Review Article: Morpholine and Thiomorpholine: A Privileged Scaffold Possessing Diverse Bioactivity Profile

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ABSTRACT

Morpholine and its thio analogue thiomorpholine are moieties with multifaceted roles, and demonstrated myriad physiological activity. This review discusses several analogues of morpholine and thiomorpholine synthesized by varied facile synthetic schemes resulting in substitution on multiple positions of the heterocycles. Both morpholine and its thio analogue have proven to act as bioactives against different molecular targets. These scaffolds have been an indispensable element of the pharmacophore and have exhibited selective enzyme inhibition against many receptors. They have also been an integral aspect of the drug discovery process. This review endeavours to condense the new trends concomitant to the various aspects of morpholine and thiomorpholine, their biological activities and their various synthetic routes.

Introduction

Field of chemistry is forging ahead progressively and hence newer molecules are synthesized in the laboratory to identify leads with target specific activity. Morpholine and thiomorpholine are heterocycles that have been chronically put to use by synthetic chemist owing to their diversity. These non-aromatic six membered saturated heterocycles are 1-oxa-4-azacyclohexane (thiomorpholine) respectively [1-6]. Morpholine is chemically a ring with two different functional group viz. ether and amine whereas thiomorpholine is a thio analog of morpholine which has the oxygen atom replaced by sulphur [7].

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Morpholine and thiomorpholine are seen as heterocyclic leitmotif showcasing versatility in their pharmacological activity. Morpholine and thiomorpholine scaffolds with favourable substitution display a diversified set of action. Thoughtfully substituted morpholine derivatives are used as antitubercular activity [8], anti-urease activity [9], antioxidant activity [10-11], antibacterial activity [12-14], as a potent anti – hypertensive agent [15-16], analgesic [17-18], anti – inflammatory [19-20] and anticancer agents [21]. Literature work has showcased the significance of morpholine substitution to enhance the selective COX-2 inhibition of NSAID's like ibuprofen and indomethacin [22]. Thiomorpholine derivatives have also been utilized for their retinal protector activity [23], antitubercular activity [24], antiprotozoal [25], dipeptidyl peptidase IV (DPP-IV) inhibitor [26] used for treatment of type 2 diabetes mellitus (T2DM), hypolipidemic [27], antimalarial [28] and antioxidant activity [29].

This diversity has made the researchers keen and propelled them to explore these privileged scaffolds.

Morpholine and thiomorpholine; two important heterocyclic rings with structure illustrated in **Figure 1**.

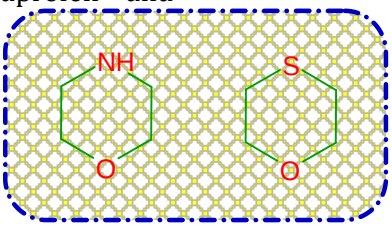


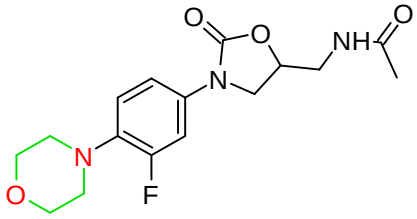
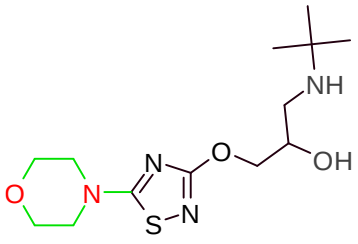
Figure 1. Morpholine and Thiomorpholine

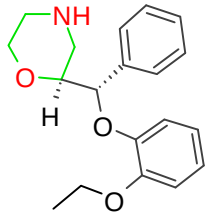
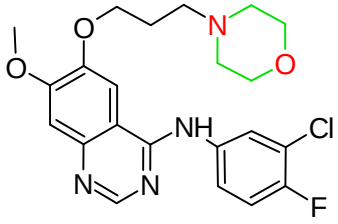
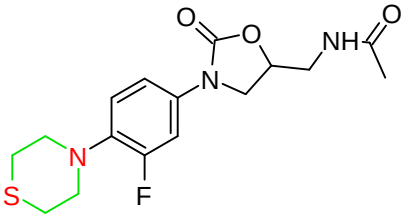
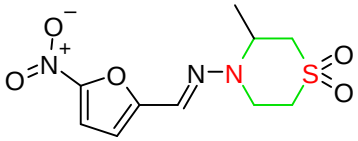
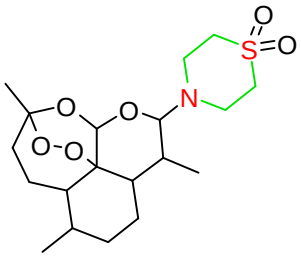
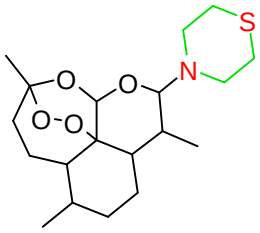
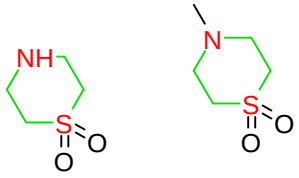
Morpholine is ring generally have application in organic synthesis, as solvent in various process, as rubber additives and corrosion inhibitors; whereas thiomorpholine has applications such as organic solvent because low cost and is a good base as well

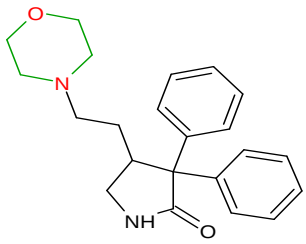
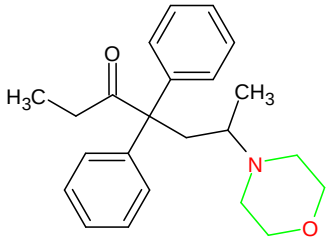
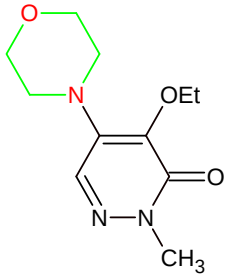
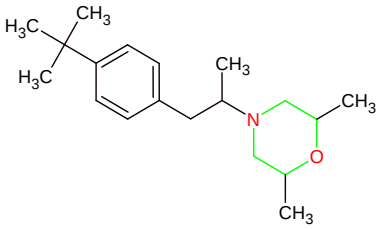
Morpholines exhibit divergent industrial utility, such as corrosion inhibitor, optical bleaching agent, fruit preservative and in dying [30].

The marketed morpholine and thiomorpholine scaffold containing drugs are depicted in the following **Table 1** [31-38].

Table 1. Marketed morpholine and thiomorpholinescaffold containing drug

Drugs	Structure	Use
Linezolid		Synthetic antibiotic,used against multi-resistant strains like streptococcus and methicillin-resistant Staphylococcus aureus (MRSA).
Timolol		Treatment of ocular hypertension and glaucoma

Reboxetine		Used as an antidepressant, panic disorder and attention deficit hyperactivity disorder.
Gefitinib		Epidermal growth factor (EGFR) receptor inhibitor used for certain breast and lung carcinoma
Sutezolid		Treatment of multidrug resistant tuberculosis (MDR)
Nifurtimox		Treatment of chagas disease caused by parasite present in faeces of triatomine bug and sleeping sickness
Artemisone		Antimalarial used against plasmodium falciparum
Artemiside		
Thiomorpholine 1,1 – dioxide (TMS) and N – methyl – thiomorpholine 1,1 – dioxide (MTMS)		Retina protector

Doxapram HCl		Respiratory stimulant
Phenadoxone		Analgesic
Emorfazone		Non-steroidal anti-inflammatory drug (NSAID)
Fenpropimorph		Fungicide

Morpholine has been synthesized by numerous methods. Many of these synthetic approaches can be applied to synthesize substituted thiomorpholine analogues by varying the functional groups on the reactants. The different methods reported for their synthesis are given in **Figure 2** [39-43].

