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Synthesis, molecular docking and *in-vivo* study of anti-hyperlipidemic activity in High fat Diet Animals for substituted morpholine derivatives

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Abstract

The present investigation involve synthesis of substituted morpholine derivative and its evaluation of in-vivo and in-silico molecular docking for determining the anti-hyperlipidemic activity. Substituted morpholine derivatives were synthesised by convenient and effective method from analogues of 1-hydroxy-1-(phenyl/substituted phenyl)-propan-2-one by reductive amination using ruthenium on carbon at 25°C-30°C and isolating the product 2-(2-hydroxyethylamino)-1-(phenyl/substituted phenyl)-propan-1-ol as Hydrochloride salt, Intramolecular cyclization of the above compound treating with Concentrated Sulphuric acid at cold condition leads to phenmetrazine derivatives which was characterized by IR, Mass, H^1 and C^{13} NMR spectrum. The molecular docking studies for the synthesised morpholine derivatives with PPARα protein showed the energy levels ranging from – 6.74kcal/mol to – 8.83 kcal/mol. The compound 1C which shows least binding energy taken for in-vivo anti-hyperlipidemic activity study in Triton 1339 rat comparing with the standard drug i.e., Phenmetrazine, Morpholine derivative (1C) shows significant reduce in total cholesterol (TC) and Plasma triglycerides level in blood compared to the standard drug. It proves that the synthesised morpholine compounds exhibit significance towards the anorectic activity.

Keywords: Antihyperlipidimicacitivity, Imine Reduction, Morpholine derivatives, PPAR α –protein

INTRODUCTION

In current scenario, the human lifestyle have been modified greatly leading to several medical complications**[1]**. Obesity is one such complication as it is a major health related complications faced by the modern society with utmost caution. From the reports of World Health Organization obesity and overweight are major risk factors from numerous chronic diseases, comprising of diabetes **[2]**, cardio-vascular diseases **[3, 4]** (CVD) and also cancer in certain cases**[5]**.

Hyperlipidemia is a condition, wherein there is a rise in lipid levels, which is otherwise referred to as fats/ fatlike substances present within the bloodstream**[6]**. Triglycerides and Cholesterol are two types of lipids present in blood. Elevation of one or both of these lipids results in hyperlipidemia**[7]**.One of the commonest phenotypic symptoms observed among hyperlipidemic individuals could be attributed with increased in body mass, falling under obese category**[8, 9]**. Reports suggests 39 % of adults above 18 years of age fall within obese category. Obesity leads to abnormal behaviorwithin the plasma lipoprotein and also serves as lead cause for disorders in lipid metabolism **[10]**. Also some underlying risks such as dementia and Alzheimer disease **[11]**. Out of many other reasons for hyperlipidemia one could be the high level of cholesterol in blood (hypercholesterolemia) **[12]** or high triglycerides (TGs) in the blood (hypertriglyceridemia) **[13]**or, in some unfortunate cases, both.

Hyperlipidemia takes the lead in initiating and propagating the process in arteriosclerosis cessation (AS) and coronary heart diseases **[14, 15]** (CHD) that result mainly high plasma lipid levels, total cholesterol **[16]** (TC), TGs and High density lipoproteins (HDLP) **[17].** Hence therapeutic treatment for hyperlipidemia and arteriosclerosis includes the incapacitation of animated plasma level of TC, TG and LDL along with increase in HDL lipid levels**[18].** The treatment of overweight is one of the major effective measures available as preventive medicines **[19].** Obesity can be treated effectively using anorectic drugs, which act mainly on the hypothalamus to reduce the body weight. Most of the anorectic drugs available in the market are amphetamines and its derivatives, which are powerful CNS (Central Nervous System) stimulants **[20].**The mode of action of these drugs involves a synergy of several metabolic reactions that attribute carbohydrate and fat metabolism**[21].**However the drugs induce side effects involving restlessness, insomnia, nervousness, irritability, etc. Some available β-amino alcohol drugs which are effective under long term treatment but undergoes dehydroxylationforming amphetamines. The side effects occur mainly as a result of sympathetic stimulation which induces gastro- intestinal irritation leading to the formation of stomach ulcer. Most of these drug category tend to form euphoria, which more likely results in habituation and frequent usage**[22].**The scientific community are taking efforts in developing a suitable API with minimal to null side effects. Morpholine derivatives are used as effective anorectics, antineoplastic drugs and anti-microbial agents.The ring structure of morpholine is an important heterocycle which is commonly present in many compounds with pharmaceutical and biological relevance **[23].**Some of them are API'S **[24, 25]** (Active Pharmaceutical Ingredients) and drug intermediates, like

