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Short communication

Tetrahydronaphthyl azole oxime ethers: The conformationally rigid analogues of oxiconazole as antibacterials☆

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Abstract

A series of novel (*Z*)- and (*E*)-2-imidazolo-/triazolo-methyl tetrahydronaphthyl oxime ethers (**7**–**28**) were synthesized as conformationally constrained analogues of oxiconazole and evaluated for antifungal and antibacterial activities. Many of these derivatives exhibited potent antibacterial activity and surprisingly none of them was active against fungal strains. The SAR studies showed that imidazole oxime ethers were more active than the corresponding triazole oxime ethers. Imidazole derivatives **8**, **11**, **12**, **15**, **18**, **19**, **21** and **23** exhibited high inhibitory activity with 1.56–0.39 μg/mL MIC values against *Klebsiella pneumoniae*, *Escherichia coli* and *Staphylococcus aureus*. These compounds represent new structure scaffolds that can be further optimized to give new antibacterial agents with structures significantly different from those of existing classes of antibiotics.

Keywords: Oxiconazole; Antimicrobials; Rigid analogues; Tetrahydronaphthyl oxime ethers; Antibacterial activity

1. Introduction

The development of antimicrobial agents (antibacterials, antifungals, antivirals and antiparasitics) to treat infections has been one of the most notable medical achievements of the past century. These advances in medical care are threatened, however, by a natural phenomenon known as ‘‘antimicrobial resistance.’’ The increased use of antibacterial and antifungal agents in recent years has resulted in the development of resistance to these drugs [1–4] with important implications for morbidity, mortality and health care costs. In spite of a large number of antibiotics and chemotherapeutics available for medical use, the antimicrobial resistance created a substantial medical need for new classes of antimicrobial agents in the last decades [5,6]. In view of the above, the design and synthesis of newer antimicrobials will always remain an area of immense significance.

Among the various pharmacophores responsible for antimicrobial activity, the azole derivatives [7–9] seem to be a viable lead structure for a more efficacious, broad spectrum, systemic antifungal drug. The azoles, which include the imidazole and triazole compounds, inhibit the synthesis of sterols in fungi by inhibiting cytochrome P450-dependent 14a-lanosterol demethylase (P-45014DM) [8,9]. Moreover, the disubstituted imidazoles are effective inhibitors of enoyl acyl carrier protein reductase (FabI), a novel antibacterial target [10,11]. Despite the growing list of azoles, their clinical value has been limited by their relatively high risk of toxicity, the emergence of drug resistance, pharmacokinetic deficiencies and/or insufficiencies in their activity [7,12–14]. This necessitates the development of more effective broad spectrum antimicrobials with fewer side effects.

Fig. 1 summarizes the commonly used azole drugs viz. miconazole, oxiconazole and fluconazole. These structures reveal the presence in all of these molecules one common pharmacophoric portion that is a phenyl ring linked by an ethyl group to

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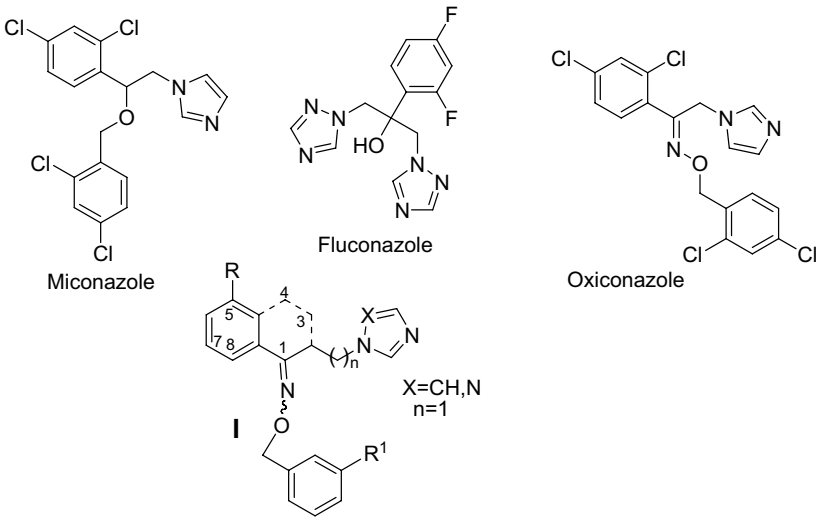


Fig. 1. Representative azole drugs.

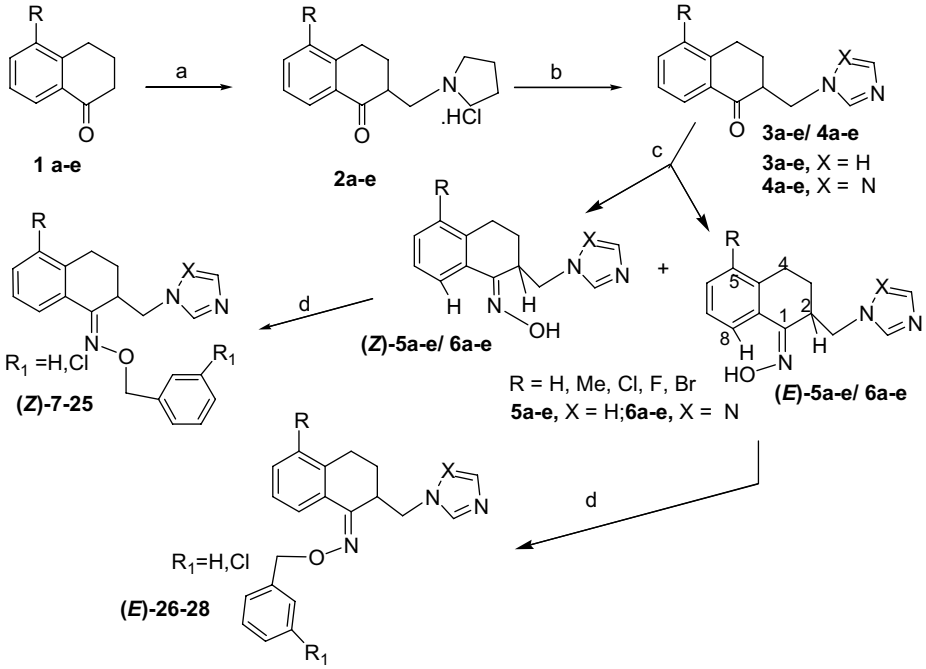
a nitrogen of azole ring (imidazole or triazole) [15]. The ethyl chain is often substituted on its C-2 by ether group as in miconazole [7], by a methyltriazolyl and hydroxyl group as in fluconazole [7], or oxime ether group as in oxiconazole [15]. The above report prompted us to investigate how the antifungal activity of these azoles would be influenced by restricting the free movement of azolylethyl chain as it is well established that the incorporation of conformational constraints in analogues of biologically active compounds enhances receptor selectivity and modulates efficacy [16]. It has been carried out by linking the C-1 carbon atom of azolylethyl chain and C-2 of the phenyl ring through two carbon spacer. Thus herein we report the synthesis, antifungal and antibacterial activities of novel tetrahydronaphthyl azole oxime ethers (**I**) (Fig. 1) as conformationally constrained or cyclic analogues of oxiconazole.

2. Chemistry

The synthetic route for the preparation of (*Z*)- and (*E*)-2-imidazolo-/2-triazolo-methyl tetrahydronaphthyl oxime ethers (**7**–**28**) is outlined in Scheme 1. Mannich reaction of 5-substituted α-tetralones (**1a**–**e**) [17–19] with pyrrolidine furnished the 2-pyrrolidin-1-yl-methyltetrahydronaphthalen-1-ones (**2a**–**e**) which on reaction with imidazole/triazole in the presence of ethanol/water resulted in the replacement of pyrrolidine moiety with imidazole/triazole (**3a**–**e**/**4a**–**e**). The keto intermediate (**3a**–**e**/**4a**–**e**) was then transformed to corresponding oxime (**5a**–**e**/**6a**–**e**) with hydroxylamine hydrochloride. The reaction was stereoselective giving (*Z*)-oxime as the major product with small amount of (*E*)-isomer (5–8%). ^{1}H NMR spectroscopy was used to assign (*Z*) or (*E*) configuration [20,21] to the geometrical isomers of imidazole (**5a**–**e**) and triazole oximes (**6a**–**e**) and it was possible to allocate signals to two different isomers. In **5a** (R = H) the C-2 proton is deshielded by the presence of the proximal hydroxyl function and must therefore be the *Z*-isomer and appeared lower field at δ 4.34–4.39 compared to the *E*-isomer (δ 4.30–4.32). This is due to the paramagnetic effect of the proximal hydroxyl oxygen [22]. Similarly in **5a** the proton at C-8 in (*E*)-isomer was deshielded and appeared at δ 8.52 compared to (*Z*)-isomer where it appeared at δ 7.95 (Section 5). Moreover, the results obtained for the chemical shift values of the groups linked directly to their iminic carbon are consistent with those reported in the literature for relevant oxime derivatives [22]. The (*Z*)-oximes (**5a**–**e**/**6a**–**e**) and (*E*)-oximes (**5a**, **5d** and **5e**) were isolated pure and reacted with proper benzyl halides in the presence of sodium hydride to furnish the desired (*Z*)-**7**–**25** and (*E*)-oximino ethers **26**–**28**. Chemical and physical data of compounds are reported in Section 5.