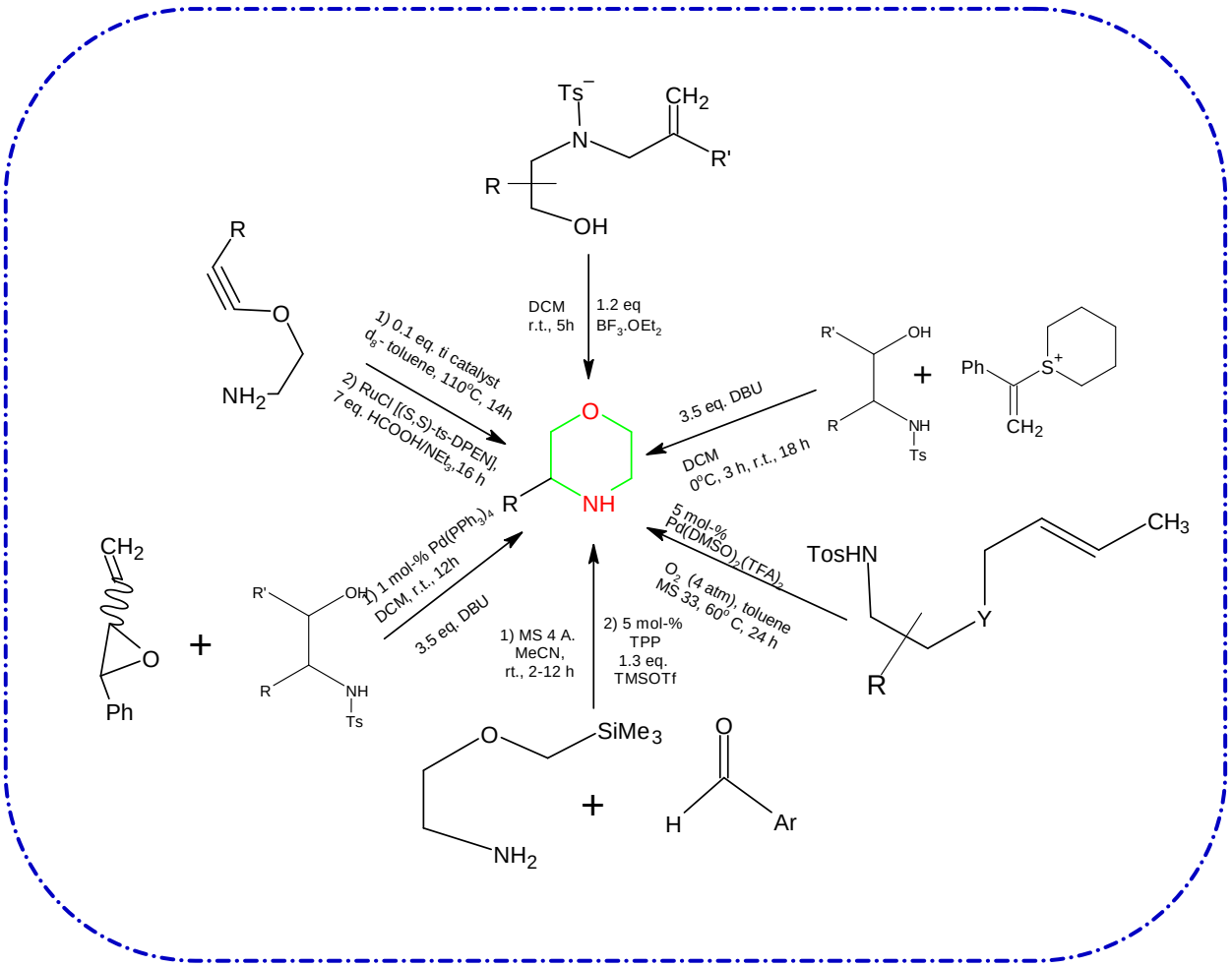


Figure 2. Various approaches for synthesis of morpholine

The various approaches for their synthesis of the thiomorpholine ring are demonstrated in **Figure 3**.

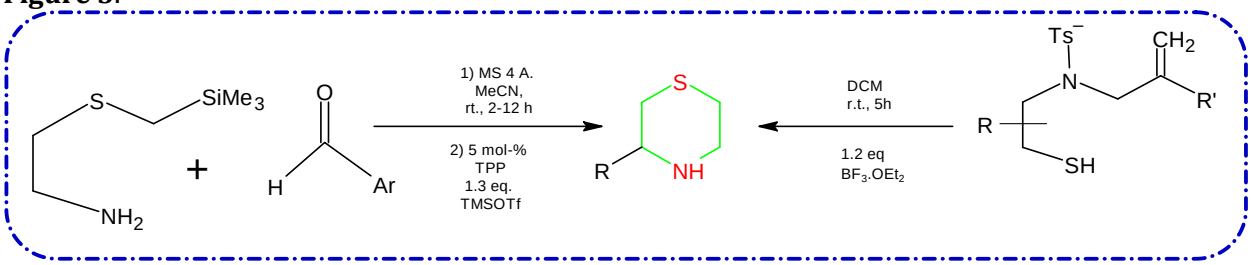


Figure 3. Various approaches for synthesis of thiomorpholine

Yıldız Uygun Cebeci *et al.* [46] reported synthesis of Schiff base and azol –β– lactum derivatives beginning from morpholine and thiomorpholine as shown in **Figure 4**. The synthesized compounds were screened for their antitubercular, antiurease, acetylcholinesterase activity and anti–oxidant capacity.

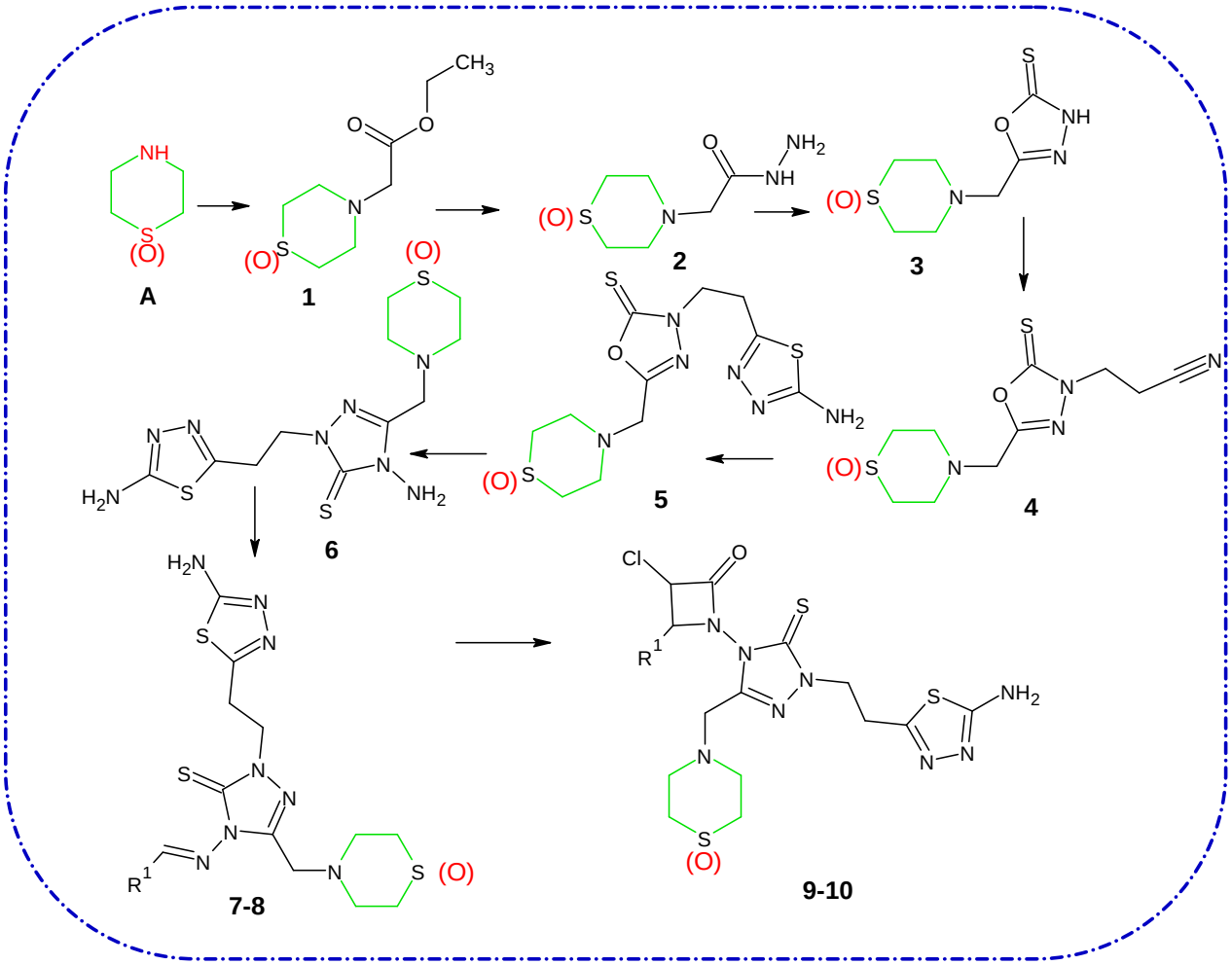
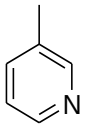
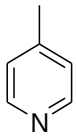
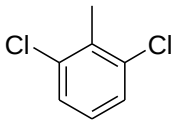
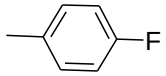
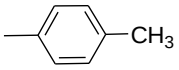
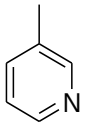
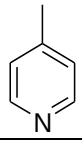
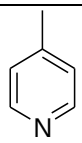
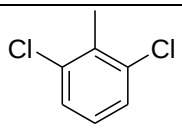
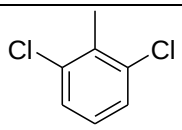
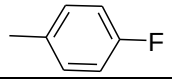


Figure 4. Synthesis of Schiff base and β-lactam derivatives from morpholine and thio- morpholine. i. $BrCH_2COOEt$, EtOH; ii. NH_2NH_2, EtOH; iii. CS_2, triethylamine, EtOH; iv. CH_2 CHCN, EtOH; v. Thiosemicarbazide, TFA, NH_3; vi. NH_2NH_2, EtOH; vii. Aldehyde, MW; viii. $ClCH_2$ COOH, dioxane, triethylamine

The compounds were analysed against Mycobacterium smegmatis taking streptomycin as the standard for anti-tubercular activity. Thiomorpholine derivative 7b and Schiff base 7c exhibited very good activity in a dose of 7.81 µg/mL. Compounds 2a and 3a, pursuing the acetohydrazide and oxadiazole ring, had shown similar effects. Good to moderate activity was observed for compound 7a, 7d which are Schiff bases of thiomorpholine series and 9a, 9b being beta-lactam derivatives of thiomorpholine. Almost all of the screened compounds exhibited good urease inhibition activity. Compound 10a and 10b compounds showed moderate inhibition for acetylcholinesterase as compared to donepezil as standard drug. Among the synthesized moieties compound 8a, 8b, 8c showed enhanced anti-oxidant activity activity as seen in **Table 2** [47-50].

