromide; Yield: 57%; oil; MS (ESI) m/z: 336 (100) $[M+1]^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.37-2.45 (m, 2H), 4.22-4.46 (m, 4H), 4.47-4.52 (m, 1H), 6.78-6.89

(m, 2H, Ar*H*), 6.98-7.00 (m, 2H, Ar*H*), 7.28-7.33 (m, 2H, Ar*H*), 7.94 (s, 1H, *triazole H*), 7.97 (s, 1H, *triazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.2, 46.0, 63.9, 73.7, 104.2, 111.4, 120.8, 125.7, 126.0, 126.7, 131.3, 131.5, 143.2, 143.3, 144.1, 152.1; IR (Neat cm^{-1}): 3017, 1624, 1506, 1487,1216, 1082, 782; Anal. Calcd. for $C_{16}H_{15}F_2N_3OS$: C, 57.30; H, 4.51; N, 12.53; Found C, 57.38; H, 4.54; N, 12.47.

6.3.20. 1-(3-(2,5-Difluorobenzyloxy)-3-(thiophen-2-yl)propyl)-1H-1,2,4-triazole ***(23)***

from **3d** and 2,5-difluorobenzylbromide; Yield: 68%; oil; MS (ESI) m/z: 336 (100) $[M+1]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36-2.51 (m, 2H), 4.24-4.46 (m, 4H), 4.48-4.52 (m, 1H), 6.95-7.0 (m, 4H, Ar*H*), 7.05-7.11 (m, 1H, Ar*H*), 7.32-7.34 (m, 1H, Ar*H*), 7.96 (s, 1H, *triazole H*), 7.98 (s, 1H, *triazole H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.1, 45.9, 63.8, 73.9, 115.6, 115.7, 116.0, 116.1, 116.2, 116.5, 125.8, 126.1, 126.7, 143.3, 143.9, 152.1; IR (Neat cm^{-1}): 3124, 2927, 1617, 1518, 1227, 768, 660; Anal. Calcd. for $C_{16}H_{15}F_2N_3OS$: C, 57.30; H, 4.51; N, 12.53; Found C, 57.35; H, 4.57; N, 12.49.

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