3. Results and discussion

Compounds **7**–**28** were evaluated for their *in vitro* antimicrobial activity against the pathogenic bacteria and fungi. The evaluation of antibacterial activity of compounds **7**–**28** against various strains of pathogenic bacteria, for example, *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* was carried out according to the broth microdilution technique described by NCCLS [23,24] and the results are reported in Table 1. The minimum inhibitory concentration (MIC) of each compound was determined against test isolates using this technique. The antibacterial activity was compared with that of standard antibacterial drug gentamycin and also with oxiconazole and the MIC values are expressed in micrograms per milliliter. Oxiconazole was found inactive against all the strains except *S. aureus* (MIC 6.25 μg/mL). Nine compounds (**7**, **8**, **11**, **12**, **15**, **18**, **19**, **22** and **23**) have shown good to moderate activity (MIC 1.563–6.25 μg/mL) as compared to gentamycin (MIC 0.78 μg/mL) against *K. pneumoniae* and all the compounds except **25** and (*E*)-isomers **26**–**28** exhibited very good to moderate activity (MIC 0.391–25 μg/mL) against *E. coli* in comparison to gentamycin (MIC 0.18 μg/mL). However, best activity was



Comp.	X	R	R_1	Comp.	X	R	R_1	Comp.	X	R	R_1
7	CH	H	H	**15**	CH	Cl	H	**23**	CH	F	Cl
8	CH	H	Cl	**16**	N	Cl	H	**24**	N	F	H
9	N	H	H	**17**	N	Cl	Cl	**25**	N	F	Cl
10	N	H	Cl	**18**	CH	Br	H	**26**	CH	H	Cl
11	CH	CH_3	H	**19**	CH	Br	Cl	**27**	CH	Cl	H
12	CH	CH_3	Cl	**20**	N	Br	H	**28**	CH	Br	Cl
13	N	CH_3	H	**21**	N	Br	Cl				
14	N	CH_3	Cl	**22**	CH	F	H				

Scheme 1. Synthesis of **7**–**25**. *Reagents*: (a) $(HCHO)_3$, pyrrolidine hydrochloride, isopropanol; (b) imidazole/1*H*-1,2,4-triazole, ethanol/water; (c) $NH_2OH \cdot HCl$, ethanol; (d) NaH, DMF, benzyl halide.

observed against *S. aureus* where 16 compounds have shown either better or comparable MIC range (0.781–12.25 μg/mL) with that of gentamycin (MIC 6.25 μg/mL). Moreover, all the compounds were inactive against the resistant strain *P. aeruginosa* at 50 μg/mL in which gentamycin also showed very weak activity (MIC 25 μg/mL).

The antifungal screening of compounds **7**–**28** against various strains of pathogenic fungi, for example, *Candida albicans*, *Cryptococcus neoformans*, *Sporothrix schenckii*, *Trichophyton mentagrophytes*, *Aspergillus fumigatus* and *Candida parapsilosis* was carried out according to broth microdilution technique described by NCCLS [23,24]. The antifungal activity was compared with that of standard antifungal drug fluconazole and oxiconazole. MIC of compounds and standard drugs were determined in 96-well tissue culture plates using RPMI 1640 media buffered with MOPS (3-[*N*-morpholino]propane sulfonic acid obtained from Sigma Chemical Co.). Out of the 22 compounds, three compounds (**7**, **12** and **18**) showed MIC at 50 μg/mL and compounds **8** and **15** were active at 25 μg/mL against *A. fumigatus*. There was no appreciable difference between the activities of (*Z*)-isomers (**8**, **15** and **19**) and (*E*)-isomers (**26**, **27** and **28**) as regards to the tested fungal species with the exception of *T. mentagrophytes* against which the (*E*)-isomers **26**–**28** were more active (MIC 12.25–25 μg/mL) than corresponding (*Z*)-isomers (MIC > 50 μg/mL). Rest of the compounds were inactive at 50 μg/mL concentration (Table 1).

In general, the antibacterial evaluation of the test compounds **7**–**28** as compared to reference drug gentamycin showed that the compounds comprising of imidazole moiety (**7**, **8**, **11**, **12**, **15**, **18**, **19**, **22** and **23**) were more active than corresponding triazole derivatives (**9**, **10**, **13**, **14**, **16**, **17**, **20**, **21**, **24** and **25**). Comparison between MIC values of the (*Z*)- and (*E*)-isomers against various strains of pathogenic bacteria revealed that the (*Z*)-isomers **8**, **15** and **19** were more potent than the corresponding (*E*)-isomers **26**, **27** and **28**. In terms of structure–activity relationship the comparison of MIC values of compounds indicated that the substitution in the naphthalene ring by different groups viz. methyl or halogens (F, Cl and Br) resulted in no appreciable change in the antibacterial activity (Table 1), whereas the substitution of chlorine in the benzyl group resulted in substantial enhancement (2- to 4-fold) of the antibacterial activity against all the tested strains. All the imidazolyl compounds showed significant activity

Table 1
Structures and *in vitro* antimicrobial activity for compounds **7**–**25** (MIC, μg/mL)

Compound	X	R	R_1	MIC (μg/mL) against bacteria				MIC (μg/mL) against fungi					
				Kp	*Ec*	*Pa*	*Sa*	*Ca*	*Cn*	*Ss*	*Tm*	*Af*	*Cp*
7	CH	H	H	6.25	0.781	>50	6.25	>50	>50	>50	>50	50	>50
8	CH	H	Cl	3.125	0.391	>50	1.563	>50	>50	>50	>50	25	>50
9	N	H	H	>50	25	>50	>50	>50	>50	>50	>50	>50	>50
10	N	H	Cl	>50	12.25	>50	12.25	>50	>50	>50	>50	>50	>50
11	CH	CH_3	H	6.25	0.781	>50	1.563	>50	>50	>50	>50	>50	>50
12	CH	CH_3	Cl	1.563	0.391	>50	0.781	>50	>50	>50	>50	50	>50
13	N	CH_3	H	>50	25	>50	>50	>50	>50	>50	>50	>50	>50
14	N	CH_3	Cl	>50	6.25	>50	6.25	>50	>50	>50	>50	>50	>50
15	CH	Cl	H	6.25	0.391	>50	1.563	>50	>50	>50	>50	25	>50
16	N	Cl	H	>50	25	>50	>50	>50	>50	>50	>50	>50	>50
17	N	Cl	Cl	>50	6.25	>50	>50	>50	>50	>50	>50	>50	>50
18	CH	Br	H	3.125	0.391	>50	1.563	>50	>50	>50	>50	50	>50
19	CH	Br	Cl	1.563	0.391	>50	0.781	>50	>50	>50	>50	>50	50
20	N	Br	H	>50	6.25	>50	12.5	>50	>50	>50	>50	>50	>50
21	N	Br	Cl	>50	3.125	>50	6.25	>50	>50	>50	>50	>50	>50
22	CH	F	H	6.25	0.781	>50	3.125	>50	>50	>50	>50	>50	>50
23	CH	F	Cl	1.563	0.391	>50	0.781	>50	>50	>50	>50	>50	>50
24	N	F	H	>50	25	>50	>50	>50	>50	>50	>50	>50	>50
25	N	F	Cl	>50	50	>50	>50	>50	>50	>50	>50	>50	>50
26	CH	H	Cl	>50	>50	>50	6.25	>50	>50	>50	25	>50	>50
27	CH	Cl	H	>50	>50	>50	3.125	50	>50	50	12.5	>50	>50
28	CH	Br	Cl	>50	>50	>50	1.56	50	>50	50	12.5	>50	>50
Gent				0.78	0.18	25	6.25	ND	ND	ND	ND	ND	ND
Flu				ND	ND	ND	ND	0.5	1.0	2.0	1.0	2.0	1.0
Oxico				>50	>50	>50	6.25	12.5	0.01	3.12	6.25	6.25	3.12

Kp, *Klebsiella pneumoniae*; *Ec*, *Escherichia coli*; *Pa*, *Pseudomonas aeruginosa*; *Sa*, *Staphylococcus aureus*; *Ca*, *Candida albicans*; *Cn*, *Cryptococcus neoformans*; *Ss*, *Sporothrix schenckii*; *Tm*, *Trichophyton mentagrophytes*; *Af*, *Aspergillus fumigatus*; and *Cp*, *Candida parapsilosis*, ND = not done; Gent = gentamycin; Flu = fluconazole; Oxico = oxiconazole.

against *S. aureus*, and compounds **12**, **19** and **23** were eight times more active than gentamycin.

The above results demonstrated that restricted analogues lacked antifungal activity despite of the fact that the azolyl and oxime ether moieties were unmodified. However, similar compounds with a benzopyran and an imidazolyl moiety [20] instead of tetrahydronaphthalene and azolomethyl moiety have been reported to display potent antifungal activity. As these compounds are skeletal analogues of oxiconazole with conformationally constrained structure due to which only a limited subset of conformations relative to the parent compound oxiconazole is possible. Therefore, the loss of overall antifungal activity of these azolomethyl tetrahydronaphthyl oxime ethers might be due to the adoption of an energetically accessible bioactive conformation suitable/appropriate for antibacterial target [25,26] rather than antifungal target.