Table 2. Activity of synthesized derivatives

Compounds	Ar	Anti tubercular activity	Anti urease activity	Acetylcholinesterase inhibitor	Anti oxidant activity	
		MIC (µg/mL)	IC_{50} (mg/mL)	IC_{50} (mg/mL)	CUPRAC (µmol TE/g)	FRAP (µmol TE/g)
2	-	7.8	-	-	4578.11	4.228
3	-	7.8	2.23	2.32	3048.61	4.649
7a		15.6	2.28	1.28	-	-
7b		7.8	4.19	4.19	-	-
7c		7.8	0.85	0.75	-	-
7d		15.6	5.96	-	-	-
8a		-	0.45	1.73	7178.35	3.187
8b		-	1.01	2.12	7265.29	4.878
8c		-	1.25	2.86	8048.11	3.803
9a		15.6	-	-	-	-
9b		15.6	0.96	1.19	-	-
10a		-	2.14	0.95	-	-
10b		-	1.33	0.88	-	-
Standard		Streptomycin 4	Thiourea 12.02	Donepezil 0.03	FP-T58 7986.12	4.119

Upinder singh *et al.* [51] reported new anti-bacterial moiety having tetrahydro-4-(2H)-thiopyran sulfoxide, thiomorpholine-S-oxide and thiomorpholine *S*, *S*–dioxide phenyl

oxazolidinone scaffold (**Table 3**). In this study, oxazolidinone class of antibiotic, linezolid 11 was modified by replacing morpholine ring by thiomorpholine S-oxide and thiomorpholine *S*, *S*-dioxide as in synthetic **Figure 5** [52]. Both In-vitro and In-vivo antimicrobial evaluation was done on various species including Escherichia coli, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumonia, Enterococcus faecium, Haemophilus influenza and Moraxella catarrhalis. An SAR studyof C-5 amide analogues of S-oxide and *S*, *S*-dioxide thiomorpholine and thiopyran oxazolidinones was performed and several novel leads with good in vitro potency against gram-positive bacteria were identified. The SAR of this series indicates a preference for small-sized lipophilic C-5 groups with the exception of well tolerated extended cinnamamides. Compound 12a (ED50 3.75 mg/kg) displayed an oral efficacy slightly superior to that for linezolid 11 (**Figure 6**) (ED50 5 mg/kg), whereas analogue 12b (ED50 6.52 mg/kg) was comparable to the drug.

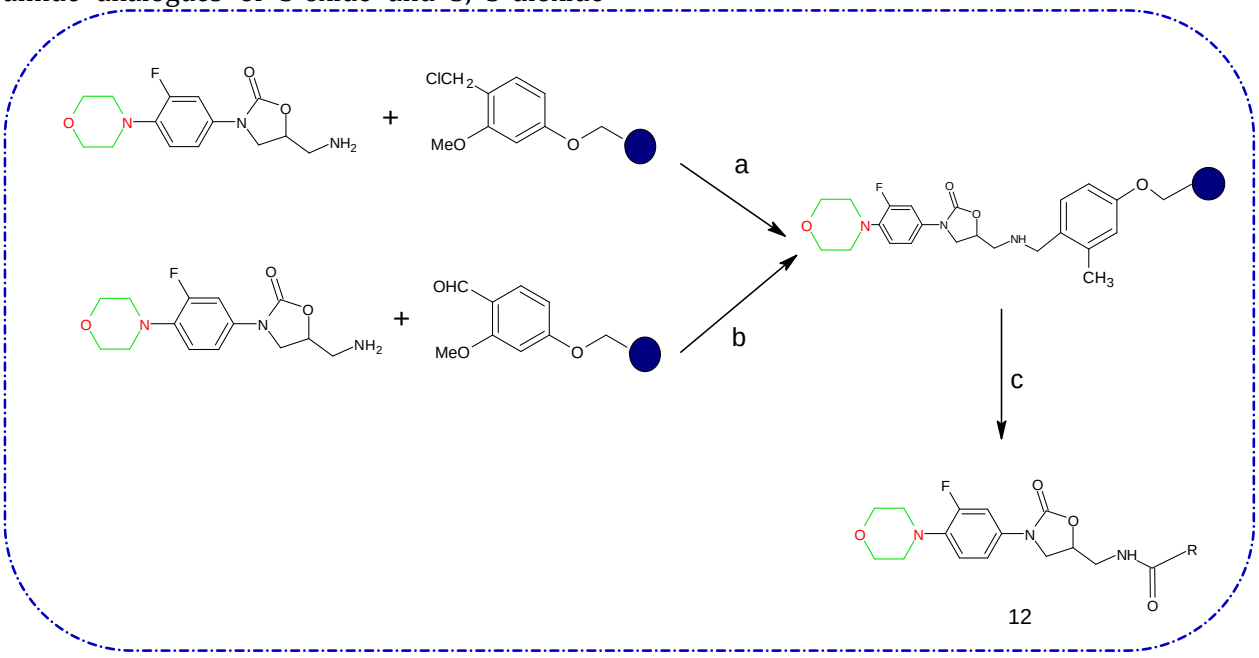


Figure 5. Solid-phase library synthesis: (a) DMF; (b) $NaBH_3CN$, MeOH, DMF, 1% AcOH; (c) (1) RCOOH, HATU, DIEA, DCM, *rt.* or RNCO, DMF or RNCS, DMF or ROCOCl, DIEA, DMF; (2) TFA, DCM

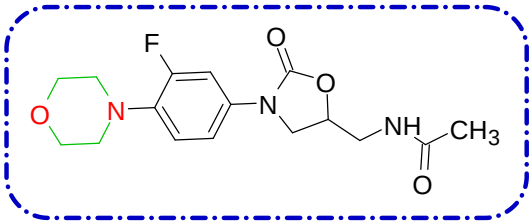


Figure 6. Linezolid (**11**)

Table 3. Substituent's on active compounds

Compound	R	X
12a	$-CH_2F$	CH
12b	$-CHF_2$	CH

The resurgence of tuberculosis (TB) and drug resistant strains of mycobacterium tuberculosis has led to the discovery of a new drug moiety with improved therapeutic efficacy and action. Also immunocompromised patients are prone to recurring fungal infections caused by

Cryptococcus neoformans, Candida albicans and Candida species. While investigating in the area of azole antimicrobials initiated by Mariangela Biava *et al*., [53] they identified compound 13 (**Figure 8**), a pyrrole derivative having good in-vitro activity against Mycobacteria and Candidae. He synthesized compounds by alternatively introducing *N*-methylpiperazine or thiomorpholine at C3 of the pyrrole and substituting para position of the phenyl ring in N1 and/or C5 of the pyrrole ring with Cl or F atoms **Figure 7**. Compound 14 (**Figure 9**), was seen to be more active compared to the lead compound 13, and had remarkable Protection Index (PI). This could be attributed to addition of a fluorine atom in a structure of 14, exhibited better activity and lower toxicity. It was found to be a more potent derivative than 13, was taken as a lead compound in this class of antimycobacterials, also proven to show anti-candida activity (**Table 4**) [54-56].

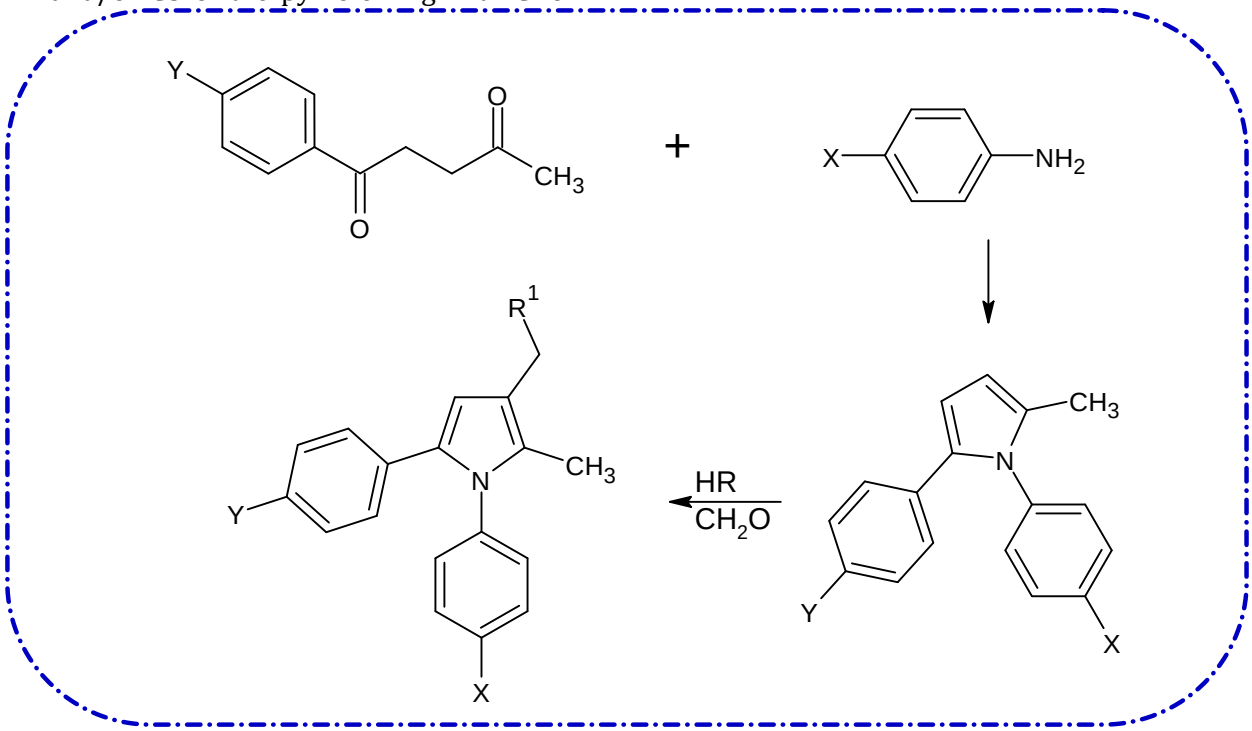


Figure 7. 1,4-diketone, obtained by reacting levulinic acid and chorobenzene in the presence of $AlCl_3$