phenmetrazine**[26, 27]**phendimetrazine, linezolid, gefitinib, buparlisib, fenpropimorph, amorolfine, etc.Literatures studies suggest that morpholine derivatives could serve as an excellent anti-hyperlipidemic agents, as studies emphasised on morpholine derivatives to exhibit excellent hypolipidemic and antioxidant activity**[28, 29].** Besides, it is trivial for identifying a suitable strategy for synthesising substituted morpholine derivatives and identifying a potent anti-hyperlipidemic agent. There are certain derivatives with morpholine rings are reported with active drug substances (shown in Figure 1).This research work reports synthesis, characterization, molecular docking and the invivo anti-hyperlipidemic study **[30]** on Triton-1339 for a series of morpholine compounds from 1-hydroxy-1-phenyl-propan-2-one and its derivatives.

MATERIALS AND METHODS

All chemicals and reagents used are of Laboratory grade and are procured from Sigma and Loba chemie. Phenylacetylcarbinol derivatives and ruthenium catalyst are used from Research and Development Centre, Malladi drugs and pharmaceutical limited, Chennai, India.

Synthesis of morpholine derivatives

The mechanism for the one-pot synthesis of morpholine compounds **1 a-f** from 1-hydroxy-1-(phenyl/substituted phenyl)-propan-2-one **2a-d** by reductive amination followed by cyclization **(See Figure 2) Scheme 1.** The lone pair of electrons present in the nitrogen atom of the β-amino alcohol **3a** approaches the electron deficient carbonyl carbon of keto alcohol **2a-d** to form Schiff's base **4a-f** with liberation of water molecule. Catalytic hydrogenation of the imine is a thermodynamically favored reaction by forming the less energy stable amine. During the catalytic reduction of imine **4a-f** using ruthenium on carbon, the imine gets adsorbed to the active surface of the ruthenium catalyst. The hydrogen atoms attached to the surface of the ruthenium get transferred to the imine in syn addition, leads to the formation of erythro amino diol**5a-f**. The erythro amino diol**5a-f** ontreatment with sulfuric acid, an alcohol gets protonated, and the lone pair on second alcohol approaches the carbon with protonated alcohol group to the formation of cyclic morpholine compound **1 a-f (See Table 1).**

Six compounds **1-a-f** were synthesised by the reaction of four different keto alcohols **2a-d** with three different β-amino alcohols **3a-c,** followed by cyclization **(Figure 3).** The cyclized morpholine compounds were isolated as hydrochloride salt and characterized using spectroscopic techniques such as mass spectral analysis, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis.

General procedure for synthesis of 2-(2-hydroxyethylamino)-1-(Phenyl/ substituted phenyl)propan-1-ol Hydrochlorides 5 a-f

1-hydroxy-1-(phenyl/substituted phenyl)-propan-2-one **2 a-d** (150 mmol) were diluted in toluene 100 mL and 1,2-aminoethanol/substituted aminoethanol**3 a-c** (145 mmol) was charged in to hydrogenator flask, 5% Ruthenium on carbon (wet) catalyst in methanol 50 mL were charged and hydrogenated at 2 – 3 kg/cm^2 hydrogen pressure for about 3 hours at 25 °C to 30 °C. The progress of the reaction was monitored by TLC [Dichloromethane: Methanol-19:1], after completion of reaction, the catalyst was separated by filtration and the hydrogenated solution was partially concentrated under reduced pressure to remove methanol. The concentrated mass was extracted using Dichloromethane 75 mL and washed with DM water 25 mL and charged fresh DM water 25 mL. The pH of the mass was adjusted to 1.5 to 2.5 using hydrochloric acid and the organic layer was separated off. The aqueous layer was concentrated under reduced pressure and triturated with isopropyl alcohol 50 mL at 10 °C – 15 °C to get 2-(2-hydroxyethylamino)-1-(Phenyl/substitutedphenyl)propan-1-ol hydrochlorides **5 a-f** as white crystalline solids with yield ranging from 82 to 91 %.

General procedure for synthesis of 3-methyl-2-Phenylmorpholine. HCl and its derivatives 1 a-f

To the mixture of sulphuric acid (840 mmoles) in DM water 2 mL was slowly added 2-(2-hydroxyethylamino)-1-(Phenyl/substituted phenyl)propan-1-ol hydrochlorides **5 a-f** (120 mmoles) at 0 - 5 °C. The mass kept under vigorous stirring for 4 to 5 hours at 0 - 5 °C. The progress of the reaction was monitored by TLC [Dichloromethane: Methanol-19:1]. The reaction mass was quenched slowly in crushed ice 500 g at below 10 °C. The pH was adjusted to 12 - 13 with sodium hydroxide solution. The product mass was extracted with dichloromethane 2 x 100 mL, organic layer was separated and washed with water 100 mL. DM Water 100 mL was charged acidified to 1.0 to 2.0 using hydrochloric acid and the organic layer was separated off. The aqueous layer was concentrated under reduced pressure and triturated with isopropyl alcohol 50 mL at 10 – 15 °C to get 3-methyl-2-Phenylmorpholine. HCl and its derivatives **1 a-f** as white crystalline solidwith yield ranging from 86 to 94 %. The isolated products were confirmed by IR, mass spectrum and ^{1}H and ^{13}C NMR spectroscopic techniques.

