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Facile synthesis, antibacterial and protease inhibition studies of *β*-amino alcohols prepared via ring opening of epoxides

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Abstract: A green ultrasound assisted convenient approach has been reported for the ring opening of epoxides. As a result, a series of *N*-phenyl piperazine and morpholine based β-amino alcohols has been synthesized under ultrasound irradiation in DMSO for 60 minutes at 70 °C. This methodology showed excellent tolerance with various epoxides and provided excellent yields upto 96%. All the synthetic derivatives (4a-e) (5c-d) significantly influence the catalytic activity of protease while 5d exhibited maximum (100%) inhibitory effect with a half-life of 40.76 minutes. Among the target derivatives, compound 4c exhibited significant antibacterial activity against *Bacillus subtilis* and *Escherichia coli* bacterial strains with zone of inhibition values 45 mm and 32 mm, respectively.

Keywords: Epoxide ring opening, *N*-phenyl piperazine, amino alcohols, protease; epoxides, antibacterial activity.

INTRODUCTION

Ultrasound assisted organic synthesis (UAOS) has been acknowledged as eco-friendly technique (Olszowka *et al*., 2021; Ramirez-Mendoza *et al*., 2021; Nimbalkar *et al*., 2018). Ultrasound irradiations are considered as efficient green energies by providing a number of benefits such as high yield, low cost, environmentally safe, fast, easily controlled with minimum waste materials (Borsoi *et al*., 2021; Esrafili *et al*., 2017). This acceleration of reaction rate is due to phenomenon of acoustic cavitation which generates higher pressure and energies within few seconds (Maleki *et al*., 2017). Ultrasound irradiation has been used as an alternate energy source to promote several organic transformations such as esterification, saponification, hydrolysis, addition/substitution reactions, alkylation, oxidation, reduction, Friedel Crafts reaction and Diels Alder reaction (Dofe *et al*., 2018; Gavrilović *et al*., 2018; Santos *et al*., 2018).

Phenyl piperazine bearing molecules are valuable therapeutic agents as they could be utilized as analgesic agent, BACE-1 and angiogenesis inhibitors, D3-dopamine receptor ligand, potent serotonin 5-HT receptor agonist, as anti-inflammatory, antimicrobial and anticancer agent (Hafeez *et al*., 2021; Akhtar *et al*., 2021). Phenyl piperazine based many drugs/medicines are available in the market such as Niaprazine and Bifeprunox (Wadenberg 2007) (fig. 1).

β-Amino alcohols display a wide range of applications in organic synthesis. They are extensively used to synthesize different natural as well as synthetic amino acids. A broad range of *β*-amino alcohol-based drugs are effective as *β*-adrenergic blockers, being used to treat angina pectoris, cardiac arrhythmias, open angle glaucoma, etc. such as ephedrine, pseudoephedrine etc. (fig. 2).

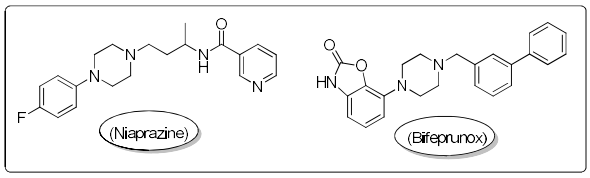

Figure 1: Phenyl piperazine containing drugs

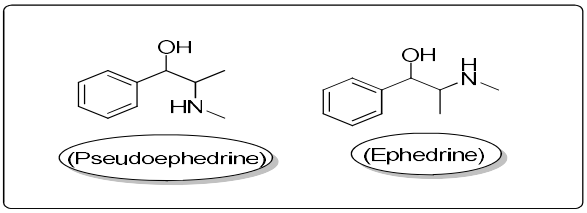

Figure 2: *β*-Amino alcohol-based drugs

A number of methodologies have been presented in literature for the ring opening of different heterocycles such as epoxides and aziridines with various nucleophiles like *C*, *N*, *S* nucleophiles (Akhtar *et al.,* 2018; Ahmad *et al.,* 2018). However, there are some issues with existing methodologies such as majority of the catalysts are not eco-unfriendly, non-reusable, moisture sensitive, less selective in accordance with the product and longer reaction times.