4. Conclusion

In conclusion, we have synthesized a series of novel (*Z*)- and (*E*)-2-imidazolo-/2-triazolo-methyl tetrahydronaphthyl oxime ethers **7**–**25** and **26**–**28** as conformationally rigid analogues of oxiconazole. Antimicrobial activity was evaluated and compared with standard drugs. The results obtained from this study suggest that restricting the free movement of ethyl chain in oxiconazole led to the compounds with high antibacterial activity and complete loss in antifungal activity. However, there was not much difference between the (*E*)- and (*Z*)-isomers as regards to the antifungal activity but the (*Z*)-isomers were found more potent than corresponding (*E*)-isomers against bacterial strains. Amongst the synthesized compounds, all the imidazolyl derivatives displayed better *in vitro* antibacterial activity against *K. pneumoniae*, *E. coli*, and *S. aureus* compared to triazolyl derivatives. Compounds **12**, **19** and **23** emerged as most active in this series and were 8-fold more active than gentamycin against *S. aureus*. Thus, these compounds represent new lead for further pharmacomodulation in this series.

5. Experimental

5.1. Chemistry

Melting points were determined in open capillaries in an electrically heated block and are uncorrected. IR spectra of all the compounds were recorded on Perkin–Elmer AC-1 spectrophotometer. ^{1}H NMR spectra were recorded on Brucker WM 200 MHz spectrometer in deuterated solvents with TMS as internal reference. FAB mass spectra were recorded on a Jeol SX 102/DA-6000 mass spectrometer/data system using argon/xenon (6 kV, 10 mA) as the FAB gas. The accelerating voltage was 10 kV and the spectra were

recorded at room temperature. The electrospray mass spectra were recorded on a Micromass Quattro II triple quadrupole mass spectrometer. Microanalyses were determined on Carlo Erba EA-1108 element analyzer within ±0.4% of the theoretical value. Thin layer chromatography was performed on 7.5 × 3.0 cm precoated silica gel plastic plates (Aldrich). For column chromatography, basic alumina from Acme Synthetic Chemicals and silica gel of 60–120 mesh from Qualigen Fine Chemicals were used. 5-Substituted 1-tetralones (**1a**–**e**) [13–15] were prepared from γ-butyrolactone and substituted benzene.

*5.1.1. General procedure of the preparation of 2-pyrrolidin-1-ylmethyltetrahydronaphthalen-1-ones (**2a**–**e**)*

Conc. HCl was added dropwise to a stirred solution of 1-tetralones (**1a**–**e**) (11 mmol) and pyrrolidine hydrochloride (10 mmol) in isopropanol (15 mL) and the pH of the solution was adjusted to 4. One-fifth portion of paraformaldehyde (20 mmol) was added to the above mixture. The reaction mixture was then heated in an oil bath at 90–95 °C for 30 min with stirring. Other four portions of paraformaldehyde were added at 15 min interval. The reaction mixture was further refluxed for 4 h. The solvent was distilled off. The residue obtained was washed with hexane (5 mL × 2) and treated with sodium bicarbonate solution to make the pH alkaline and extracted with dichloromethane (15 mL × 3). Combined organic extracts were dried over Na_2SO_4 and distilled to afford the Mannich bases (**2a**–**e**) in good yield.

*5.1.1.1. 2-Pyrrolidin-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one (**2a**). With 1-tetralone (**1a**)*: yield 91%; oil; MS (ESI): *m/z* 230 ($M^+ + 1$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.72–1.80 (m, 5H, N–CH_2–CH_2–CH_2, H-3), 2.20–2.87 (m, 10H, H-2, H-3, H-4, N(CH_2–)$_3$), 6.97–7.21 (m, 3H, ArH), 7.96–7.92 (d, 1H, $J = 8.04$ Hz, H-8); IR (Neat): 2931, 2790, 1681, 1352, 1151, 744 cm^{-1}.

*5.1.1.2. 5-Methyl-2-pyrrolidin-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one (**2b**). With 5-methyl-1-tetralone (**1b**)*: yield 86%; oil; MS (ESI): *m/z* 244 ($M^+ + 1$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.78–1.82 (m, 5H, N–CH_2–CH_2–CH_2, H-3), 2.30–2.98 (m, 13H, ArCH_3, H-2, H-3, H-4, N(CH_2–)$_3$), 7.04–7.15 (m, 2H, ArH), 7.89–7.93 (d, 1H, $J = 7.94$ Hz, H-8); IR (Neat): 2898, 1692, 1607, 1315, 708 cm^{-1}.

*5.1.1.3. 5-Fluoro-2-pyrrolidin-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one (**2d**). With 5-fluoro-1-tetralone (**1d**)*: yield 83%; oil; MS (ESI): *m/z* 248 ($M^+ + 1$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.78 (m, 5H, N–CH_2–CH_2–CH_2, H-3), 2.47–2.93 (m, 10H, H-2, H-3, H-4, N(CH_2–)$_3$), 7.17 (s, 1H, ArH), 7.52–7.60 (m, 1H, ArH), 7.93–7.97 (d, 1H, $J = 7.84$ Hz, H-8); IR (Neat): 2931, 2364, 1687, 1602, 760 cm^{-1}.

*5.1.1.4. 5-Chloro-2-pyrrolidin-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one (**2c**). With 5-chloro-1-tetralone (**1c**)*: yield 78%; oil; MS (ESI): *m/z* 264 ($M^+ + 1$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.79 (m, 5H, N–CH_2–CH_2–CH_2, H-3), 2.43–2.98 (m, 10H, H-2, H-3, H-4, N(CH_2–)$_3$), 7.29 (s, 1H, ArH), 7.53–7.57 (m, 1H, ArH), 7.93–7.97 (d, 1H, $J = 7.85$ Hz, ArH); IR (KBr): 2960, 2810, 1684, 1352, 776 cm^{-1}.

*5.1.1.5. 5-Bromo-2-pyrrolidin-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one (**2e**). With 5-bromo-1-tetralone (**1e**)*: yield 79%; oil; MS (ESI): *m/z* 308 ($M^+ + 1$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.54 (m, 4H, N–CH_2–CH_2–CH_2), 1.96–2.19 (m, 3H, H-2, H-3), 2.94–3.32 (m, 6H, H-4, N(CH_2–)$_3$), 7.13–7.18 (m, 1H, ArH), 7.39–7.45 (m, 1H, ArH), 7.81–7.85 (m, 1H, H-8); IR (Neat): 2932, 1687, 1597, 1358, 769 cm^{-1}.

*5.1.2. General procedure of the preparation of 2-azol-1-ylmethyl-5-substituted-3,4-dihydro-2H-naphthalen-1-ones (**3a**–**e**)/(**4a**–**e**)*

To a suspension of **2a**–**e** (4.11 mmol) in ethanol/water (6 mL, 2:3) was added appropriate azole (imidazole/1*H*-1,2,4-triazole, 4.93 mmol) and the reaction mixture was heated for 3–6 h at 90 °C. The organic solvent was distilled off and the compound was extracted with dichloromethane (5 mL × 3). The organic layer was washed with water and dried over sodium sulphate and distilled to give **3a**–**e**/**4a**–**e** in excellent yield.

*5.1.2.1. 2-Imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one (**3a**). With **2a** and imidazole*: yield 74%; MS (ESI): *m/z* 227 ($M^+ + 1$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.71–1.79 (m, 1H, H-3), 2.06–2.11 (m, 1H, H-3), 2.78–3.05 (m, 3H, H-4, H-2), 4.37–4.46 (m, 2H, NCH_2), 6.92 (s, 1H, ArH), 7.02 (s, 1H, ArH), 7.16–7.36 (m, 2H, ArH), 7.44–7.49 (m, 2H, ArH), 8.02–8.06 (d, 1H, $J = 7.79$ Hz, H-8); IR (Neat): 3117, 2932, 1676, 1600, 1076, 716 cm^{-1}.

*5.1.2.2. 2-Imidazol-1-ylmethyl-5-methyl-3,4-dihydro-2H-naphthalen-1-one (**3b**). With **2b** and imidazole*: yield 81%; MS (ESI): *m/z* 241 ($M^+ + 1$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.73–1.76 (m, 1H, H-3), 2.02–2.11 (m, 1H, H-3), 2.37 (s, 3H, ArCH_3), 2.77–2.99 (m, 3H, H-2, H-4), 4.37–4.45 (m, 2H, NCH_2), 6.94 (s, 1H, ArH), 7.03 (s, 2H, ArH), 7.10–7.14 (d, 1H, $J = 3.5$ Hz, ArH), 7.51 (s, 1H, ArH), 7.92–7.96 (d, 1H, $J = 8.01$ Hz, H-8); IR (Neat): 3112, 2935, 1676, 1609, 1079, 713 cm^{-1}.

*5.1.2.3. 5-Fluoro-2-imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one (**3c**). With **2c** and imidazole*: yield 87%; oil; MS (ESI): *m/z* 245 ($M^+ + 1$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.67–1.82 (m, 1H, H-3), 1.98–2.31 (m, 1H, H-3), 2.74–3.06 (m, 3H, H-2, H-4), 4.27–4.38 (m, 2H, NCH_2), 6.86–6.97 (m, 2H, ArH), 7.13–7.19 (m, 2H, ArH), 7.45 (s, 1H, ArH), 7.97 (s, 1H, ArH); IR (Neat): 2925, 2367, 1594, 1351, 762 cm^{-1}.

*5.1.2.4. 5-Chloro-2-imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one (**3d**). With **2d** and imidazole*: yield 85%; oil; MS (ESI): *m/z* 261 ($M^+ + 1$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.72–1.80 (m, 1H, H-3), 2.27–2.29 (m, 1H, H-3), 2.89–3.13 (m, 3H, H-2, H-4), 4.73–4.99 (m, 2H, NCH_2), 7.21–7.33

(m, 1H, ArH), 7.56–7.73 (m, 3H, ArH), 7.94–7.98 (m, 1H, ArH); IR (Neat): 2935, 1682, 1588, 1081, 761, 669 cm^{-1}.