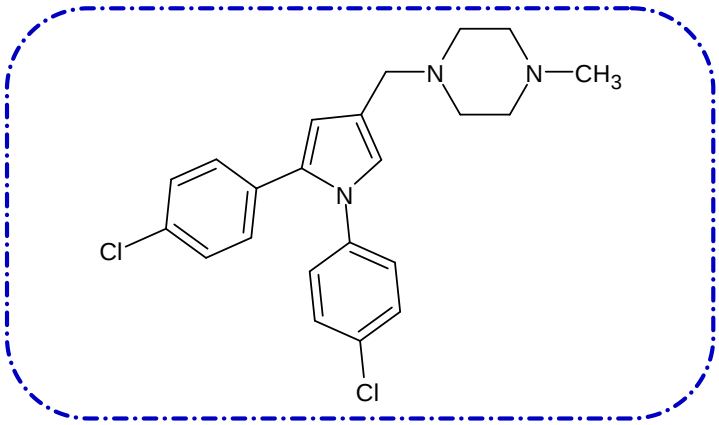


Figure 8. Compound **13**

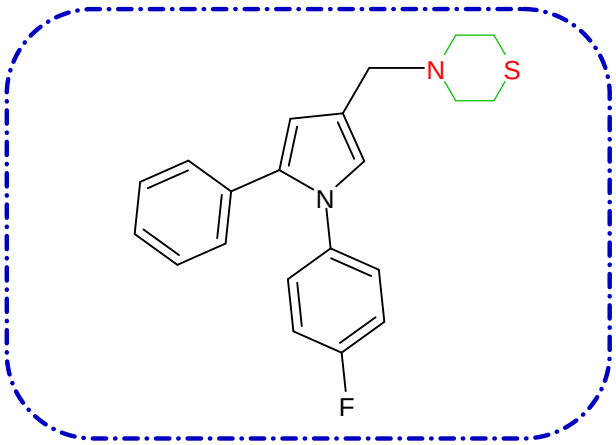


Figure 9. Compound **14**

Table 4. Minimum inhibitory concentraton of active derivatives

Compound	MIC (µg/mL)				
	M.smegmatis 103599	M.marinum 6423	M.gordonae 6427	M.avium 103317	Inhibition of intramacrophagic mycobacteria
13	25	100	>100	0.4	1
14	>16	>16	>16	2	3
Rifampin	32	0.6	0.6	0.3	3

A series of structurally similar thiomorpholine derivatives displaying hypocholesterolemic and antioxidant activity have been synthesized by Tooulia *et al*. [57]. **Figure10** reveals an antioxidant moiety as the thiomorpholine *N*-substituent. The derivatives were found to inhibit the ferrous/ascorbate-induced lipid peroxidation of microsomal membrane lipids, with IC50 values as low as 7.5µM. The most active compound 15 (**Figure 11**) decreases the triglyceride, total cholesterol, and low-density lipoprotein levels in the plasma (**Table 5)** [58-61].

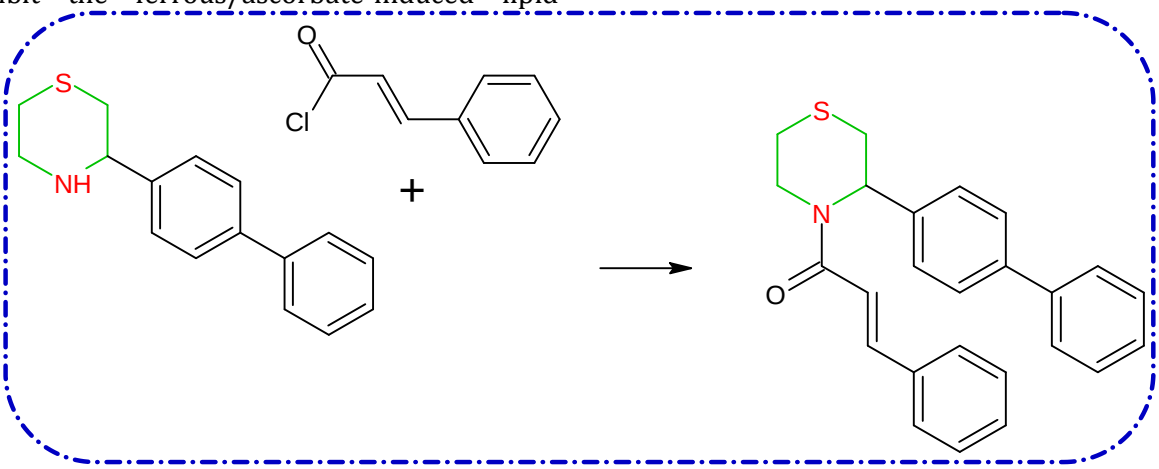


Figure 10. 3-arylthiomorpholines or unsubstituted thiomorpholine reacted with the related acyl or alkyl chlorides in the presence of trimethylamine

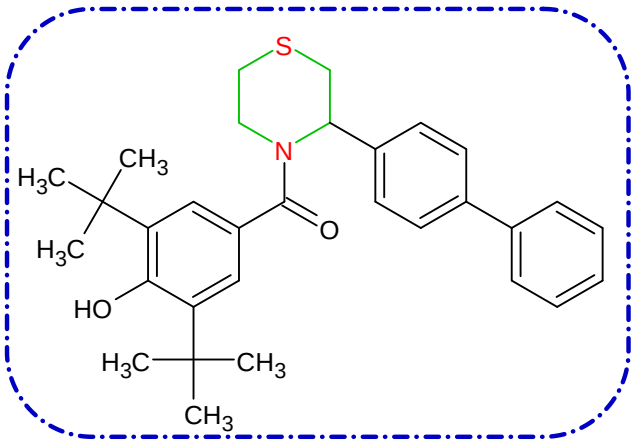


Figure 11. Compound **15**

Table 5. IC50 of compound 15

Compound	Lipid peroxidation inhibition: IC_{50} (mM)
15	200

The main activity of thiomorpholine derivatives could be attributed to biphenyl ring. The plausible mechanism could be inhibition of enzyme squalene synthase which reduces formation of cholesterol and antioxidant property of moieties that prevents oxidation of LDL. The given moiety was successful in reducing plasma triglyceride, total cholesterollevels and LDL by 80%, 78%, 76% respectively. The given moiety can thus be used as novel compound as an antiatherogenic agent. Thirteen thiomorpholine-bearing compounds were designed and synthesized using **Figure12** by Bei han *et al*. [62] as dipeptidyl peptidase IV (DPP-IV) inhibitors, with natural and non-natural L-amino acids as the starting materials.

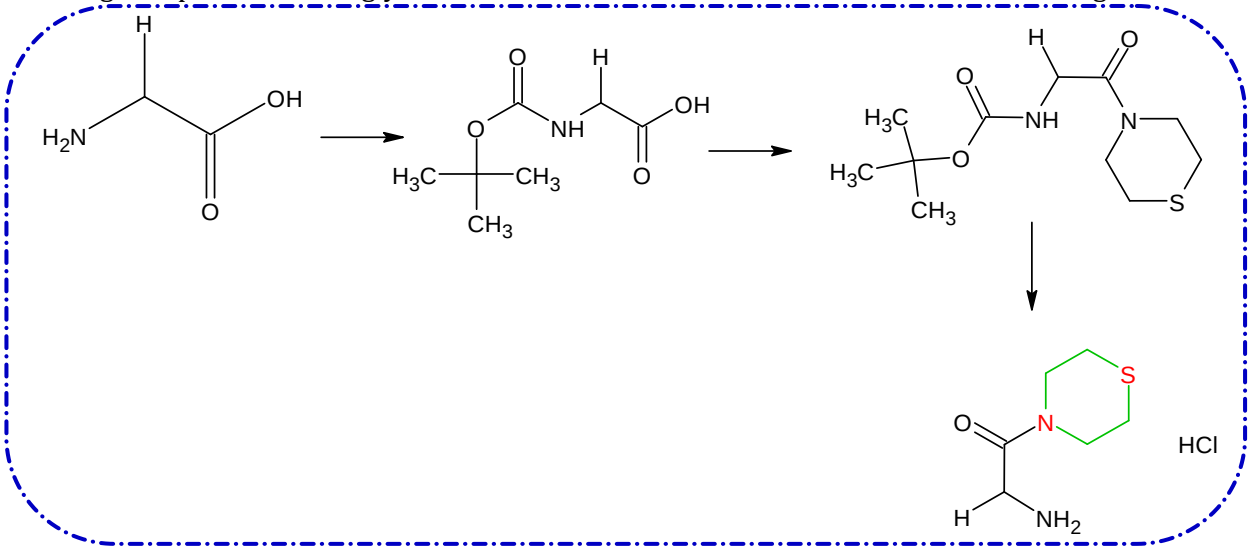


Figure 12. Synthetic route of the target compounds **4a–4k**. Reagents and conditions: (i) 1 mol/L NaOH, $(Boc)_2O$, 0 8C *rt.*; (ii) thiomorpholine, EDC, *rt.*; (iii) 7 mol/L HCl/EtOAc

Table 6. Substituent's and activity of synthesized derivatives

Compound	R_1 or structure	Inhibition (%, 10 µmol/L)
16a	1-Methylethyl	74.6
16b	2-Methylpropyl	77.9
16c	1,1-Dimethylethyl	74.4

Compounds 16a, 16b and 16c thiomorpholine-bearing compounds as good inhibitors of DPP-IV in vitro with IC50 values of 6.93, 6.29 and 3.40 µmol/L respectively (**Table 6**). Importantly, compound 16c, which had the biggest group at the α -position of carbonyl of the three, can significantly reduce the plasma glucose area under the curve (AUC) by 15.0% and 21.6%, respectively at the doses of 50 mg/kg and 150 mg/kg body weight, that is to say, it showed better hypoglycemic ability in vivo than the other two compounds [63-65].