IN-VIVO EXPERIMENT AND METHODOLOGY

Animal Used: Animal model which is effective for carrying out in-vivo experiments have been subjected for extensive research by the scientific community for determining the diet quality, its relationship with physical activity and most importantly the progression in chronic disease. Present study involve artificially induced hyperlipidemia in Male Wistar rats. The animals are procuredfrom King Institute of Preventive Medicine, Chennai and were maintained within polypropylene cages at temperature ranges within 21 ± 1 °C ; relative humidity of 50 ± 5% with 12/12 light/dark cycles. The animals were fasted between 6.00 am and 11.00 pm, if required. The study protocols were thoroughly approved under Institutional Animal Ethics Committee (Clearance number: IAEC-ERI-LC-15).

Test samples: The compound were dissolved in a vehicle containing 0.9% NaCl, 0.5% CMC, 0.2% Tween-80 and 98.4% distilled water. The vehicle alone served as negative control. The dose was fixed as 25 mg/kg. The treatments were given through oral gavage, once daily for four weeks.

Induction of obesity: The animals were induced obese by feeding a High Fat Diet (HFD) for four weeks prior to the

experimental study**[31, 32, 33]**. Eighteen male Wistar rats were randomized into three groups containing six animals in each group, which were categorized on the basis of their body weight. The treatment was given for four weeks, orally. Group I consisted of HFD fed animals treated with vehicle. Group II consisted of HFD animals treated with established drug and the animals in Group III consisted of HFD fed animals treated with the derivative **[34, 35]**.

Study: The animals were euthanized under mild CO_2 anesthesia. Blood samples were collected at 0, 15 and 30^{th} day after treatment in EDTA coated tubes, from orbital sinus. Blood was centrifuged at 3500 rpm for 15 min, serum was separated and stored at 4 °C for biochemical analyses. For histological examinations, the liver and adipose tissues were fixed in 10% buffered formalin with PBS **[36, 37]**.

Biochemical estimation: The Feed intake and body weight were measured at regular interval. Serum total cholesterol, triglycerides and HDL-cholesterol (Agape Dignostics) levels were measured **[38]** using commercial spectrophotometric kits, on the same day of collection.Livers were harvested, fixed in 10% buffered formalin and stained with haematoxylin – eosin. Representative microphotographs were presented for (A) HFD control (B) **1c** (50 mg/kg) and (C) phenmetrazine**1f** (50 mg/kg), respectively

Statistics: All the data generated in this study were presented as mean ± SD. One way ANOVA followed either by Student's *t*- test or by Tukey's HSD (SPSS, version 11.5) were used to assess the statistical significance and the data were considered significant at $P \leq 0.05$.

MOLECULAR DOCKING STUDY OF COMPOUNDS

To examine the theoretical binding orientation of the synthesised compounds**1 a-e** with protein PPAR-ALPHA (1i7g) **[39],** Above synthesized derivatives has been compared with the phenmetrazine**1f.** The role of PPAR alpha in fatty acid oxidation and PPAR gamma in adiposity differentiation, lipid storage has been characterized extensively. The crystal structure of PPAR-Alpha was retrieved from RCSB Protein Data Bank and AutoDock 4 software was used for molecular docking studies. The structures of the synthesised ligands 1a-e were sketched as 3D structure using chemBioDraw ultra, 11.0 software. The PPAR-alpha crystal structure was downloaded and binding site was analyzed by CASTp server. After making the protein file and ligand file, auto grid file were prepared and followed by auto dock analysis was made **[40]**. The docking results of the ligands **1a-f** with the protein PPARα (1I7G) are tabulated in **Table 3.**

Table 1: Synthesis of morpholine derivatives 1 a-f

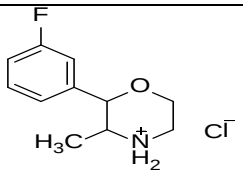
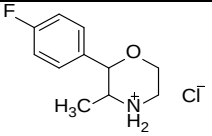
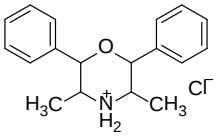
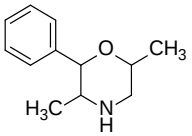
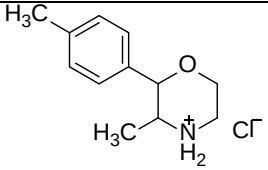
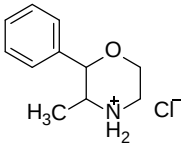
Entry	Keto alcohols, 2	β-amino alcohols, 3	Structure of product, 1	Yield %
1a	2a	3a		93.2
1b	2b	3a		92.5
1c	2c	3b		87.7
1d	2c	3c		86.4
1e	2d	3a		94.3
1f	2c	3a		93.2