*5.1.2.5. 5-Bromo-2-imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one (**3e**). With **2e** and imidazole*: yield 89%; oil; MS (ESI): *m/z* 305 ($M^+ + 1$, 100%), 307 ($M^+ + 2$, 95%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.73–1.81 (m, 1H, H-3), 2.05–2.14 (m, 1H, H-3), 2.78–2.97 (m, 3H, H-2, H-4), 4.37–4.45 (m, 2H, NCH_2), 6.93–7.04 (m, 2H, ArH), 7.42–7.61 (m, 3H, ArH), 7.88–7.92 (m, 1H, ArH); IR (Neat): 2928, 1683, 1603, 1355, 1117, 768 cm^{-1}.

*5.1.2.6. 2-(1,2,4)-Triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one (**4a**). With **2a** and 1-H-1,2,4-triazole*: yield 84%; oil; MS (ESI): *m/z* 228 ($M^+ + 1$, 100%), 229 ($M^+ + 2$, 57%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.81–1.96 (m, 1H, H-3), 2.15–2.25 (m, 1H, H-3), 2.95–3.03 (m, 2H, H-4), 3.07–3.09 (m, 1H, H-2), 4.43–4.79 (dd, 2H, $J = 6.13$, 14.08 Hz, NCH_2), 7.19–7.34 (m, 2H, ArH), 7.43–7.47 (d, 1H, $J = 7.44$ Hz, ArH), 7.87 (s, 1H, *triazole H*), 7.98–8.02 (d, 1H, $J = 7.78$ Hz, H-8), 8.18 (s, 1H, *triazole H*); IR (Neat): 2925, 1681, 1350, 1141, 1357, 762, 680 cm^{-1}.

*5.1.2.7. 5-Methyl-2-(1,2,4)-triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one (**4b**). With **2b** and 1-H-1,2,4-triazole*: yield 87%; oil; MS (ESI): *m/z* 242 ($M^+ + 1$, 100%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.78–1.90 (m, 1H, H-3), 2.13–2.22 (m, 1H, H-3), 2.37 (s, 3H, ArCH_3), 2.96–3.09 (m, 3H, H-2, H-4), 4.44–4.79 (dd, 2H, $J = 6.18$, 14.09 Hz, NCH_2), 7.04 (s, 1H, ArH), 7.10–7.14 (d, 1H, $J = 14.08$ Hz, ArH), 7.82 (m, 2H, ArH, *triazole H*), 8.21 (s, 1H, *triazole H*); IR (Neat): 2939, 1683, 1352, 1140, 680 cm^{-1}.

*5.1.2.8. 5-Fluoro-2-(1,2,4)-triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one (**4c**). With **2c** and 1-H-1,2,4-triazole*: yield 76%; oil; MS (ESI): *m/z* 246 ($M^+ + 1$, 100%), 247 ($M^+ + 2$, 20%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.82–1.92 (m, 1H, H-3), 2.16–2.25 (m, 1H, H-3), 2.97–3.08 (m, 2H, H-4), 3.08–3.15 (m, 1H, H-2), 4.44–4.80 (dd, 2H, $J = 6.14$, 14.15 Hz, NCH_2), 7.19–7.34 (m, 2H, ArH), 7.64–7.80 (m, 1H, ArH), 7.92 (s, 1H, *triazole H*), 8.23 (s, 1H, *triazole H*); IR (Neat): 2927, 1685, 1580, 1320, 1246, 1012, 679 cm^{-1}.

*5.1.2.9. 5-Chloro-2-(1,2,4)-triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one (**4d**). With **2d** and 1-H-1,2,4-triazole*: yield 79%; oil; MS (ESI): *m/z* 262 ($M^+ + 1$, 100%), 263 ($M^+ + 2$, 39%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.79–1.81 (m, 1H, H-3), 2.18–2.24 (m, 1H, H-3), 2.86–2.99 (m, 2H, H-4), 3.02–3.12 (m, 1H, H-2), 4.66–4.79 (dd, 2H, $J = 4.88$, 14.18 Hz, NCH_2), 7.32 (s, 1H, ArH), 7.56–7.60 (d, 1H, $J = 7.74$ Hz, ArH), 7.92 (s, 1H, *triazole H*), 7.93–7.97 (d, 1H, $J = 8.72$ Hz, H-8), 7.99 (s, 1H, *triazole H*); IR (Neat): 2933, 1681, 1275, 1013, 680 cm^{-1}.

*5.1.2.10. 5-Bromo-2-(1,2,4)-triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one (**4e**). With **2e** and 1-H-1,2,4-triazole*: yield 81%; oil; MS (ESI): *m/z* 307 ($M^+ + 1$, 100%), 309 ($M^+ + 3$, 30%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.81 (m, 1H, H-3), 1.90–1.96 (m, 1H, H-3), 2.92–3.09 (m, 3H, H-2, H-4), 4.44–4.79 (dd, 2H, $J = 4.76$, 14.16 Hz, NCH_2), 7.15 (s, 1H, ArH), 7.56–7.60 (d, 2H, $J = 8.03$ Hz, ArH), 7.92 (s, 1H, *triazole* H), 8.21 (s, 1H, *triazole H*); IR (Neat): 2926, 1679, 1275, 1013, 679 cm^{-1}.

*5.1.3. General procedure of the preparation of 2-azol-1-ylmethyl-7-substituted-3,4-dihydro-2H-naphthalen-1-one oximes (**5a–e**/**6a–e**)*

Hydroxylamine hydrochloride (13.33 mmol) was added to a solution of **3a–e/4a–e** (4.44 mmol) in absolute ethanol (10 mL) and the mixture was refluxed for 3–4 h at 90 °C. The organic solvent was distilled off and the compound was basified by aqueous saturated potassium bicarbonate. The oxime was isolated as solid in 92% yield and the diastereomers separated on silica gel (230–400 mesh) column with chloroform as an eluent giving mainly the (*Z*)-oximes (**5a–e/6a–e**) with small amount (5–8%) of (*E*)-isomers (**5a–e/6a–e**). Further, proceeded for next step with (*Z*)- and (*E*)-isomers **5a–e/6a–e**. ^1H NMR data of representative (*Z*)- and (*E*)-oximes (**5a–e/6a–e**) are given below.

*5.1.3.1. (Z)-2-Imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one oxime (**5a**). With **3a***: yield 71%; m.p. 161–62 °C; MS (ESI): *m/z* 242 ($M^+ + 1$, 100%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.62–1.69 (m, 1H, H-3), 1.81–1.89 (m, 1H, H-3), 2.68–2.93 (m, 2H, H-4), 3.94–4.06 (m, 2H, NCH_2), 4.34–4.38 (m, 1H, H-2), 7.03 (s, 2H, *imidazole H*), 7.13–7.31 (m, 3H, ArH), 7.55 (s, 1H, *imidazole H*), 7.91–7.95 (d, 1H, $J = 7.42$ Hz, H-8); IR (KBr): 2924, 1600, 1445, 1351, 1137, 677 cm^{-1}.

*5.1.3.2. (E)-2-Imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one oxime (**5a**). With **3a***: yield 7%; m.p. 161–162 °C; MS (ESI): *m/z* 242 ($M^+ + 1$, 100%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.75–1.79 (m, 1H, H-3), 1.97–2.02 (m, 1H, H-3), 2.87–2.96 (m, 2H, H-4), 3.96–4.05 (m, 2H, NCH_2), 4.30–4.32 (m, 1H, H-2), 6.97 (s, 2H, *imidazole H*), 7.23–7.35 (m, 3H, ArH), 7.51 (s, 1H, *imidazole H*), 8.51–8.47 (d, 1H, $J = 8.82$ Hz, H-8); IR (KBr): 3409, 2927, 2238, 1659, 1596, 1441, 970 cm^{-1}.

*5.1.3.3. (Z)-5-Methyl-2-imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one oxime (**5b**). With **3b***: yield 72%; m.p. 156–158 °C; MS (ESI): *m/z* 256 ($M^+ + 1$, 100%); ^1H NMR (300 MHz, $CDCl_3$): δ 1.73–1.91 (m, 2H, H-3), 2.36 (s, 3H, ArCH_3), 2.64–2.74 (m, 1H, H-4), 2.87–2.90 (m, 1H, H-4), 3.97–4.04 (m, 2H, NCH_2), 4.33–4.37 (m, 1H, H-2), 6.98–7.12 (m, 4H, ArH), 7.60 (s, 1H, *imidazole H*), 7.76–7.78 (d, 1H, $J = 4.0$ Hz, ArH); IR (KBr): 2927, 1594, 1381, 1024, 700 cm^{-1}.

*5.1.3.4. (Z)-5-Fluoro-2-imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one oxime (**5c**). With **3c***: yield 62%; m.p. 182–84 °C; MS (ESI): *m/z* 260 ($M^+ + 1$, 100%), 262 ($M^+ + 3$, 30%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.79–1.83 (m, 2H, H-3), 2.75–2.89 (m, 2H, H-4), 3.94–4.04 (m, 2H, NCH_2),

4.25–4.35 (m, 1H, H-2), 6.87–7.09 (m, 4H, ArH), 7.24 (s, 1H, ArH), 7.55 (s, 1H, *imidazole H*); IR (KBr): 2930, 1595, 1350, 1078, 987, 774 cm^{-1}.