A. Ma velazquez *et al*. [66] synthesis new methylthiomorpholine compounds and compared its cardiovascular effects with cardiovascular drugs such as captopril, losartan and omapatrilat. People of Republic of China discovered a moiety named Changrolin 17 (**Figure 13**) which was an anti – arrhythmic drug. Further it was modified by American Hospital Supply Corporation, Illionois.

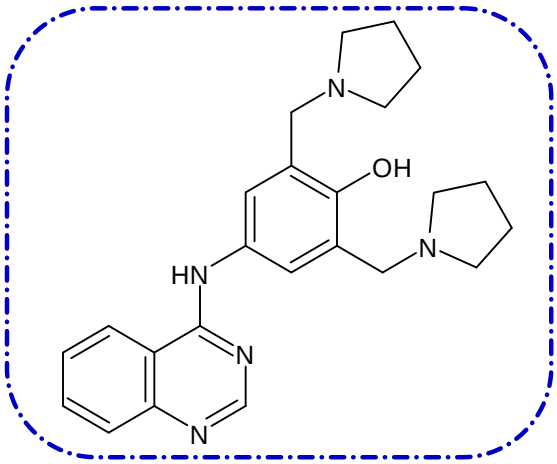


Figure 13. Changrolin (**17**)

They studied the structure and found out that phenol and methyl pyrrolidine rings were necessary for the moiety to show cardiovascular effects and hence the pyrrolidine ring was exchanged for a methylthiomorpholine ring. Considering the evolution of newer antihypertensive agents this novel methylthiomorpholinphenol compounds with cardiovascular effects, justify the need to search for medicines that promote a reduction in the blood pressure, such as monotherapy, to achieve a good protection for most hypertensive patients and a decrease in adverse reactions. Captopril showed the lowest ED50 among all the compounds. Contrarily, it was determined that captopril's ED50 (**Table 7**) is three folds lower compared to 20, 21 and four times lower than 18, 19, 20 (**Figure 14**). Out of the synthesized molecule, compounds 20 showcased the better diminish of both systolic and diastolic pressure; it also showed foremost heart rate decreasing effect [67-68].

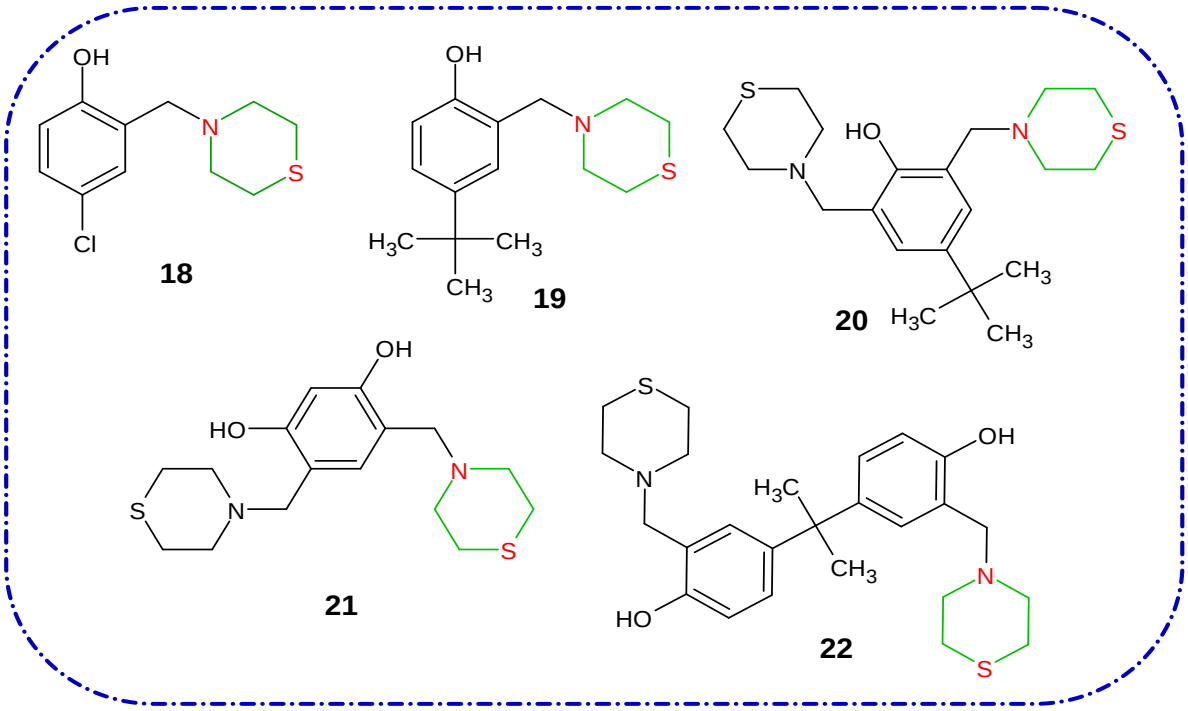


Figure 14. Compounds **18-22**

Table 7. Mean effective dose of synthesized compounds and positive controls

Compound	**ED_{50} (mg/kg)**
18	2.2122
19	1.0410
20	0.4111
21	0.3631
22	1.4091
Captopril	0.00062
Losartan	0.02815
Omapatrilat	0.0058

Levin and coworkers synthesized a series of tumor necrosis factor-α-converting enzyme (TACE) inhibitors bearing a thiomorpholine sulfonamide hydroxamate incorporated with propargylic ether as shown in **Figure 15**. Compound 23 displayed superior in vitro activity towards both in-cell and isolated enzyme also active orally against models of TNF-α production and collagen-instigated arthritis model designed for the therapy against rheumatoid arthritis.

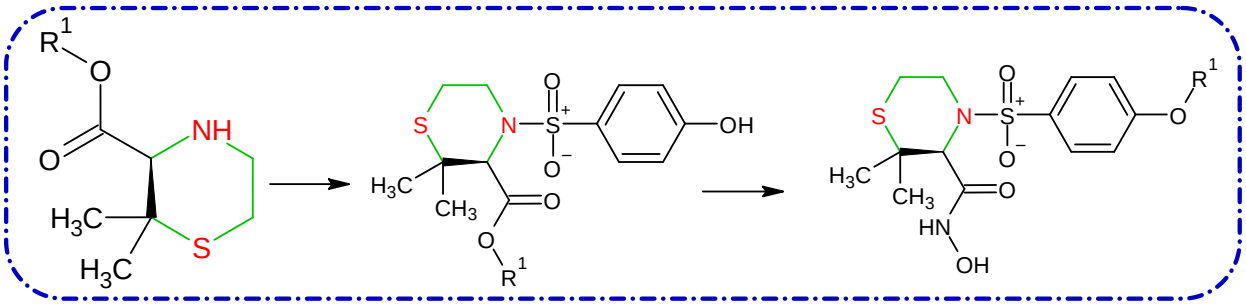


Figure 15. Reagents: (i) a—4-HOPhSO$_2$Cl, BTSA; b—MeOH; (ii) R^1 OH, PPh$_3$, DEAD; (iii) HCl (g) or LiI; (iv) a—(COCl)$_2$, DMF; b—NH$_2$OH

Investigation of computational models of compound 24 (**Figure 16**) bounded to agonist binding site of TACE suggested that the 6th position of the thiomorpholine ring being exposed to solvent, can be altered by adding asubstituent that could change the physical characteristics of the ligand with minimal loss of enzyme inhibitory activity. The alcohols of compound 23 were less reactive compared to the butynyl derivatives 24 in the TACE FRET assay, with the shortest chain analogue, 23, exhibiting more potency. The TACE activity is not hindered significantly with increase in chain length, although activity in T-helper cells displayed a drastic decreases in compound 23 (89% inhibition at 1 lM, IC50 = 140 nM).

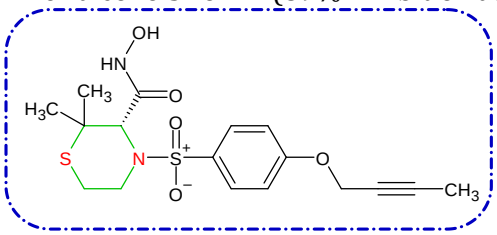


Figure 16. Compound **24**

A class of 2-(thiophen-2-yl) dihydroquinolines linked with morpholine, *N*-substituted piperazine and thiomorpholine coupled were designed and synthesized by Marvadi *et al*. [94] shown in **Figure17**.