Table 2 : Statistical weight data of relative organs

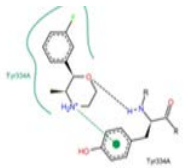
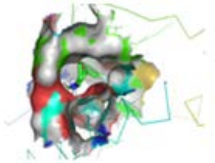
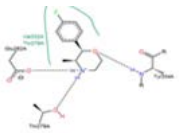
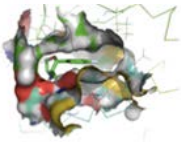
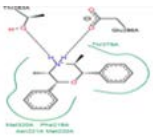
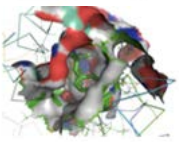
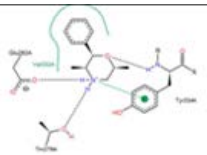
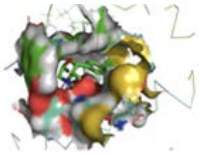
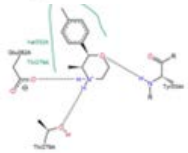
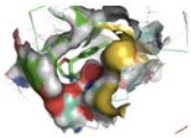
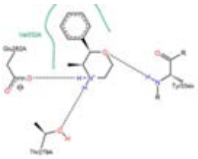
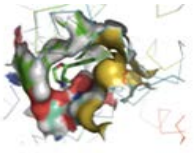
Groups	Relative liver weight	Relative adipose tissue weight	Relative spleen weight
Untreated control	2.683 ± 0.19^{a}	1.359 ± 0.64^{c}	0.208 ± 0.02^{a}
Entry **1c**	2.736 ± 0.32^{a}	0.550 ± 0.18^{a}	0.204 ± 0.02^{a}
Established drug **1f**	2.359 ± 0.17^{a}	0.913 ± 0.19^{c}	0.208 ± 0.05^{a}

Where a, c are the relation of significance between the variables. $P < 0.05$

Table 3 : Docking results of the isolated products with protein PPARα (1I7G)

Entry	Binding amino acid Residues	Binding Energy(kcal/mol)	Inhibition Constant uM	VDW_HB desolv_energy (kcal/mol)	Ligand efficiency
1a	THR`279/OG1 with 14 atoms, GLU`282/OE1 with 15 atoms, TYR`334/N with 21 atoms	-7.58	2.79	-6.04	0.54
1b	THR`279/OG1 with 14 atoms, GLU`282/OE1 with 15 atoms, TYR`334/N with 21 atoms	-6.74	11.38	-5.37	0.48
1c	THR`283/HG1 with 14 atoms, GLU`286/OE2 with 15 atoms	-8.83	335.79	-7.98	0.44
1d	THR`279/OG1 with 14 atoms, GLU`282/OE1 with 15 atoms, TYR`334/N with 21 atoms	-7.04	6.92	-5.76	0.50
1[e]	THR`279/OG1 with 14 atoms, GLU`282/OE1 with 15 atoms, TYR`334/N with 21 atoms	-7.15	5.77	-5.82	0.51
1f	THR`279/OG1 with 14 atoms, GLU`282/OE1 with 15 atoms,	-6.83	9.8	-5.5	0.53

Table 4 Binding of synthesised ligands with aminoacids with protein PPARα (1i7g**)**

Entry	**Binding with amino acids**	**Binding with PPARα (1i7g)**
1a		
1b		
1c		
1d		
1e		
1f		