*5.1.3.5. (Z)-5-Chloro-2-imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one oxime (**5d**). With **3d***: yield 70%; m.p. 189–191 °C; MS (ESI): *m/z* 276 ($M^+ + 1$, 100%), 278 ($M^+ + 3$, 33%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.74–1.82 (m, 2H, H-3), 2.71–2.96 (m, 2H, H-4), 3.90–4.03 (m, 2H, NCH_2), 4.24–4.37 (m, 1H, H-2), 7.01 (s, 2H, *imidazole H*), 7.16–7.20 (m, 1H, H-7), 7.22–7.24 (d, 1H, $J = 7.91$ Hz, ArH), 7.56 (s, 1H, *imidazole H*), 7.88–7.92 (d, 1H, $J = 7.45$ Hz, H-8); IR (KBr): 2954, 1593, 1496, 1392, 1153, 1085, 677 cm^{-1}.

*5.1.3.6. (E)-5-Chloro-2-imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one oxime (**5d**). With **3d***: yield 6%; m.p. 196–197 °C; MS (ESI): *m/z* 276 ($M^+ + 1$, 100%), 278 ($M^+ + 3$, 33%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.79–2.04 (m, 2H, H-3), 2.75–2.96 (m, 2H, H-4), 3.96–4.01 (m, 2H, NCH_2), 4.20–4.29 (m, 1H, H-2), 6.89 (s, 2H, *imidazole H*), 7.17–7.21 (m, 1H, H-7), 7.58 (s, 1H, *imidazole H*), 7.64–7.68 (d, 1H, $J = 7.84$ Hz, H-6), 8.54–8.60 (d, 1H, $J = 8.20$ Hz, H-8); IR (KBr): 2957, 2234, 1648, 1593, 1363, 1017, 706 cm^{-1}.

*5.1.3.7. (Z)-5-Bromo-2-imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one oxime (**5e**). With **3e***: yield 74%; m.p. 162–164 °C; MS (ESI): *m/z* 321 ($M^+ + 1$, 100%), 223 ($M^+ + 3$, 82%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.79–1.87 (m, 2H, H-3), 2.66–2.97 (m, 2H, H-4), 3.98–4.09 (m, 2H, NCH_2), 4.21–4.47 (m, 1H, H-2), 7.04 (s, 1H, *imidazole H*), 7.12–7.35 (m, 3H, ArH), 7.60 (s, 1H, *imidazole H*), 7.92–7.96 (d, 1H, $J = 7.28$ Hz, H-8); IR (KBr): 2954, 1593, 1392, 1085, 677 cm^{-1}.

*5.1.3.8. (E)-Bromo-2-imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one oxime (**5e**). With **3e***: yield 6%; m.p. 162–63 °C; MS (ESI): *m/z* 321 ($M^+ + 1$, 100%), 323 ($M^+ + 3$, 82%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.81–2.05 (m, 2H, H-3), 2.85–3.01 (m, 2H, H-4), 3.97–4.08 (m, 2H, NCH_2), 4.18–4.38 (m, 1H, H-2), 6.88–7.28 (m, 2H, H-7, *imidazole H*), 7.61 (s, 1H, *imidazole H*), 7.65–7.68 (d, 1H, $J = 6.92$ Hz, H-6), 8.46–8.51 (d, 1H, $J = 8.85$ Hz, H-8); IR (KBr): 2928, 2340, 1655, 1630, 1382, 1084, 723 cm^{-1}.

*5.1.3.9. (Z)-2-(1,2,4)-Triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one oxime (**6a**). With **4a***: yield 77%; m.p. 174–175 °C; MS (ESI): *m/z* 243 ($M^+ + 1$, 100%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.72–1.88 (m, 2H, H-3), 2.70–2.79 (m, 1H, H-4), 2.92–3.01 (m, 1H, H-4), 4.08–4.12 (m, 1H, H-2), 4.24–4.60 (dd, 2H, $J = 5.16$, 13.18 Hz, NCH_2), 7.16–7.34 (m, 3H, ArH), 7.90–7.97 (d, 1H, $J = 7.03$ Hz, H-8), 7.97 (s, 1H, *triazole H*), 8.11 (s, 1H, *triazole H*); IR (KBr): 2816, 2364, 1597, 1352, 671 cm^{-1}.

*5.1.3.10. (Z)-5-Methyl-2-(1,2,4)-triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one oxime (**6b**). With **4b***: yield 68%; m.p. 167–169 °C; MS (ESI): *m/z* 257 ($M^+ + 1$, 100%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.76–1.91 (m, 2H, H-3), 2.33 (s, 3H, $ArCH_3$), 2.73 (m, 1H, H-4), 2.90–2.96 (m, 1H, H-4), 3.97–4.01 (m, 1H, H-2), 4.23–4.60 (dd, 2H, $J = 5.1$, 13.64 Hz, NCH_2), 6.98–7.09 (m, 2H, ArH), 7.79–7.83 (d, 1H, $J = 8.0$ Hz, ArH), 7.98 (s, 1H, *triazole H*), 8.25 (s, 1H, *triazole H*); IR (KBr): 2924, 1600, 1445, 1351, 765, 677 cm^{-1}.

*5.1.3.11. (Z)-5-Fluoro-2-(1,2,4)-triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one oxime (**6c**). With **4c***: yield 58%; m.p. 201–203 °C; MS (ESI): *m/z* 261 ($M^+ + 1$, 100%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.75–1.88 (m, 2H, H-3), 2.67–2.96 (m, 2H, H-4), 3.96–4.03 (m, 1H, H-2), 4.16–4.22 (m, 2H, NCH_2), 6.87–7.18 (m, 3H, ArH), 7.94 (s, 1H, *triazole H*), 8.11 (s, 1H, *triazole H*); IR (KBr): 2820, 2364, 1593, 1351, 756, 660 cm^{-1}.

*5.1.3.12. (Z)-5-Chloro-2-(1,2,4)-triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one oxime (**6d**). With **4d***: yield 64%; m.p. 193–195 °C; MS (ESI): *m/z* 277 ($M^+ + 1$, 100%), 278 ($M^+ + 3$, 20%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.77–1.89 (m, 1H, H-3), 2.67–2.75 (m, 1H, H-3), 2.82–2.97 (m, 2H, H-4), 3.96–4.02 (m, 1H, H-2), 4.23–4.47 (dd, 2H, $J = 5.63$, 14.63 Hz, NCH_2), 7.08–7.41 (m, 3H, ArH), 7.98 (s, 1H, *triazole H*), 8.30 (s, 1H, *triazole H*); IR (KBr): 2822, 2384, 1593, 1349, 669 cm^{-1}.

*5.1.3.13. (Z)-5-Bromo-2-(1,2,4)-triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one oxime (**6e**). With **4e***: yield 61%; m.p. 174–175 °C; MS (ESI): *m/z* 322 ($M^+ + 1$, 100%), 323 ($M^+ + 2$, 70%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.76–1.88 (m, 2H, H-3), 2.82–2.99 (m, 2H, H-4), 3.97–4.04 (m, 1H, H-2), 4.24–4.57 (dd, 2H, $J = 7.24$, 13.46 Hz, NCH_2), 7.29–7.43 (m, 2H, ArH), 7.77–7.81 (d, 1H, $J = 9.14$ Hz, H-8), 7.92 (s, 1H, *triazole H*), 8.18 (s, 1H, *triazole H*); IR (KBr): 3446, 2366, 1592, 762, 673 cm^{-1}.

*5.1.3.14. (E)-5-Bromo-2-(1,2,4)-triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one oxime (**6e**). With **4e***: yield 5%; m.p. 169–170 °C; MS (ESI): *m/z* 321 (M^+, 70%), 323 ($M^+ + 2$, 100%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.78–2.11 (m, 2H, H-3), 2.90–2.98 (m, 2H, H-4), 3.98–4.02 (m, 1H, H-2), 4.29–4.54 (dd, 2H, $J = 6.19$, 13.37 Hz, NCH_2), 7.10–7.40 (m, 2H, ArH), 7.96 (s, 1H, *triazole H*), 8.24 (s, 1H, *triazole H*), 8.50–8.45 (d, 1H, $J = 9.18$ Hz, H-8); IR (KBr): 3470, 2681, 1633, 1508, 1451, 970, 737 cm^{-1}.

*5.1.4. General procedure of the preparation of 2-azol-1-ylmethyl-3,4-dihydro-2H-napthalen-1-one oxime ethers (**7–28**)*

A solution of (*E*)-, (*Z*)-oxime (**5a/5d/5e**), (**5a–e/6a–e**) (0.416 mmol) in dimethyl sulphoxide (DMSO) (0.5 mL) was added dropwise to stirred suspension of sodium hydride (0.833 mmol) in DMSO (0.5 mL). The reaction mixture was stirred at room temperature for 5 min and benzyl bromide or 3-chlorobenzyl bromide (0.416 mmol) was added dropwise to it. Stirred for 15 min to 1 h for the completion of the reaction. The reaction was discontinued, and treated with water (5 mL) and extracted with ethyl acetate (3 mL × 3). The

combined organic layer was washed with water (10 mL × 6), dried over sodium sulphate and concentrated to give the crude product which was chromatographed on a 230–400 mesh silica gel column using chloroform as an eluent to get the desired oximino ethers **7–28** in good yield.