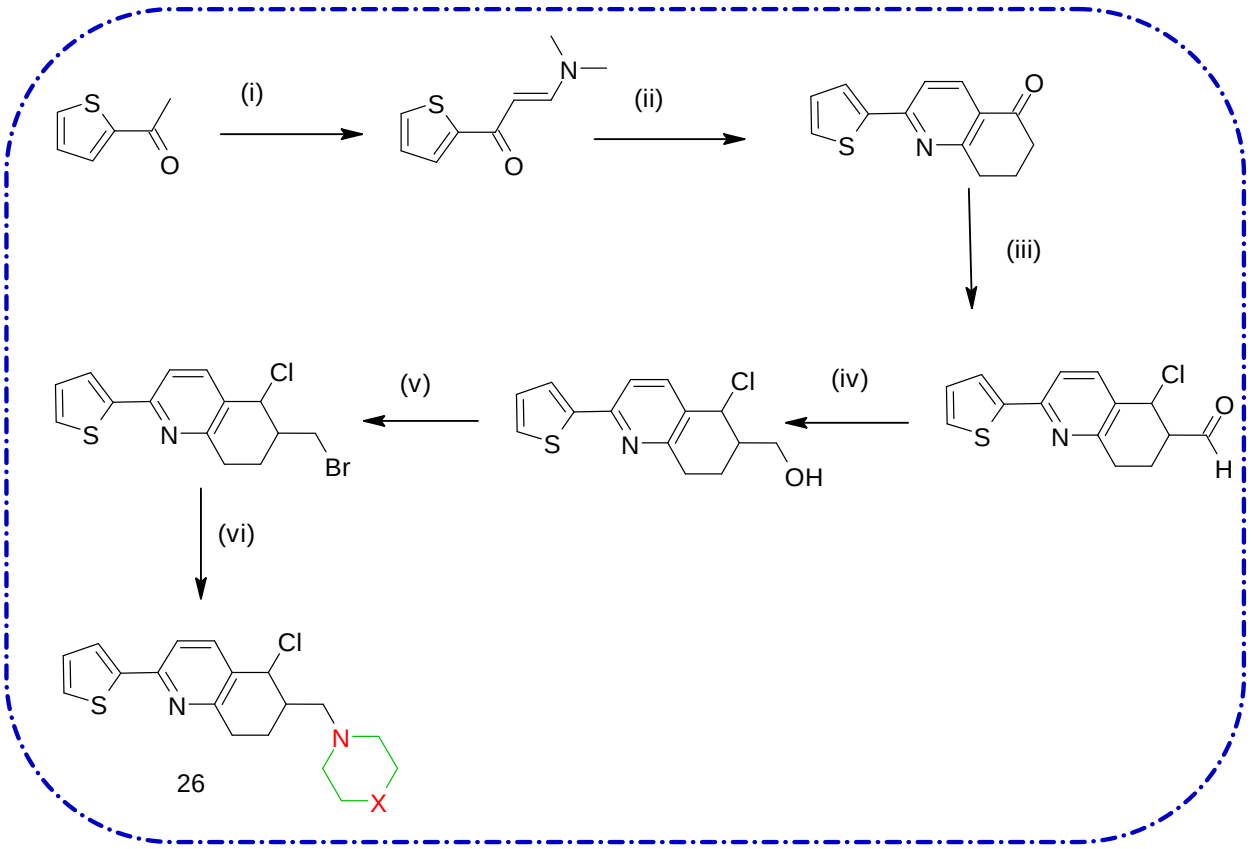


Figure 17. Synthesis of 2-(thiophen-2-yl) dihydroquinoline derivatives. Reagents and conditions: (i) DMF-DMA, xylene, reflux, 7 h, 95%; (ii) Cyclohexane-1,3-dione, NH_4OAc, $CeCl_37H_2OeNaI$, propan-2-ol, reflux, 4 h, 86%; (iii) $POCl_3$-DMF, $CHCl_3$, 60 C, 4 h, 84%; (iv) $NaBH_4$, MeOH, *rt*., 1.5 h, 88%; (v) PBr_3, diethyl ether, *rt*., 1 h, 82%; (vi) K_2CO_3, acetone, *rt*., 12 h, 72-94%

Table 8. Substituent and MIC of active molecules

Compound	R	MIC (µg/ml)
26a	Morpholine	6.25
26b	Thiomorpholine	25
Isoniazid	-	0.1
Rifampicin	-	0.2
Ciprofloxacine	-	1.56
Ethambutol	-	3.13

Structure-activity relationship (SAR) indicated interesting in vitro antimycobacterial activity patterns against M. tuberculosis H37Rv (MTB). To note that, thiomorpholine analog 26b is less potent than parent 2-(thiophen-2-yl) dihydro quinoline 25 (MIC: 12.5 mg/mL) whereas morpholine analog 26a exhibited better potency than both 25 and 26b (**Table 8**) [75-78].

α-Glucosidase inhibitory activity of synthesized 4-(5-fluoro-2-substituted-1*H*-benzimidazol-6-yl) morpholine derivatives was evaluated by Menteşe *et al.* [79] (**Figure18**). The synthesized derivatives displayed a considerable α-glucosidase inhibitory activity in comparison with the standard, acarbose. Compound 27 (**Figure 19**) with methoxy substituted benzene ring showed superior inhibition with IC50 = 0.18 ± 0.01 µg/mL among the screened derivatives. In vitro and computational studies emphasized that electron-releasing groups like methyl or methoxy substituted on phenyl ring and improved resonance effect play an eminent part in the activity, could be a promising lead for future investigation [80-83].

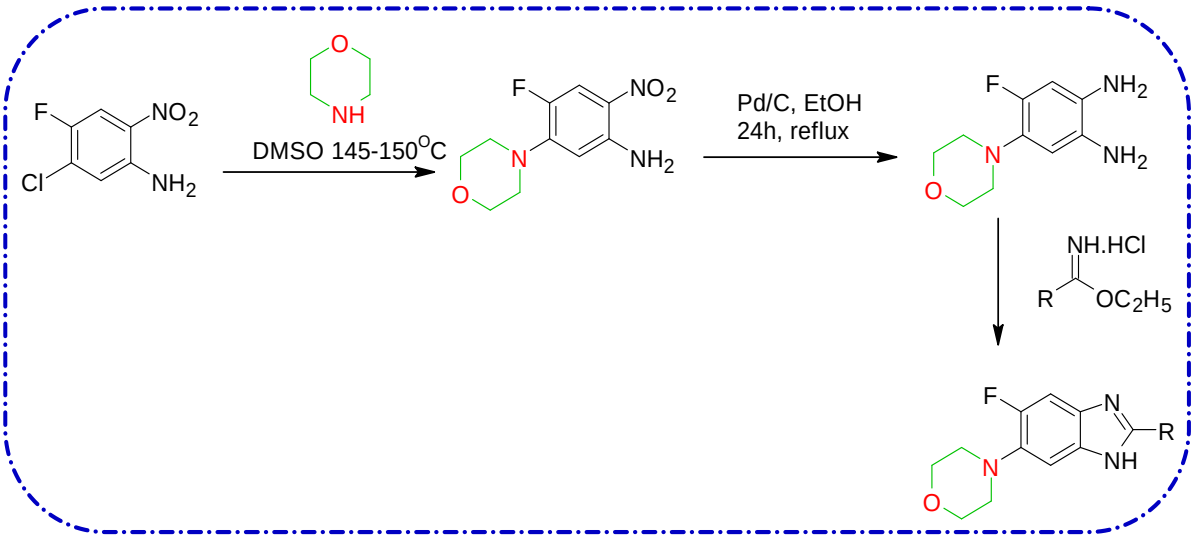


Figure 18. Synthetic approach for the preparation of target compound

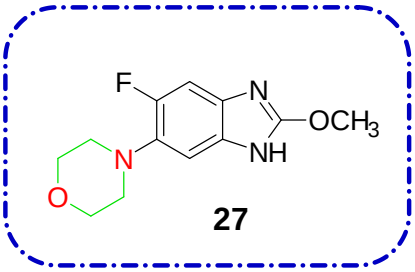


Figure 19. Compound **27**

29 monobactam derivatives were synthesized by Heiran *et al*. [84] having a morpholine nucleus attached on the nitrogen of the lactam ring (**Figure 20**). The compounds were studied for their inducible nitric oxide synthase (iNOS) inhibitory effect. Amongst the morpholino-β-lactam hybrids, the compounds 28a, 28b, 28c, 29a, 29b, 30a, 30b and 30c exhibited greater inhibition compared with standard drug dexamethasone with anti-inflammatory ratio of 32. IC50 values values obtained were relevant compared with doxorubicin used as the standard (IC50< 0.01 mM) against HepG2 cells, biocompatibility and nontoxic behavior (**Table 9**) [85-92].