Therefore, it is imperative to use improved, catalyst free, high yielding and environment friendly methodology which could activate epoxides and amines. Keeping in view the emerging importance of green synthesis of 2-amino alcohols with shorter reaction time and with high

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yield, herein, we report the catalyst free synthesis of phenyl piperazine and morpholine based 2-amino alcohols *via* epoxide ring opening under ultrasound irradiations. Antibacterial activity and enzyme inhibiting potential of newly synthesized compounds have also been discussed here.

MATERIALS AND METHODS

General experimental part

Chemicals and solvents were purchased from Alfa-Aesar (United States), Daejung (Korae), Merck (United States) and Scharlau (Germany). For ultrasound irradiation, Elmasonic E 30 H apparatus was utilized. The spots which were not visible under UV-light were detected with I_2-vapors. Silica gel (70-230 mesh, ASTM) purchased from Scharlau was used to get pure compounds. Solvents of analytical grades were used such as DCM, MeOH, *n*-hexane and ethyl acetate. Gallenkamp digital melting point apparatus was used to find out melting points of compounds. IR and NMR spectra were recorded on Bruker Fourier transform spectrometer and Bruker spectrometer, respectively.

Common preparation method of β-amino alcohols (4a-e) (5c-d)

Amine (0.6 mmol) and epoxides (3a-e) (0.93 mmol) in DMSO were mixed in a test tube and sonicated in a water filled sonication bath for a proper length of time (60 min.) at suitable temperature (70 oC). Upon TLC (hexane: ethyl acetate, 6:4) analysis work up was done via solvent extraction (EtOAc/H2O). All the epoxides (3a-e) were synthesized as per reported methodology by the reaction of epichlorohydrin with phenols (Guruswamy and Arul 2016).

Antibacterial activity

Disc diffusion method was used to assess antibacterial activity of all compounds (4a-e) (5c-d) (Faiz *et al*., 2019). 100 µL Suspensions of microorganisms were poured on nutrient agar media *via* sterilized loop. Specific concentration of compound solution (5 mg/100 µL) in chloroform was infused on the sterilized discs of filter paper. Whereas ciprofloxacin was deposited on agar plates, already inoculated with bacterial cells. At 4°C the plates were stored for 60 minutes and then incubated at 37°C for 24 hrs. By measuring the inhibition zone in mm, antibacterial activity was evaluated.

Minimum inhibitory concentration (MIC)

Resazurin microtiter-plate assay was used to calculate MIC of all compounds. For this purpose, 100 µL solution was used containing 100 mg/mL (w/v) and 10 mg/mL concentrations of compounds and standard antibiotic, respectively in ten percent DMSO. This solution was filled in 1st row of 96 well plates (must contain 50 µL of the test compounds) and remaining plates were filled with 50 µL of nutrient broth. After filling all plates, 10 µL resazurin indicator and then 10 µL of microbial suspensions were transferred to each well. Column with all solutions of compounds, ciprofloxacin (as positive controls), ten percent DMSO (negative control), microbial solutions with nutrient broth were incubated at 37 °C for 24 hrs and then temperature was decreased to 25°C for 48 hrs. By the observation of color change, MIC values were measured (Batool *et al*., 2019).

Determination of inhibitory rate of protease

500 µL of purified protease solution was incubated at 37 °C with 950 µL of 2% casein solution (10mM tris-HCl; pH 8.0) with 500 µL of synthesized compound. 10% Trichloracetic acid (TCA) was added to finish the reaction and the optical density (O.D.) was monitored at λ_{600} in UV-Visible spectrophotometer. V_n was considered as reaction rate and V_0 denoted for casein free protease system (control) and then inhibitory rate of protease (%) $(100 \times (V_0 - V_n) / V_0)$ was calculated (Folquitto *et al*., 2017).

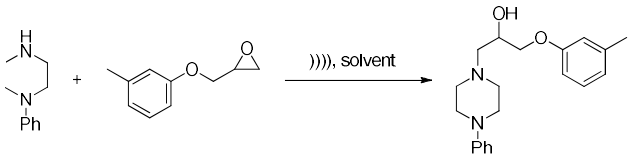
STATISTICAL ANALYSIS

Triplicates results of antibacterial potential are denoted as mean values ± standard deviation. Statistical analysis was carried out using MS Excel 2010. Experimental data was compared *via* one-way ANOVA. 0.05 Probability value was found in statistical analysis.