*5.1.4.1. (Z)-2-Imidazol-1-ylmethyl-3,4-dihydro-2H-napthalen-1-one O-benzyl-oxime (**7**). With (Z)-**5a** and benzyl bromide*: yield 82%; oil; MS (ESI): *m/z* 332 ($M^+ + 1$, 100%), 333 ($M^+ + 2$, 22%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.83–1.90 (m, 1H, H-3), 2.48 (m, 1H, H-3), 2.71–2.90 (m, 2H, H-4), 3.84–3.97 (m, 2H, NCH_2), 4.18–4.25 (m, 1H, H-2), 5.24 (s, 2H, PhCH_2–O–), 6.85 (s, 1H, *imidazole H*), 7.02 (s, 1H, *imidazole H*), 7.16–7.26 (m, 5H, ArH), 7.28–7.44 (m, 4H, ArH), 7.98–8.02 (d 1H, $J = 7.82$ Hz, H-8); IR (Neat): 2926, 1596, 1352, 1088, 700 cm^{-1}. Anal. Calcd for $C_{21}H_{21}N_3O$: C, 76.13; H, 6.34; N, 12.68. Found: C, 76.57; H, 6.39; N, 12.59.

*5.1.4.2. (Z)-2-Imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-(3-chloro-benzyl)-oxime (**8**). With (Z)-**5a** and 3-chloro-benzyl chloride*: yield 82%; oil; MS (ESI): *m/z* 366 ($M^+ + 1$, 100%), 367 ($M^+ + 2$, 15%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.80–1.86 (m, 1H, H-3), 2.56 (m, 1H, H-3), 2.67–2.95 (m, 1H, H-4), 3.89–4.00 (m, 2H, NCH_2), 4.20–4.25 (m, 1H, H-2), 5.19 (s, 2H, PhCH_2–O–), 6.89 (s, 1H, *imidazole H*), 7.00 (s, 1H, *imidazole H*), 7.13–7.17 (d, 2H, $J = 7.65$ Hz, ArH), 7.22–7.30 (m, 4H, ArH), 7.40–7.43 (d, 2H, $J = 6.1$ Hz, ArH), 7.96–8.00 (d, 1H, $J = 7.49$ Hz, H-8); IR (Neat): 3014, 2840, 1527, 1041, 759, 671 cm^{-1}. Anal. Calcd for $C_{21}H_{20}N_3OCl$: C, 69.13; H, 5.48; N, 11.52. Found: C, 68.97; H, 4.86; N, 11.68.

*5.1.4.3. (Z)-2-(1,2,4)-Triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-benzyl-oxime (**9**). With (Z)-**6a** and benzyl bromide*: yield 73%; oil; MS (ESI): *m/z* 333 ($M^+ + 1$, 100%), 334 ($M^+ + 2$, 20%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.79–1.90 (m, 1H, H-3), 2.66–2.75 (m, 1H, H-3), 2.88–3.00 (m, 2H, H-4), 3.95–4.00 (m, 1H, H-2), 4.17–4.53 (m, 2H, NCH_2), 5.22 (s, 2H, PhCH_2–O–), 7.13–7.16 (d, 2H, $J = 6.78$ Hz, ArH), 7.16–7.26 (m, 3H, ArH), 7.26–7.40 (m, 3H, ArH), 7.89 (s, 1H, *triazole H*), 7.89–7.96 (d, 1H, $J = 13.02$ Hz, H-8), 8.01 (s, 1H, *triazole H*); IR (Neat): 3433, 2925, 1597, 1352, 762, 669 cm^{-1}. Anal. Calcd for $C_{20}H_{20}N_4O$: C, 72.28; H, 6.02; N, 16.86. Found: C, 72.23; H, 6.30; N, 16.97.

*5.1.4.4. (Z)-2-(1,2,4)-Triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-(3-chloro-benzyl)-oxime (**10**). With (Z)-**6a** and 3-chloro-benzyl chloride*: yield 71%; oil; MS (ESI): *m/z* 367 ($M^+ + 1$, 100%), 369 ($M^+ + 3$, 20%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.79–1.83 (m, 1H, H-3), 2.77–2.88 (m, 1H, H-3), 2.92–2.97 (m, 2H, H-4), 4.01–4.06 (m, 1H, H-2), 4.18–4.46 (m, 2H, NCH_2), 5.17 (s, 2H, PhCH_2–O–), 7.14 (s, 1H, ArH), 7.18–7.21 (d, 2H, $J = 6.18$ Hz, ArH), 7.24–7.29 (m, 3H, ArH), 7.40 (s, 1H, ArH), 7.92–7.95 (d, 1H, $J = 7.04$ Hz, H-8), 7.97 (s, 1H, *triazole H*), 7.98 (s, 1H, *triazole H*); IR (Neat): 2927, 2858, 1359, 1210, 1019, 762, 669 cm^{-1}. Anal. Calcd for $C_{20}H_{19}N_4OCl$: C, 65.48; H, 5.18; N, 15.27. Found: C, 65.42; H, 5.09; N, 15.25.

*5.1.4.5. (Z)-2-Imidazol-1-ylmethyl-5-methyl-3,4-dihydro-2H-naphthalen-1-one O-benzyl-oxime (**11**). With (Z)-**5b** and benzyl bromide*: yield 69%; oil; MS (ESI): *m/z* 346 ($M^+ + 1$, 100%), 347 ($M^+ + 2$, 30%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.75–2.21 (m, 2H, H-3), 2.29 (s, 3H, ArCH_3), 2.69 (m, 2H, H-4), 3.84–3.90 (m, 2H, NCH_2), 4.19–4.24 (m, 1H, H-2), 5.23–5.25 (d, 2H, $J = 4.21$ Hz, PhCH_2–O–), 6.85 (s, 1H, *imidazole H*), 6.96–7.10 (m, 4H, ArH), 7.36–7.40 (m, 5H, ArH), 7.88–7.92 (d, 1H, $J = 8.01$ Hz, H-8); IR (Neat): 3124, 2933, 2851, 1509, 1283, 1081, 659 cm^{-1}. Anal. Calcd for $C_{22}H_{23}N_3O$: C, 76.52; H, 6.66; N, 12.17. Found: C, 76.43; H, 6.30; N, 12.03.

*5.1.4.6. (Z)-2-Imidazol-1-ylmethyl-5-methyl-3,4-dihydro-2H-naphthalen-1-one O-(3-chloro-benzyl)-oxime (**12**). With (Z)-**5b** and 3-chloro-benzyl chloride*: yield 83%; oil; MS (ESI): *m/z* 380 ($M^+ + 1$, 100%), 382 ($M^+ + 3$, 30%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.68–1.80 (m, 2H, H-3), 2.33 (s, 3H, ArCH_3), 2.70–2.84 (m, 2H, H-4), 3.87–3.98 (m, 2H, NCH_2), 4.16–4.23 (m, 1H, H-2), 5.17–5.19 (d, 2H, $J = 3.91$ Hz, PhCH_2–O–), 6.88 (s, 1H, *imidazole H*), 6.96–7.11 (m, 3H, ArH), 7.22–7.30 (m, 3H, ArH), 7.39–7.42 (d, 2H, $J = 5.34$ Hz, ArH), 7.85–7.89 (d, 1H, $J = 8.05$ Hz, H-8); IR (Neat): 3016, 2940, 2368, 1669, 1507, 1031, 669 cm^{-1}. Anal. Calcd for $C_{22}H_{22}N_3OCl$: C, 69.56; H, 5.79; N, 11.06. Found: C, 69.43; H, 5.82; N, 11.01.

*5.1.4.7. (Z)-5-Methyl-2-(1,2,4)-triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-benzyl-oxime (**13**). With (Z)-**6b** and benzyl bromide*: yield 81%; oil; MS (ESI): *m/z* 347 ($M^+ + 1$, 100%), 348 ($M^+ + 2$, 20%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.77–1.91 (m, 1H, H-3), 2.32 (s, 3H, ArCH_3), 2.61–2.69 (m, 1H, H-3), 2.84–2.98 (m, 2H, H-4), 3.96–3.97 (m, 1H, H-2), 4.15–4.46 (dd, 2H, $J = 13.57$, 4.99 Hz, NCH_2), 5.20 (s, 2H, PhCH_2–O–), 6.96–7.09 (m, 3H, ArH), 7.09–7.26 (m, 4H, ArH), 7.40 (s, 1H, ArH), 7.88–7.89 (m, 2H, ArH); IR (Neat): 2939, 2363, 1595, 1351, 683 cm^{-1}. Anal. Calcd for $C_{21}H_{22}N_4O$: C, 72.83; H, 6.35; N, 16.18. Found: C, 72.82; H, 6.38; N, 16.17.

*5.1.4.8. (Z)-5-Methyl-2-(1,2,4)-triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-(3-chloro-benzyl)-oxime (**14**). With (Z)-**6b** and 3-chloro-benzyl chloride*: yield 83%; oil; MS (ESI): *m/z* 381 ($M^+ + 1$, 100%), 383 ($M^+ + 3$, 20%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.75–1.87 (m, 1H, H-3), 2.33 (s, 3H, ArCH_3), 2.72 (m, 1H, H-3), 2.74 (m, 2H, H-4), 4.02 (m, 1H, H-2), 4.17–4.44 (dd, 2H, $J = 13.64$, 5.49 Hz, NCH_2), 5.15–5.17 (d, 2H, $J = 3.66$ Hz, PhCH_2–O–), 6.97–7.05 (m, 3H, ArH), 7.26–7.29 (d, 2H, $J = 6.25$ Hz, ArH), 7.39 (s, 1H, ArH), 7.84–7.88 (d, 1H, $J = 8.03$ Hz, H-8), 7.91 (s, 1H, *triazole H*), 7.95 (s, 1H, *triazole H*); IR (Neat): 3127, 2936, 1672, 1209, 759, 672 cm^{-1}. Anal. Calcd for

$C_{21}H_{21}N_4OCl$: C, 66.22; H, 5.51; N, 14.71. Found: C, 66.19; H, 5.60; N, 14.68.