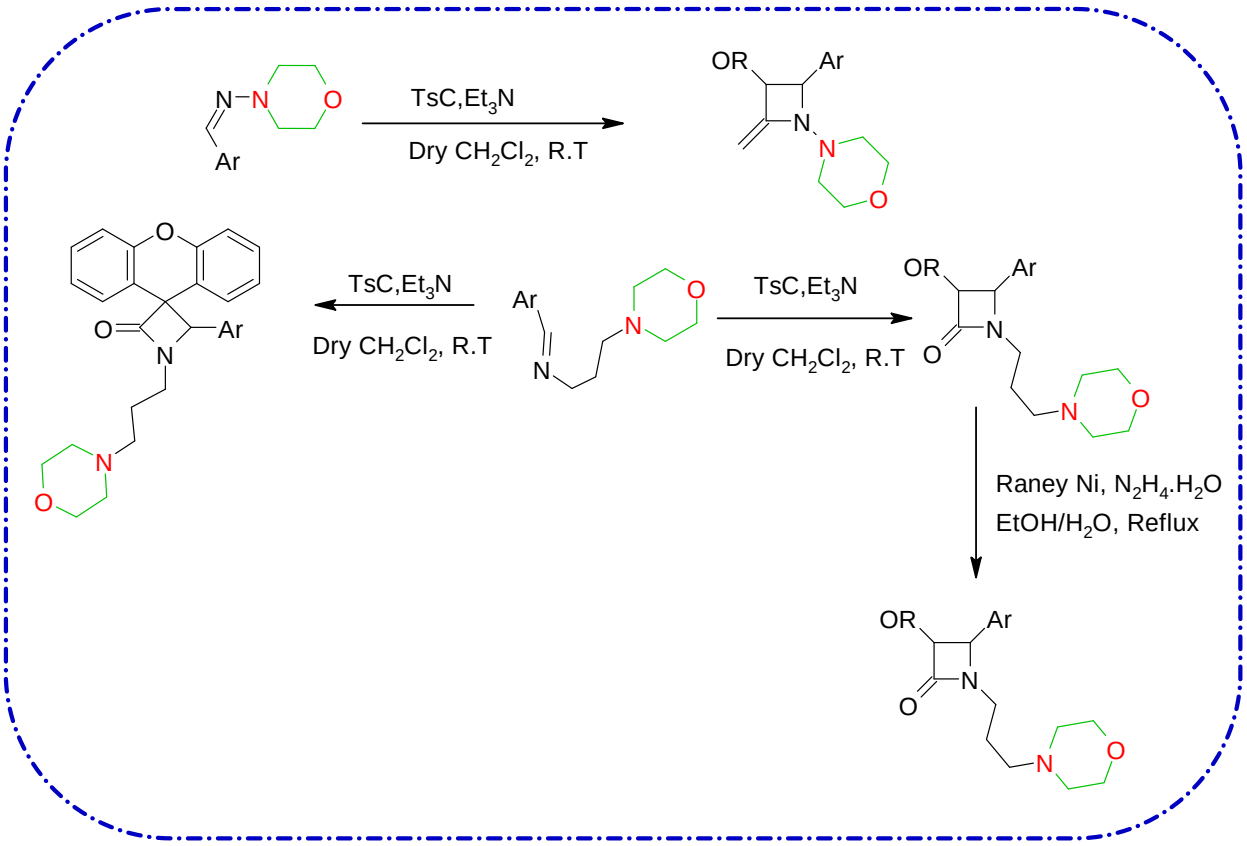


Figure 20. General synthetic Scheme of β-lactam

Table 9. Substituent and activity of derivatives

Compound	Ar	R	IC_{50} (mM)	Anti-inflammatory Ratio
28a	3-$NO_2C_6H_4$	C_6H_5	0.48 ± 0.04	38
28b	2-NO_2 C_6H_4	4-Cl C_6H_4	0.51 ± 0.01	62
28c	4-CN C_6H_4	C_6H_5	0.22 ± 0.02	51
29a	4-NO_2 C_6H_4	2,4-C_{l2} C_6H_4	0.12 ± 0.00	72
29b	3-NO_2 C_6H_4	Naphthyl	0.25 ± 0.05	51
30a	4-NH_2 C_6H_4	2,4-$Cl_2C_6H_3$	0.82 ± 0.07	35
30b	4-NH_2 C_6H_4	Naphthyl	0.44 ± 0.04	55
30c	3-NH_2 C_6H_4	Naphthyl	0.60 ± 0.04	99

Wang *et al.* [93]. Synthesized novel morpholine-substituted diarylpyrimidines as potent human immunodeficiency virus (HIV-1) non-nucleoside reverse transcriptase inhibitors (NNRTIs) with significantly improved water solubility shown in **Figure 21**. The biological evaluation results showed that four most promising compound 31a, 31b,31c,31d displayed excellent activity towards HIV-1 strain having EC50 in the range of 58 to 87 nM, being far more effective than Nevirapine also equivalent to Etravirine (**Table 10**)[94-98].

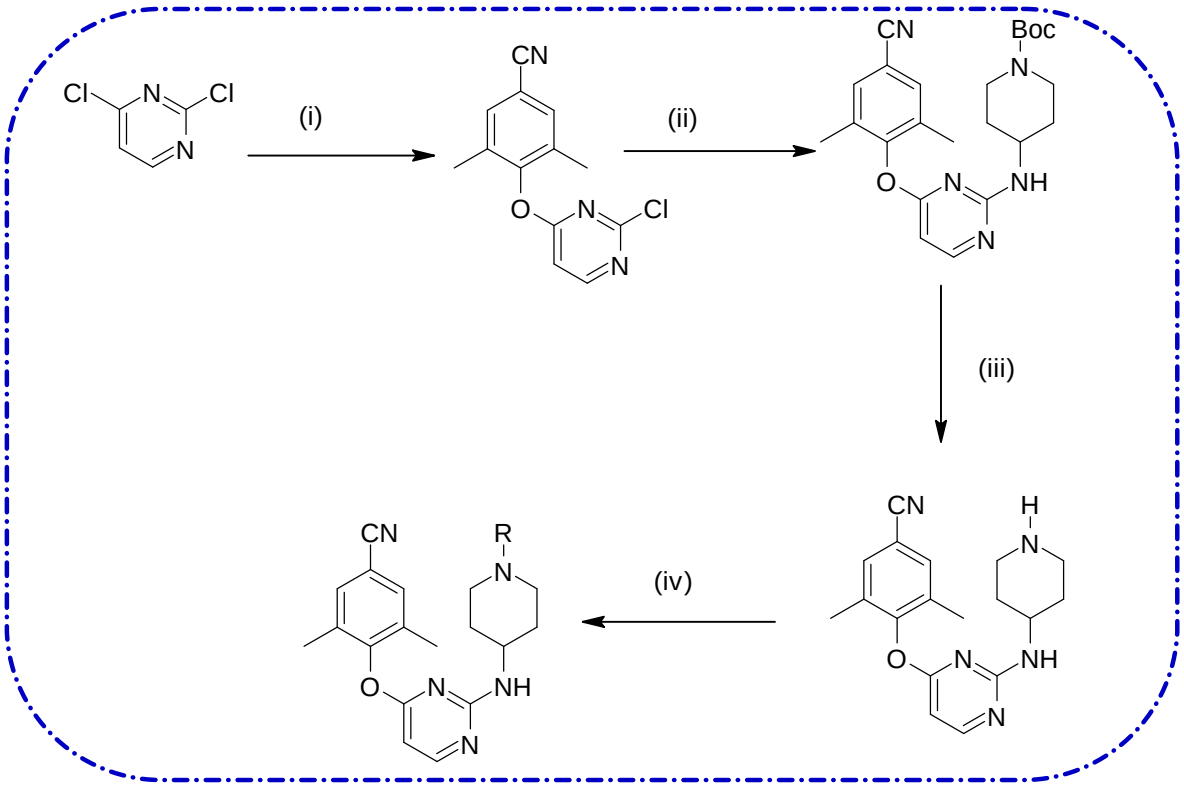
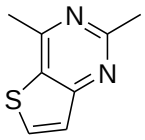
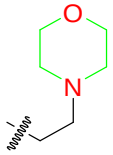
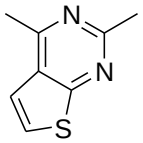
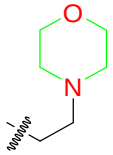
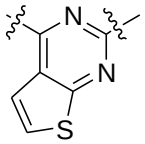
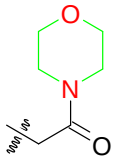
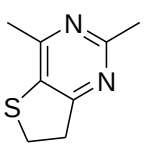
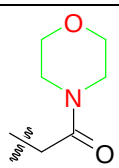


Figure 21. Reagents and conditions: (i) 3,5-dimethyl-4-hydroxybenzonitrile, DMF, K_2CO_3, *rt.*; (ii) *N*-(*tert*-butoxycarbonyl)-4-aminopiperidine, DMF, K_2CO_3, 100 °C; (iii) TFA, DCM, r. t.; (iv) 4-(2-chloroethyl) morpholine or 4-(2-chloroacetyl) morpholine, DMF, Cs_2CO_3, 60 °C

Table 10. Substituent and mean effective dose of synthesized compounds

Compound	Central Scaffold	R	EC50
31a			0.087 ± 0.021
31b			0.065 ± 0.021
31c			0.082 ± 0.043
31d			0.082 ± 0.043

The anticancer potentiality of hydrazones of morpholine scaffold were screened towards human cancinoma cell lines Human breast adenocarcinoma (MCF-7) and Human hepatocellular liver carcinoma (HepG2) by Taha *et al.* [99] The synthetic pathway is depicted in **Figure 22**. Analogs 35 had indistinguishable cytotoxic activity towards HepG2 compared to doxorubicin taken as standard. Compounds 32, 33 and 34 displayed potent cytotoxicity against MCF7 in comparison to the standard drug Tamoxifen (**Table 11**) [100-103].