RESULTS

Reaction conditions for the reaction of phenyl piperazine with 2-((*m*-tolyloxy) methyl) oxirane were optimized by screening of various factors such as reaction time, solvents (EtOH, DMSO, CH_3CN, DMF, THF and CH_2Cl_2) and temperature under ultrasound irradiations. Table 1 elaborates the optimization conditions for the reaction. After optimization of reaction conditions (DMSO, 70°C, 60 min.), a variety of epoxides were treated with phenyl piperazine and morpholine to obtain targeted molecules in 62-96% yield range as depicted in Scheme 1.

Table 1: Optimization of reaction conditions using ultrasound irradiation



Entry	Solvent	Temperature (°C)	Time (min.)	Yield (%)
1	EtOH	rt	80	0
2	EtOH	70	60	80
3	DMF	70	60	90
4	DMSO	70	60	96
5	CH_3CN	70	60	76
6	THF	70	60	60
8	CH_2Cl_2	70	60	53

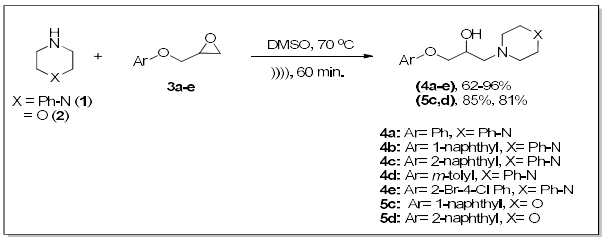
Table 2: Spectral studies of beta-amino alcohols (4a-e) (5c,d)

Compound	M.P (^oC)	Yield (%)	FT-IR (cm^{-1})ν_{max} / ^{1}HNMR (500 MHz, $CDCl_3$)/ ^{13}CNMR (100 MHz, $CDCl_3$)/ MS (EI) (m/z)
4a	57	62	3340, 2928, 1503, 1244, 1179/ 7.28-7.35 (m, 4H), 6.88-7.02 (m, 6H), 4.18-4.26 (m, 1H), 4.00-4.09 (m, 2H), 3.58 (s, 1H), 3.22-3.34 (m, 4H), 2.88-2.95 (m, 2H), 2.63-2.76 (m, 4H)/ 158.64, 151.07, 129.52, 121.08, 120.04, 116.23, 114.54, 70.02, 65.53, 60.69, 53.37, 49.15/$[M + H]^+$ 313.1876.
4b	106	67	3426, 2834, 1600, 1149, 1177/ 7.75-7.81 (m, 3H), 7.47 (t, 1H, J=4 Hz), 7.37 (t, 1H, J = 8Hz), 7.28-7.32 (m, 2H), 7.20-7.24 (m, 2H), 6.97 (d, 2H, J = 8Hz), 6.90 (t, 1H, J = 4Hz), 4.23-4.27 (m, 1H), 4.17 (d, 2H, J = 4Hz), 3.59 (s, 1H), 3.23-3.30 (m, 4H), 2.88-2.91 (m, 2H), 2.65-2.75 (m, 4H)/156.70, 151.20, 134.50, 129.48, 129.17, 129.13, 127.63, 126.81, 126.44, 123.78, 119.92, 118.85, 116.17, 106.83, 70.29, 65.66, 60.62, 53.39, 49.32/ $[M + H]^+$ 363.2031.
4c	161	68	3365, 2914, 1597, 1218, 1149/ 7.76-7.81 (m, 4H), 7.46-7.49 (m, 1H), 7.36-7.39 (m, 1H), 7.32-7.28 (m, 2H), 7.20-7.24 (m, 2H), 6.97 (d, 2H, J = 4 Hz), 6.91 (t, 1H, J = 4Hz), 4.23-4.27 (m, 1H), 4.17 (d, 2H, J = 4Hz), 3.23-3.30 (m, 4H), 2.88-2.91 (m, 2H), 2.65-2.75 (m, 4H)/ 156.71, 151.21, 129.49, 129.17, 129.14, 127.69, 126.82, 126.44, 123.79, 119.92, 118.86, 116.17, 106.84, 70.30, 65.65, 60.62, 53.40, 49.31/ $[M + H]^+$ 363.2031.
4d	161	96	3217, 1238, 1250, 29, 15/ 7.28-7.32 (m, 2H), 7.20 (t, 1H, J = 8Hz), 6.96-6.98 (dd, 2H, J = 8Hz), 6.91 (t, 1H, J = 4 Hz), 6.77-6.82 (m, 3H), 4.16-4.20 (m, 1H), 4.01-4.06 (m, 2H), 3.22-3.29 (m, 4H), 2.86-2.89 (m, 2H), 2.62-2.70 (m, 4H), 2.37 (s, 3H)/ 158.75, 151.20, 139.56, 129.25, 129.17, 121.90, 119.93, 116.17, 115.48, 111.45, 70.16, 65.74, 60.67, 53.39, 49.27, 21.55/ $[M + H]^+$327.2033.
4e	94	67	3095, 2928, 1595, 1227, 1179/ 7.46 (d, 1H, J = 4Hz), 7.15-7.23 (m, 4H), 6.78-6.88 (m, 3H), 4.12-4.19 (m, 1H), 3.97-4.03 (m, 2H), 3.13-3.24 (m, 4H), 2.80-2.87 (m, 2H), 2.61-2.73 (m, 4H)/ 151.01, 142.80, 133.10, 130.16, 127.99, 126.56, 121.90, 114.80, 114.30, 112.85, 73.60, 68.25, 65.49, 54.89, 49.09/ $[M + H]^+$426.0535.
5c	83	85	3552, 2941, 1627, 1182, 1071/ 7.73-7.80 (m, 3H), 7.44-7.49 (m, 1H), 7.34-7.39 (m, 1H), 7.17-7.28 (m, 2H), 4.19-4.26 (m, 1H), 4.13 (d, 2H, J = 8Hz), 3.72-3.82 (m, 4H), 2.76-2.68 (m, 2H), 2.50-2.66 (m, 4H)/ 156.59, 134.45, 129.49, 129.10, 127.68, 126.80, 126.46, 123.81, 118.81, 106.73, 70.13, 66.91, 65.36, 61.14, 53.77/ $[M + H]^+$288.1562.
5d	43	81	3231, 2957, 1606, 1160, 1070/ 7.16-7.28 (m, 1H), 6.73-6.81 (m, 3H), 4.09-4.17 (m, 1H), 3.99 (d, 2H, J = 8 Hz), 3.69-3.77 (m, 4H), 3.37 (s, 1H), 2.56-2.72 (m, 4H), 2.46-2.53 (m, 2H), 2.34 (s, 3H)/ 158.67, 139.54, 129.22, 121.87, 115.40, 111.37, 70.03, 67.00, 65.45, 61.13, 53.78, 21.55/ $[M + H]^+$ 252.1556.