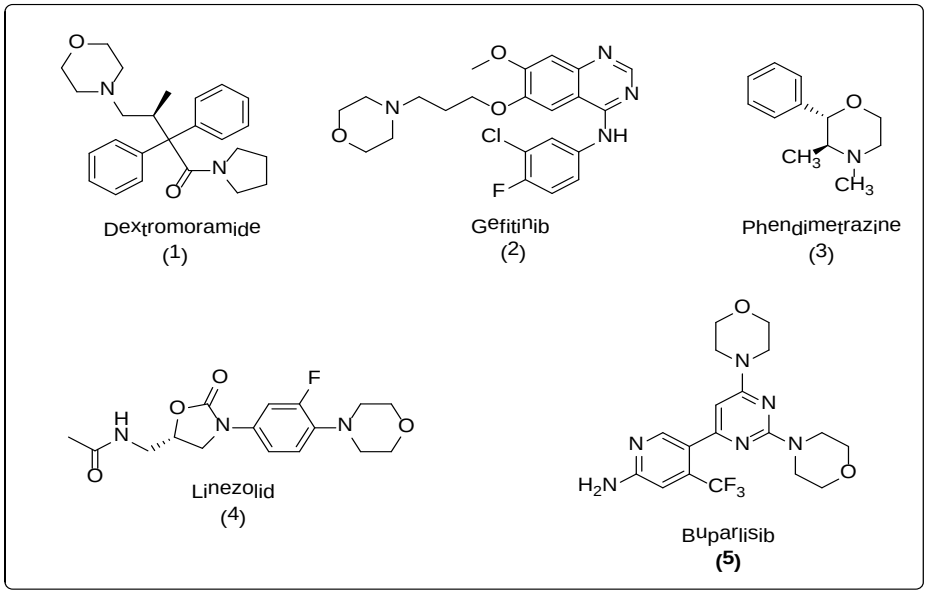


Figure 1 :**Active drugs containing morpholine ring**

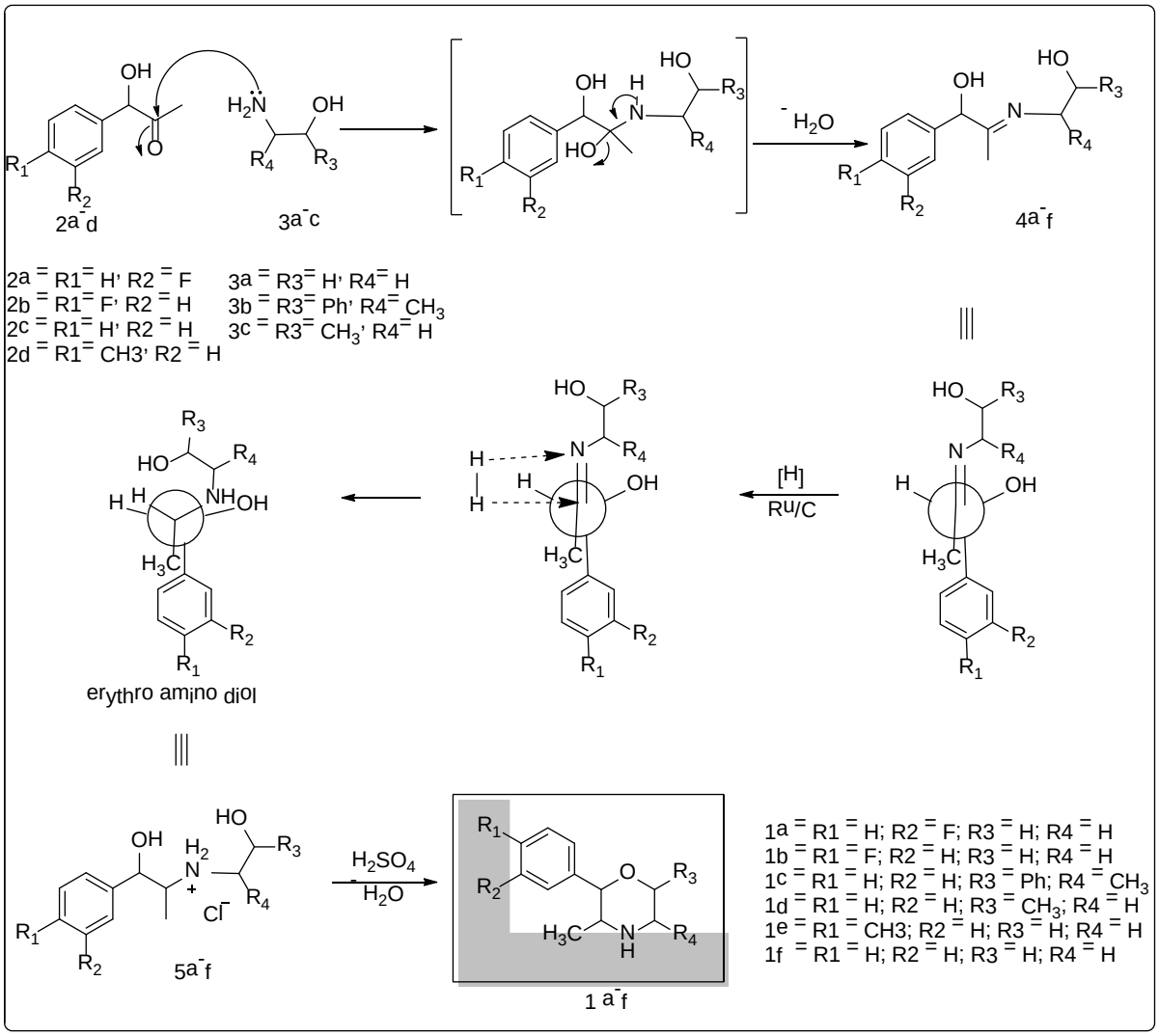


Figure 2: Scheme 1 representing plausible mechanism for the synthesis of compounds 1 a-f