*5.1.4.9. (Z)-5-Chloro-2-imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-benzyl-oxime (**15**). With (Z)-**5d** and benzyl bromide*: yield 78%; oil; MS (ESI): *m/z* 366 ($M^+ + 1$, 100%), 368 ($M^+ + 3$, 30%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.74–1.76 (m, 1H, H-3), 2.70–2.74 (m, 1H, H-3), 2.88–2.98 (m, 2H, H-4), 3.86–3.90 (m, 2H, NCH_2), 4.12–4.16 (m, 1H, H-2), 5.22–5.25 (d, 2H, $J = 4.19$ Hz, PhCH_2–O–), 6.85 (*s*, 1H, *imidazole H*), 7.06 (s, 1H, *imidazole H*), 7.10–7.15 (d, 2H, $J = 10.31$ Hz, ArH), 7.16–7.23 (m, 3H, ArH), 7.36–7.40 (m, 3H, ArH), 7.91–7.99 (m, 1H, ArH); IR (Neat): 2932, 1674, 1588, 1507, 1081, 761 cm^{-1}. Anal. Calcd for $C_{21}H_{20}N_3OCl$: C, 68.94; H, 5.47; N, 11.49. Found: C, 68.76; H, 5.50; N, 11.37.

*5.1.4.10. (Z)-5-Chloro-2-(1,2,4)-triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-benzyl-oxime (**16**). With (Z)-**6d** and benzyl bromide*: yield 72%; oil; MS (ESI): *m/z* 367 ($M^+ + 1$, 100%), 369 ($M^+ + 3$, 30%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.72–1.78 (m, 1H, H-3), 2.55–2.63 (m, 1H, H-3), 2.75–2.86 (m, 2H, H-4), 3.84–3.98 (m, 1H, H-2), 4.06–4.31 (dd, 2H, $J = 13.4$, 4.76 Hz, NCH_2), 5.12 (s, 2H, PhCH_2–O–), 6.98–7.02 (d, 2H, $J = 8.42$ Hz, ArH), 7.07–7.12 (d, 2H, $J = 8.84$ Hz, ArH), 7.18–7.30 (m, 4H, ArH), 7.80 (s, 1H, *triazole H*), 7.89 (s, 1H, *triazole H*); IR (Neat): 2927, 2857, 1737, 1505, 1018, 767, 700 cm^{-1}. Anal. Calcd for $C_{20}H_{19}N_4OCl$: C, 65.48; H, 5.18; N, 15.27. Found: C, 65.44; H, 5.27; N, 15.31.

*5.1.4.11. (Z)-5-Chloro-2-(1,2,4)-triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-(3-chloro-benzyl)-oxime (**17**). With (Z)-**6d** and 3-chlorobenzyl chloride*: yield 79%; oil; MS (ESI): *m/z* 401 ($M^+ + 1$, 100%), 403 ($M^+ + 3$, 30%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.72–1.86 (m, 1H, H-3), 2.17–2.27 (m, 1H, H-3), 2.54–2.96 (m, 2H, H-4), 3.99–4.09 (m, 1H, H-2), 4.16–4.40 (dd, 2H, $J = 12.6$, 5.36 Hz, NCH_2), 5.14 (s, 2H, PhCH_2–O–), 7.13–7.17 (d, 2H, $J = 7.8$ Hz, ArH), 7.21–7.38 (m, 5H, ArH), 7.51 (s, 1H, *triazole H*), 7.92–7.96 (d, 2H, $J = 8.36$, ArH); IR (Neat): 2924, 2366, 1596, 1352, 1018, 678 cm^{-1}. Anal. Calcd for $C_{20}H_{18}N_4OCl$: C, 59.57; H, 4.44; N, 13.94. Found: C, 59.48; H, 4.60; N, 13.92.

*5.1.4.12. (Z)-5-Bromo-2-imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-benzyl-oxime (**18**). With (Z)-**5e** and benzyl bromide*: yield 79%; oil; MS (ESI): *m/z* 411 ($M^+ + 1$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.77–1.84 (m, 1H, H-3), 2.65–2.73 (m, 1H, H-3), 2.82–2.98 (m, 2H, H-4), 3.86–3.97 (m, 2H, NCH_2), 4.20–4.25 (m, 1H, H-2), 5.25 (s, 2H, PhCH_2–O–), 6.85 (s, 1H, ArH), 7.02 (s, 1H, *imidazole H*), 7.12–7.16 (d, 2H, $J = 7.37$ Hz, ArH), 7.26–7.31 (m, 4H, ArH), 7.36–7.40 (d, 2H, $J = 8.29$ Hz, ArH), 7.98–8.02 (d, 1H, $J = 7.41$ Hz, H-8); IR (Neat): 2937, 2366, 1507, 1453, 1219, 760 cm^{-1}. Anal. Calcd for $C_{21}H_{20}N_3OBr$: C, 61.46; H, 4.87; N, 10.24. Found: C, 61.42; H, 4.91; N, 10.18.

*5.1.4.13. (Z)-5-Bromo-2-imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-(3-chloro-benzyl)-oxime (**19**). With (Z)-**5e** and 3-chlorobenzyl chloride*: yield 66%; oil; MS (ESI): *m/z* 445 ($M^+ + 1$, 100%), 447 ($M^+ + 3$, 30%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.80–1.90 (m, 1H, H-3), 2.73–2.77 (m, 1H, H-3), 2.77–2.91 (m, 2H, H-4), 3.87–4.0 (m, 2H, NCH_2), 4.18–4.28 (m, 1H, H-2), 5.19 (s, 2H, PhCH_2–O–), 6.89 (s, 1H, *imidazole H*), 7.05 (s, 1H, *imidazole H*), 7.17–7.21 (d, 2H, $J = 7.64$ Hz, ArH), 7.21–7.30 (m, 3H, ArH), 7.40–7.43 (d, 2H, $J = 6.25$ Hz, ArH), 7.95–7.99 (d, 1H, $J = 7.99$ Hz, H-8); IR (Neat): 2926, 2366, 1598, 1352, 1099, 669 cm^{-1}. Anal. Calcd for $C_{21}H_{19}N_3OBrCl$: C, 58.69; H, 4.27; N, 9.44. Found: C, 58.66; H, 4.74; N, 9.18.

*5.1.4.14. (Z)-5-Bromo-2-(1,2,4)-triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-benzyl-oxime (**20**). With (Z)-**6e** and benzyl bromide*: yield 68%; oil; MS (ESI): *m/z* 412 ($M^+ + 1$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.67–1.85 (m, 2H, H-3), 2.62–3.01 (m, 2H, H-4), 3.95–3.97 (m, 1H, H-2), 4.16–4.46 (dd, 2H, $J = 13.79$, 5.71 Hz, NCH_2), 5.22 (s, 1H, PhCH_2–O–), 7.0–7.21 (m, 1H, ArH), 7.31 (m, 2H, ArH), 7.31–7.39 (m, 5H, ArH), 7.82 (s, 1H, *triazole H*), 7.97 (s, 1H, *triazole H*); IR (Neat): 2929, 2860, 1599, 1453, 1016, 758 cm^{-1}. Anal. Calcd for $C_{20}H_{19}N_4OBr$: C, 58.39; H, 4.62; N, 13.62. Found: C, 58.29; H, 4.70; N, 13.62.

*5.1.4.15. (Z)-5-Bromo-2-(1,2,4)-triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-(3-chloro-benzyl)-oxime (**21**). With (Z)-**6e** and 3-chlorobenzyl chloride*: yield 80%; oil; MS (ESI): *m/z* 446 ($M^+ + 1$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.67–1.85 (m, 2H, H-3), 2.62–2.71 (m, 1H, H-4), 2.89–2.97 (m, 1H, H-4), 3.95 (m, 1H, H-2), 4.16–4.46 (dd, 2H, $J = 5.77$, 13.74 Hz, NCH_2), 5.22 (s, 2H, PhCH_2–O–), 7.00–7.26 (m, 3H, ArH), 7.26–7.40 (m, 3H, ArH), 7.40 (s, 1H, ArH), 7.82 (s, 1H, *triazole H*), 7.88 (s, 1H, *triazole H*); IR (Neat): 2926, 2366, 1598, 1353, 1015, 679 cm^{-1}. Anal. Calcd for $C_{20}H_{18}N_4OBrCl$: C, 53.87; H, 4.04; N, 12.57. Found: C, 53.82; H, 4.09; N, 12.49.

*5.1.4.16. (Z)-5-Fluoro-2-imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-benzyl-oxime (**22**). With (Z)-**5c** and benzyl bromide*: yield 78%; oil; MS (ESI): *m/z* 350 ($M^+ + 1$, 100%), 351 ($M^+ + 2$, 22%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.74–1.89 (m, 1H, H-3), 2.69–2.71 (m, 1H, H-3), 2.78–2.88 (m, 2H, H-4), 3.83–3.91 (m, 2H, NCH_2), 4.18 (m, 1H, H-2), 5.23–5.25 (d, 2H, $J = 3.16$ Hz, PhCH_2–O–), 6.85 (s, 1H, *imidazole H*), 7.03 (s, 1H, *imidazole H*), 7.13–7.26 (m, 2H, ArH), 7.26–7.30 (m, 3H, ArH), 7.30–7.40 (m, 3H, ArH), 7.65–7.72 (dd, 1H, $J = 10.3$, 2.5 Hz, ArH); IR (Neat): 2927, 2373, 1595, 1351, 1025, 761, 602 cm^{-1}. Anal. Calcd for $C_{21}H_{20}N_3OF$: C, 72.20; H, 5.73; N, 12.03. Found: C, 72.16; H, 5.84; N, 12.08.