Table 3: ZI and MIC values for antibacterial potential of targeted molecules

Compound	*Bacillus subtilis*		*Escherichia coli*	
	ZI (mm)[a**]	MIC (mg/mL) [a**]	ZI (mm) [a**]	MIC (mg/mL) [a**]
4a	32 ±0.75	2.0 ± 0.00	29 ± 1.5	5.0 ± 0.80
4b	ND[*]	2.0 ± 0.01	10 ±1.45	4.0 ± 1.25
4c	45 ± 0.25	5.0 ± 0.00	32 ± 1.25	1.0 ±0.25
4d	ND[*]	ND[*]	ND[*]	ND[*]
4e	27 ± 1.90	1.0 ± 0.25	19 ±1.50	1.0 ± 0.75
5c	32 ± 0.25	3.0 ± 0.00	ND[*]	1.0 ± 1.008
5d	37 ± 0.90	4.0 ± 0.00	ND[*]	1.0 ± 0.80
Ampicillin	18 ± 1.0	9.0 ± 1.1	12 ± 0.6	16 ± 1.1
Ibuprofen	15 ± 0.9	14.0 ± 1.0	11 ± 0.5	21 ± 1.4
Ciprofloxacin	29.3 ± 1.0	0.3 ± 0.0	31.1 ± 1.2	2.2 ± 0.1

[*]N.D. means not determined.
[a]Experiments were performed in triplicates and expressed as mean ± SD
[**]$p<0.05$, was considered significant



Scheme 1: Synthesis of targeted derivatives (4a-e) (5c,d)

Biological Screening

Antibacterial activity

Antibacterial activity of the synthesized derivatives has been scrutinized against *Bacillus subtilis* and *Escherichia coli*. The minimum inhibitory concentration (MIC) and zone of inhibition (ZI) values are presented in Table 3. Results indicated that all synthesized compounds displayed significant antibacterial activity especially against *Bacillus subtilis*. As compound **4c** exhibited maximum zone of inhibition value (45mm) as compared to standard drugs and positive control (29.3mm).