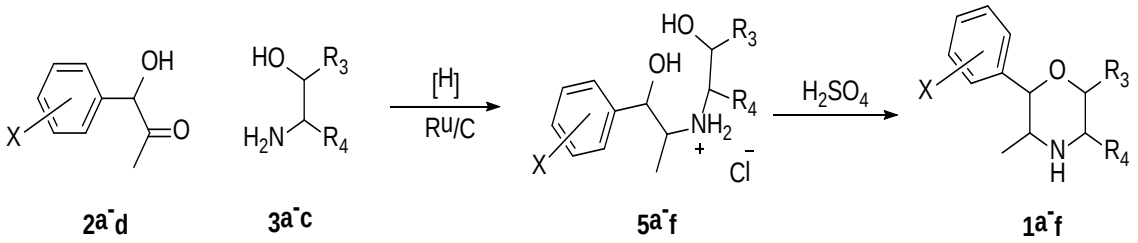


Figure 3: Scheme 2 representing synthesis of morpholine derivatives from 1-Hydroxy-1-(phenyl/substituted phenyl)-propan-2-one

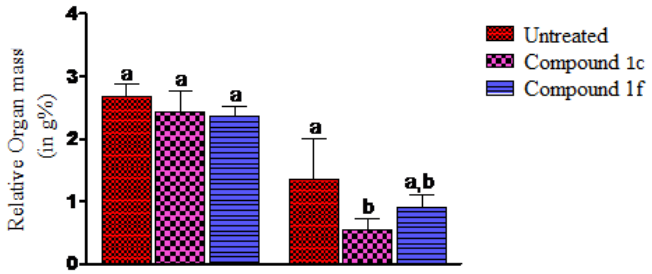


Figure 4: **Effect of 1c and 1f on relative organ weight of the HFD fed animals after four weeks of treatment at 25 mg/kg concentration (Values indicate mean ± SD for six animals; values having same alphabet in a group did not vary significantly (Tukey's HSD; $P \leq 0.05$))**

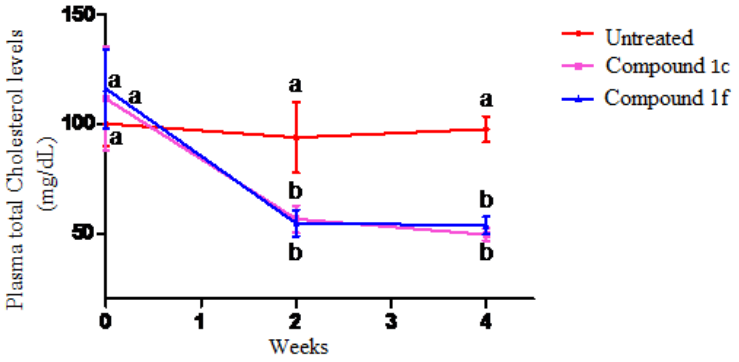


Figure 5: Effect of 1c and 1f on plasma total cholesterol levels of the HFD fed animals at 25mg/kgconcentration (Values indicate mean ± SD for six animals; values having same alphabet for a week did not vary significantly (Tukey's HSD; $P \leq 0.05$))

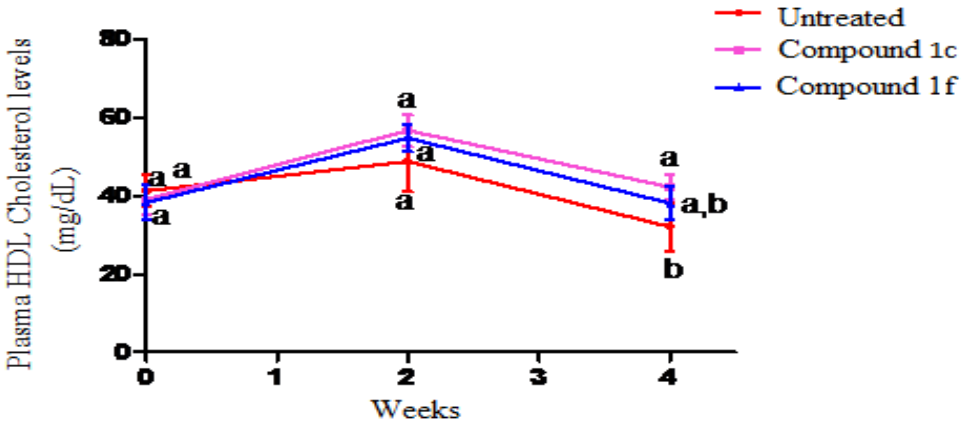


Figure 6: Effect of 1c and 1f on plasma HDL cholesterol levels of the HFD fed animals at 25 mg/kg concentration. Values indicate mean ± SD for six animals; values having same alphabet for a week did not vary significantly (Tukey's HSD; $P \leq 0.05$)