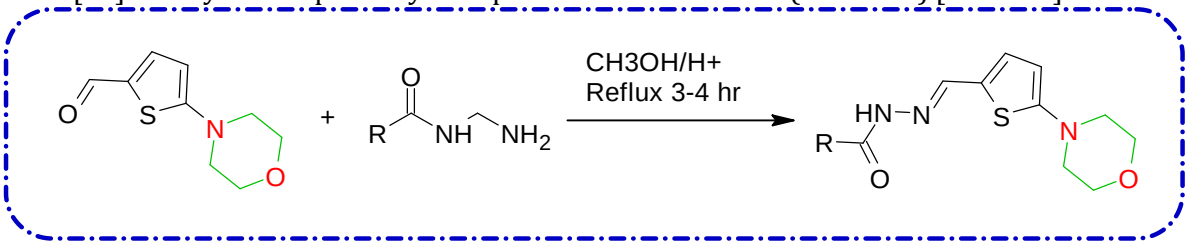
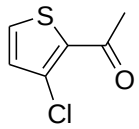
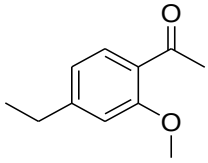
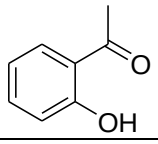
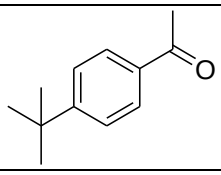


Figure 22. Synthetic Scheme for morpholinothiophene hydrazones

Table 11. Substituent and IC50of active molecules

Compound	R	Anticancer activity data (IC50 values in µmol/L)	
		HepG2	MCF-7
32		19.95 ± 0.63	7.08 ± 0.42
33		-	1.26 ± 0.34
34		40.0 ± 0.93	11.22 ± 0.22
35		6.31 ± 1.03	-
Doxorubicin		6.00 ± 0.80	-
Tamoxifen		-	11.00 ± 0.40

Morpholine substituted 2-amino-4-phenylthiazole derivatives were worked on by Zhang and co-workers having structural similarities to the drug Crizotinib (**Figure 23**). Compound 45 exhibited excellent growth inhibitory effects on the tested cell lines, most effective towards human colon cancer cell line HT29 with 2.01 µM as the IC50 value (**Table 12**) [104-109].

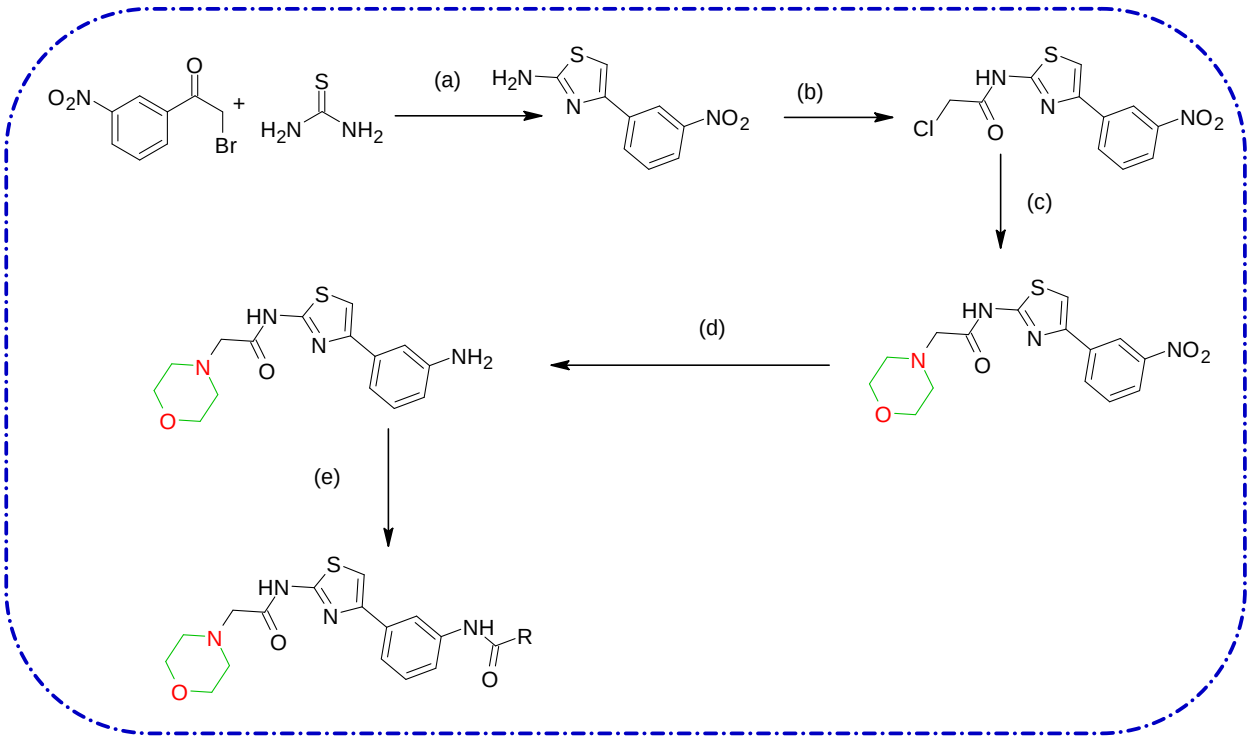


Figure 23. General synthesis of the target compounds. Reagents and conditions: (a) thiourea, ethanol, and reflux; (b) chloroacetyl chloride, CH_2Cl_2, Et_3N, *rt.*; (c) morpholine, ethanol, K_2CO_3, *rt.*; (d) $SnCl_2{\cdot}2H_2O$, ethanol, reflux; (e) substituted acyl chloride, CH_2Cl_2, Et_3N, r.t

Table 12. Substituent and activity of Compound **36**

Compound	R	IC50 (μM)			
		A549	HeLa	HT29	Karpas299
36	3,4-diCl phenyl	17.32	10.86	2.19	11.12
Crizotinib		2.26	1.09	1.10	0.02

Ali *et al*. [110] developed certain thiazolo [3, 2 *a*]pyrimidin-5-ones linked through an ethylene bridge to various amines **Figure24**. The newly synthesized compounds 4–6(a–c) were subjected to in vitro anticancer evaluation using National Cancer Institute tumor screening. The target compounds displayed against Renal UO-31 cancer cell line with cell growth promotion 52.72–64.52%. Compounds 37a and 38b are considered as a promising leading scaffold for further development of potential PI3Ka inhibitors. Compounds 37a and 38b displayed low activity at 100 μM 265 against mTOR and moderate activity against PI3Ka with IC50 values 266 of 120 and 151 μM, respectively (**Table 13**) [111-114].

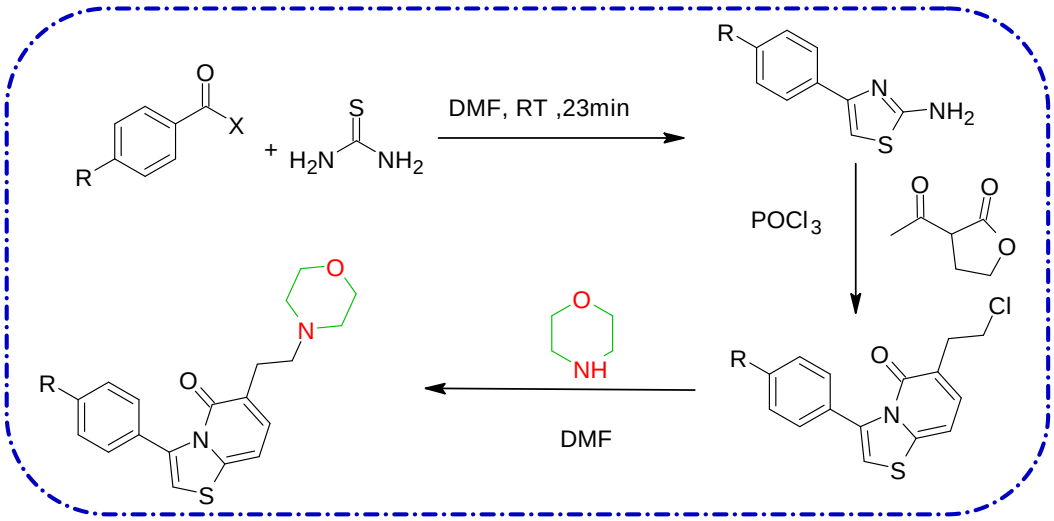
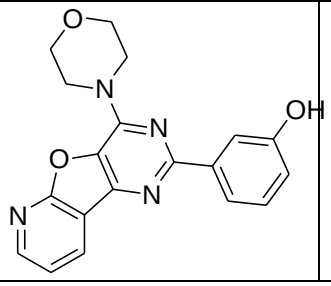


Figure 24. Synthesis of thiazolo [3,2-*a*] pyrimidin-5-ones

Table 13. Substituent and IC50 of synthesized derivatives

Compounds	R	mTOR		PI3Ka	
		% Inhibition	IC50	% Inhibition	IC50
37a	H	10	-	44	120
37b	Cl	14	-	40	151
Control		-	0.091	-	0.001

Conclusion

With plethora of utility and immense pharmacological activity the morpholine and thiomorpholinehave been viewed as a supreme scaffold. In the present review we discussed morpholine and thiomoropholine ring bearing derivatives along with their synthetic pathway and reported activity. With this aim, the morpholine and thiomorpholine derivatives synthesized and their pharmacological activity are summarized herein. Reported work hitherto needs to be studied and analysed order to identify newer leads. This review can aid for newer work in this arena.

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Conflict of Interest

The authors declare that this article content has no conflict of interest.

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