Enzyme inhibitory activity

Results depicted in fig. 3, 4(a) and 4(b) presented the inhibitory influence of phenyl piperazine and morpholine derivatives (**4a-e**) (**5c-d**) on the activity of serine protease and their half-lives. All synthesized derivatives displayed strong inhibitory effect on the protease activity. Among all derivatives, compound **4b** having naphthyl ring attached to phenyl piperazine exhibited highest inhibitory effect at different time intervals (from 20-60 minutes) with 20.26 minutes half-life. 100% Inhibition of serine protease was obtained with **5d** having maximum half-life (40.76 minutes). The inhibitory effect might be due to presence of halogen groups at aryl ring was responsible to reduce activity of protease. On the other hand, naphthalene ring attached to morpholine and phenyl piperazine ring in derivatives, **5c** and **4c** displayed lower inhibition rate than other. In conclusion it can be assumed that aryl rings attached to morpholine and phenyl piperazine moieties have a positive contribution to the inhibition effect of protease enzyme.

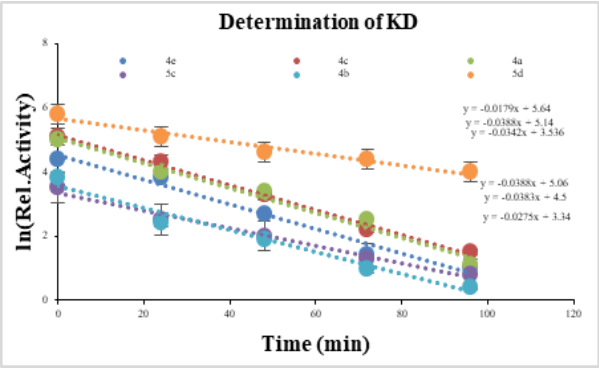


Fig. 3: Determination of half-life of phenyl piperazine and morpholine derivatives.

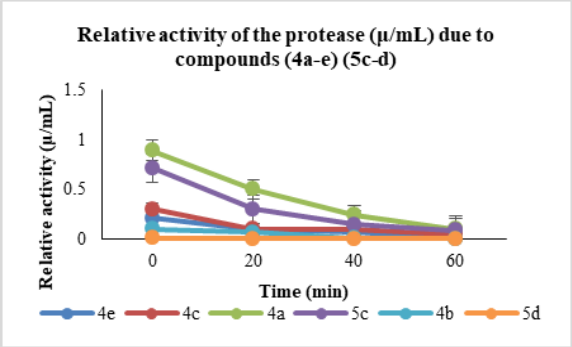


Fig. 4(a): Relative activity of protease (µ/mL)

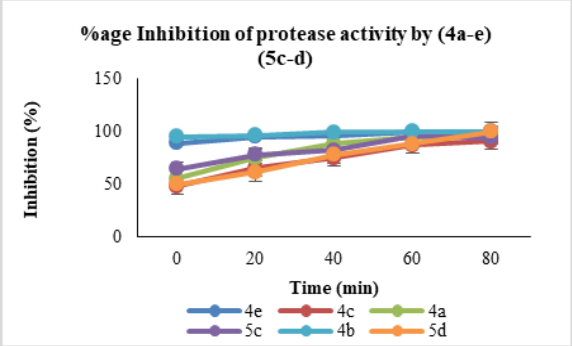


Fig 4(b): %age inhibition of protease

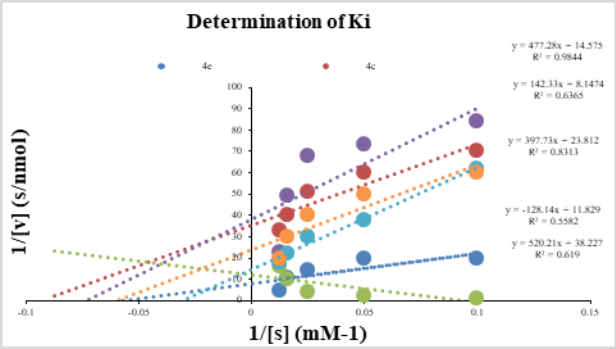


Fig. 5: Determination of inhibition type and kinetic parameter.