*5.1.4.17. (Z)-5-Fluoro-2-imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-(3-chloro-benzyl)-oxime (**23**). With (Z)-**5c** and 3-chlorobenzyl chloride*: yield 73%; oil; MS (ESI): *m/z* 384 ($M^+ + 1$, 100%), 386 ($M^+ + 3$, 22%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.83–1.84 (m, 1H, H-3), 2.71–2.75 (m, 1H, H-3), 2.86–2.96 (m, 2H, H-4), 3.86–3.97

(m, 2H, NCH_2), 4.13–4.17 (m, 1H, H-2), 5.16–5.18 (d, 2H, $J = 4.91$ Hz, PhCH_2–O–), 6.85 (s, 1H, *imidazole H*), 6.98 (s, 1H, ArH), 6.99–7.32 (m, 5H, ArH), 7.38–7.40 (d, 2H, $J = 4.17$ Hz, ArH), 7.40–7.59 (m, 1H, ArH); IR (Neat): 2928, 2858, 2374, 1575, 1458, 1023, 768 cm^{-1}. Anal. Calcd for $C_{21}H_{19}N_3OFCl$: C, 65.71; H, 4.95; N, 10.95. Found: C, 65.70; H, 4.94; N, 10.84.

*5.1.4.18. (Z)-5-Fluoro-2-(1,2,4)-triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-benzyl-oxime (**24**). With (Z)-**6c** and benzyl bromide*: yield 74%; oil; MS (ESI): *m/z* 351 ($M^+ + 1$, 100%), 352 ($M^+ + 2$, 22%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.80–2.18 (m, 2H, H-3), 2.63–2.94 (m, 2H, H-4), 3.95–3.97 (m, 1H, H-2), 4.15–4.38 (m, 2H, NCH_2), 5.21 (s, 2H, PhCH_2–O–), 6.86–7.20 (m, 5H, ArH), 7.26–7.38 (m, 3H, ArH), 7.78–7.82 (d, 1H, $J = 7.68$ Hz, H-8), 7.88 (s, 1H, *triazole H*); IR (Neat): 3436, 2366, 1597, 1352, 1014, 767, 672 cm^{-1}. Anal. Calcd for $C_{20}H_{19}N_4OF$: C, 68.57; H, 5.42; N, 16.18. Found: C, 68.62; H, 5.34; N, 16.17.

*5.1.4.19. (Z)-5-Fluoro-2-(1,2,4)-triazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-(3-chloro-benzyl)-oxime (**25**). With (Z)-**6c** and 3-chlorobenzyl chloride*: yield 73%; oil; MS (ESI): *m/z* 385 ($M^+ + 1$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.80–1.84 (m, 1H, H-3), 2.71–2.78 (m, 1H, H-3), 2.83–2.94 (m, 2H, H-4), 3.93–4.03 (m, 1H, H-2), 4.14–4.39 (m, 2H, NCH_2), 5.20 (s, 2H, PhCH_2–O–), 7.06–7.16 (m, 3H, ArH), 7.20–7.38 (m, 3H, ArH), 7.39 (s, 1H, ArH) 7.89 (s, 1H, *triazole H*), 7.96 (s, 1H, *triazole H*); IR (Neat): 2363, 1598, 1353, 1015, 763, 678 cm^{-1}. Anal. Calcd for $C_{20}H_{18}N_4OFCl$: C, 62.42; H, 4.68; N, 14.56. Found: C, 62.39; H, 4.54; N, 14.57.

*5.1.4.20. (E)-2-Imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-(3-chloro-benzyl)-oxime (**26**). With (E)-**5a** and 3-chloro-benzyl chloride*: yield 91%; oil; MS (ESI): *m/z* 366 ($M^+ + 1$, 100%), 367 ($M^+ + 2$, 15%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.79–1.83 (m, 1H, H-3), 2.49 (m, 1H, H-3), 2.62–2.88 (m, 1H, H-4), 3.89–4.00 (m, 2H, NCH_2), 5.08–5.19 (m, 1H, H-2), 5.21 (s, 2H, PhCH_2–O–), 6.90–7.12 (m, 2H, ArH), 7.16–7.29 (m, 6H, ArH), 7.38–7.42 (d, 2H, $J = 6.1$ Hz, ArH), 8.44–8.49 (d, 1H, $J = 7.63$ Hz, H-8); IR (Neat): 3012, 2976, 2838, 1524, 1112, 761, 681 cm^{-1}. Anal. Calcd for $C_{21}H_{20}N_3OCl$: C, 69.13; H, 5.48; N, 11.52. Found: C, 69.08; H, 5.33; N, 11.41.

*5.1.4.21. (E)-5-Chloro-2-imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-benzyl-oxime (**27**). With (E)-**5d** and 3-chloro-benzyl chloride*: yield 86%; oil; MS (ESI): *m/z* 401 ($M^+ + 1$, 100%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.76–1.78 (m, 1H, H-3), 2.69–2.73 (m, 1H, H-3), 2.84–2.93 (m, 2H, H-4), 3.88–3.91 (m, 2H, NCH_2), 5.07–5.16 (m, 1H, H-2), 5.19–5.22 (d, 2H, $J = 4.14$ Hz, PhCH_2–O–), 6.86 (s, 1H, *imidazole H*), 7.04 (s, 1H, *imidazole H*), 7.10–7.22 (m, 5H, ArH), 7.37–7.41 (m, 3H, Ar), 8.37–8.42 (d, 1H, $J = 7.59$ Hz, H-8); IR (Neat): 2933, 2837, 1588, 1507, 1089, 762 cm^{-1}. Anal. Calcd for $C_{21}H_{20}N_3OCl$: C, 68.94; H, 5.47; N, 11.49. Found: C, 68.87; H, 5.51; N, 11.41.

*5.1.4.22. (E)-5-Bromo-2-imidazol-1-ylmethyl-3,4-dihydro-2H-naphthalen-1-one O-(3-chloro-benzyl)-oxime (**28**). With (E)-**5e** and 3-chlorobenzyl chloride*: yield 66%; oil; MS (ESI): *m/z* 445 ($M^+ + 1$, 100%), 447 ($M^+ + 3$, 33%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.81–1.92 (m, 1H, H-3), 2.71–2.75 (m, 1H, H-3), 2.79–2.90 (m, 2H, H-4), 3.86–4.01 (m, 2H, NCH_2), 5.10–5.14 (m, 1H, H-2); 5.18 (s, 2H, PhCH_2–O–), 6.87 (s, 1H, *imidazole H*), 7.05 (s, 1H, *imidazole H*), 7.18–7.22 (d, 2H, $J = 7.63$ Hz, ArH), 7.20–7.31 (m, 3H, ArH), 7.43–7.45 (d, 2H, $J = 6.25$ Hz, ArH), 8.32–8.29 (d, 1H, $J = 7.61$ Hz, H-8); IR (Neat): 2925, 2367, 1599, 1352, 1091, 672 cm^{-1}. Anal. Calcd for $C_{21}H_{19}N_3OClBr$: C, 58.69; H, 4.27; N, 9.44. Found: C, 58.61; H, 4.22; N, 9.39.

5.2. In vitro antifungal and antibacterial activities' evaluation by MIC assay

The prepared (*Z*)- and (*E*)-2-imidazolo-/2-triazolo-methyl benzocycloalkyl oxime ethers (**7–28**) were evaluated for their *in vitro* antifungal activity against *C. albicans*, *C. neoformans*, *S. schenckii*, *T. mentagrophytes*, *A. fumigatus* (all strains are patients' isolates) and *C. parapsilosis* (ATCC 22019) and antibacterial activity against *K. pneumoniae* (ATCC 27736), *E. coli* (ATCC 9637), *P. aeruginosa* (ATCC BAA427), and *S. aureus* (ATCC 25923). In this process, minimum inhibitory concentration of compounds **7–28** was tested according to standard microbroth dilution as per NCCLS [19,20] protocol. Briefly, testing was performed in flat-bottomed 96-well tissue culture plates (CELLSTAR® Greiner Bio-one GmbH, Germany) in RPMI 1640 medium buffered with MOPS (3-[*N*-morpholino]propane sulfonic acid, Sigma Chemical Co., MO, USA) for fungal strains and in Muller Hinton broth (Titan Biotech Ltd, India) for bacterial strains. The concentration range of tested compounds was 50–0.36 μg/mL for standard compounds. Initial inocula of fungal and bacterial strain were maintained at $1–5 \times 10^3$ cells/mL. These plates were incubated in a moist chamber at 35 °C and absorbance at 492 nm was recorded on Versa Max microplate reader (Molecular Devices, Sunnyvale, USA) after 48 h for *C. albicans* and *C. parapsilosis*, 72 h for *A. fumigatus*, *S. schenckii*, and *C. neoformans* and 96 h for *T. mentagrophytes* while bacterial strains were incubated for 24 h. MIC was determined as 90% inhibition of growth with respect to the growth control, was observed by using SOFTmax Pro 4.3 Software (Molecular Devices, Sunnyvale, USA).

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