Kinetic study

Kinetic analysis of phenyl piperazine derivatives morpholine derivatives (4a-e) (5c-d) was implemented by plotting the function of rate 1/[V] against concentration of inhibitor 1/[S]. The type of inhibition was determined by Lineweaver burk plot. When a plot is drawn for the enzyme and inhibitor, the lines on the plot describe the type of inhibition. In case of competitive inhibition, enzyme lines compete with substrates line in the plot and showed decrease in enzyme concentration in the course of time. While, in uncompetitive inhibition, the lines of enzyme and substrates showed identical slopes on plot. In this regard, 4a was categorized as competitive inhibitor. As shown in fig. 5, good graphical match of all other compounds to the mode of an uncompetitive inhibition was observed. The Ki values of 4b, 4c and 5c were 4.04

μM, 12.5 μM and 14.30 μM, respectively. Ki of 4e was 16.6 μM under the same conditions.

DISCUSSION

Preliminary reaction was failed to obtain the expected beta amino alcohol at room temperature. However, by increasing temperature from 40-70 ^{o}C with ultrasound irradiation, required products were obtained in 75-90% yield range within 60 minutes. DMSO provided the highest yield (96%) within 60 minutes. CH_3CN, THF, CH_2Cl_2 provided 76, 60 and 53% yields respectively. Therefore, DMSO was selected as best solvent for this SN_2 type reaction at 70 ^{o}C with 60 min. of sonication (Table 1). Substrate scope was estimated *via* reaction of different epoxides 3a-e with phenyl piperazine and morpholine. Highest yield (96%) was obtained in case of epoxide 3d with electron donating methyl group in comparison to epoxide 3e with electron withdrawing groups Cl and Br which provided only 67% yield. Morpholine based beta amino alcohols 5c and 5d were also obtained in good yields 85 and 81%, respectively.

The structure elucidation of all the synthesized molecules was done by Proton NMR, Carbon NMR, FT-IR and mass spectrometry. In FT-IR spectrum of representative molecule 4a, characteristic peak of OH of *β*-amino alcohol appeared at 3340 cm^{-1} while aromatic carbon double bond carbon exhibited the peak at 1503 cm^{-1}. Proton NMR spectrum of the compound 4a, revealed characteristic OH peak as singlet at δ 3.58, while aromatic signals appeared as multiplet at δ 6.88-7.35. However, hydrogens of piperazine ring appeared as multiplet at δ 3.22-3.34 and δ 2.63-2.76 respectively. The carbon NMR spectrum showed the characteristic peak of carbon with OH at δ 65.53 while methylene linked to both sides of this carbon reverberated at δ 60.69 and δ 70.02 respectively. However, the aromatic carbon appears at 158.64, 151.07, 129.52, 121.08, 120.04, 116.23, 114.54 respectively. Other derivatives of the series were also analyzed in the similar manner.

Structure activity relationship (SAR)

SAR revealed that excellent activity of compound 4c against *Bacillus subtilis* was due to the presence of naphthalene ring (Philips *et al*., 2007). Similar behavior was observed in case of *Escherichia coli*, as 4c maximal inhibited the growth of bacteria by depicting ZI value 32mm (Table 3). Morpholine derivative containing naphthalene ring in compound 5c also displayed higher ZI value (32mm) as compared to positive control (in case of *Bacillus subtilis*). However, an arbitrary behavior was seen for compound 4b which displayed no zone of inhibition. Moreover, a significant antibacterial activity of compound 5d against *Bacillus subtilis* might be associated with electron donating methyl group present at meta position of the aryl ring.

The structure activity relationship for the inhibitory effect revealed that the attachment of naphthyl ring to *β*-amino alcohol enhances the inhibitory effect by giving 100% inhibition of serine protease. While the inhibitory effect is lowered in the presence of phenyl and morpholine ring with halogen substituent.

CONCLUSION

A catalyst free ultrasound assisted synthesis of *N*-phenyl piperazine and morpholine based *β*-amino alcohols has been reported. This environmentally friendly protocol gave targeted derivatives in moderate to excellent yield range (62-96%) within short reaction time. Furthermore, enzyme inhibition potential of the designed series exhibited satisfactory result by displaying maximum inhibition potential of serine protease. Among all compounds, 5d showed maximum inhibition (100%) with a half-life of protease enzyme 40.76 minutes. In addition to this, antibacterial study of the synthesized derivatives reveals that compound 4c was the most potent one against *Bacillus subtilis* and *Escherichia coli* by displaying zone of inhibition values 45mm and 32mm, respectively. The biological profile of these derivatives showed that these molecules would be helpful for synthesizing clinically effective and safe drugs under mild reaction conditions.

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