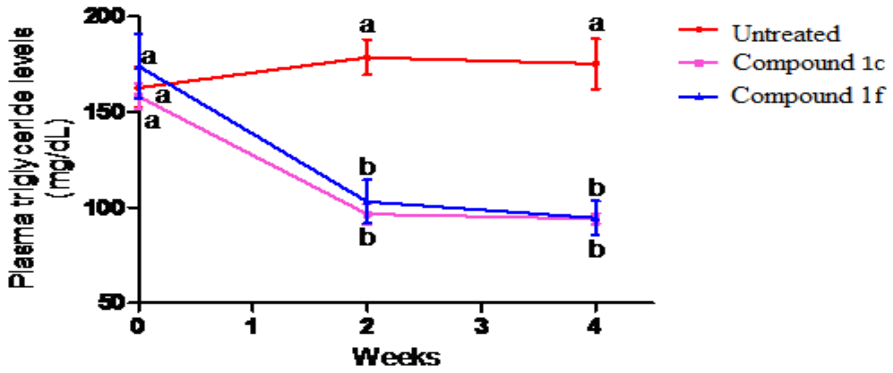
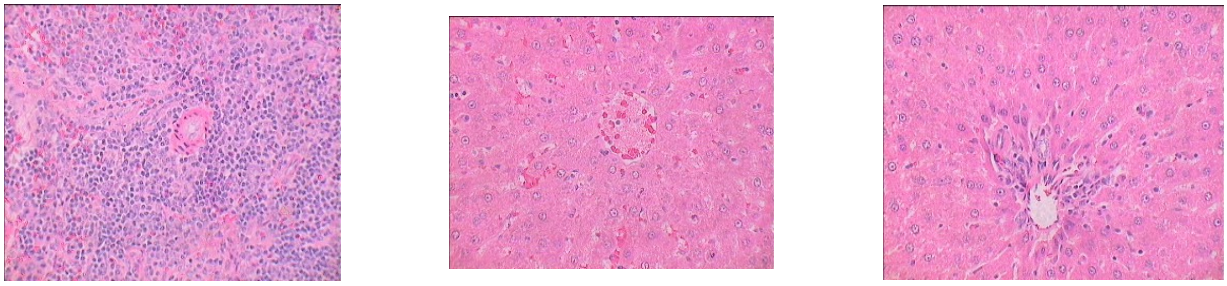
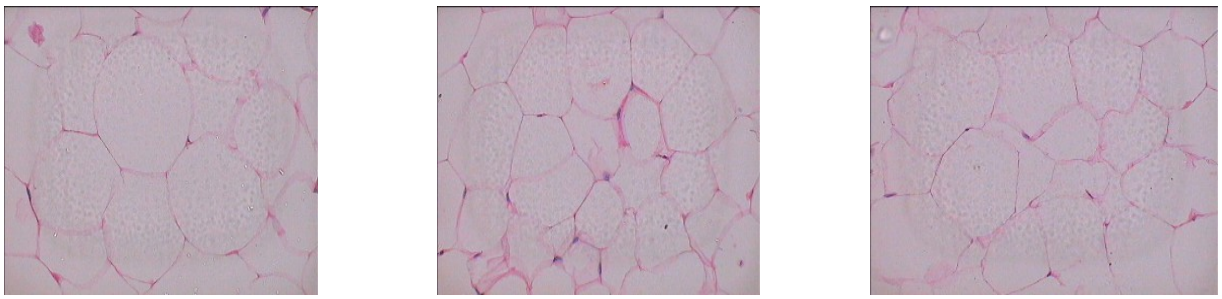


Figure 7: Effect of 1c and 1f on plasma triglyceride levels of the HFD fed animals at 25 mg/kg concentration. Values indicate mean ± SD for six animals; values having same alphabet for a week did not vary significantly (Tukey's HSD; *P* ≤ 0.05)



HFD control ***1c*** ***1f***

Figure 8: Effect of obesity drugs on the liver histology of HFD fed animals after four weeks of treatment



HFD control ***1c*** ***1f***

Figure 9: Effect of obesity drugs on the adipocyte histology of HFF fed animals after four weeks of treatment

RESULTS

Results of invivo studies:

The animals treated with Established drug and Derivative showed some reduction in the relative liver mass, but the reduction is not significant. The reduction in reteroperitoneal fat mass (RP fat mass) was significant in DE treated animals, and it was superior to that of ED**(Figure 1)**. The reduction in plasma total cholesterol and triglyceride levels were same for ED and DE and they were significantly deviate from untreated animals **(Figure 2 and 4)**, where a,b,crepresents the relative significance level between controlled, compound **1c** and established **1f** group ($P < 0.05$). The DE treated animals showed significant elevation in HDL-c levels at 30th day, when compared to the untreated animals **[39]**.From the biochemical estimation result we can see that there is not much significance difference between the activity of phenmetrazine**1f** and 3,5-dimethyl-2,6-diphenylmorpholine Hydrochloride **1c**. On the first day blood sample collection hardly any significant difference in activity was observed between the uncontrolled, established and derivative group. However, the next two results show that the there is a significant difference between uncontrolled and other two groups but these two groups does not differ in activity among themselves.

Liver samples of HFD fed animals showed excessive Mono-nuclear cell infiltration and liver damage while it was reduced in treated animals. Histopathology pictures showed that liver for HFD controlled is totally damaged due high fat deposition however fat deposition is comparatively lesser in the case of phenmetrazine**1f** and its derivative 3,5-dimethyl-2,6-diphenylmorpholine Hydrochloride**1c**.

Reteroperitoneal adipose tissue were harvested, fixed in 10% buffered formalin and stained with haematoxylin – eosin. Representative microphotographs were presented for ((A) HFD control (B) **1c** (50 mg/kg) and (C) phenmetrazine**1f** (50 mg/kg), respectively. The adipocytes of HFD fed animals were hypertrophied; the degree of hypertrophy was less in treated animalsAdipocyte histology report showed that the development of adipose tissue which is responsible for fat collection and deposition is least in case of derivative than phenmetrazine.

From the above data we can infer that relative decrease in liver weight and spleen weight in all the groups are almost same however reduction of adipose tissue weight is prominent in derivative.

Molecular Docking Studies

It is concluded from the molecular docking studies that the ligands 1 a-e showed significant binding energy ranging from - 6.74 to – 8.83, whereas phenmetrazine**1f** showed the binding energy as – 6.83 respectively. The binding of the synthesised ligands/compounds with protein PPARα (1i7g) are shown in **Table 4.**

DISCUSSION

Morpholines represents the hetrocylic class of compound which are identified to have showcased great pharmacological interest in the recent years [41]. The derivatives are being subjected to wide array of pharmacological applications and biological activities that involve anti-inflammatory [42], local anesthetic[43], analgesic[44], HIV-protease inhibitors[45], appetite suppressant[46], anticancer [47], antidepressant [48], selective inhibitor of protein kinase [49], antiplatelet [50], neuroprotective [51],antituberculosis [52] andantimalarial [53] and hypolipidemic activities [54]. It has become quite trivial for the scientific community to venture their interest in developing numerous pharmacological derivatives with potent biological activities. It is pivotal for the pharmaceutical industry in utilizing morpholine based derivatives for their active pharmacokinetic property. **Phenmetrazine is one such derivatives of morpholine that substitute** amphetamine with **morpholine** ring. This compound in particular has been commercially used as appetite suppressant and however with excessive usage/ abuse of drug results in withdrawal of the drug from the market [55]. The present study intends to find an effective approach for synthesising phenmetrazinebased derivatives via in-situ formation of Schiff's base using various substituted keto alcohols. These morpholine based compounds appeared to be synthesised organically. Despite their application remains to be quite majorly restricted within its application as simple base or otherwise as N-alkylating agent. Basically the morpholines are derived naturally from the amino acids/ alcohols, thereby with introduction with chirality appears quite often involving chiral pool approach as the compounds tend to be limited in their approach of chiral pool. Therefore in the present study involves synthesising phenmetrazine based derivatives via in-situ formation of Schiff's base using various substituted keto alcohols**[56]**.

In present day, lifestyle related disorders have raised serious concerns considerably. Obesity and related disorders are life threatening amongst the general population, on a global aspects. Adipose tissue in general, remains to serve not only for storage site of fat and also functions as an endocrine organ [**10, 11**]. Adipose tissue grows by two mechanisms: hyperplasia and hypertrophy, the latter occurring prior to hyperplasia to meet the need for additional fat storage capacity as obesity progresses. As obesity could generally be characterized as adipocyte hypertrophy which is followed by an increased level of angiogenesis, infiltration of immune cell, overproduction, and, consequently, by increased production of proinflam-matoryadipocytokines and FFAs, which are potentially involved in the pathogenesis of insulin resistance**[57] [58]**.

From the obtained result, it was found that the plasma level and liver mass reported from the test organism was decreased significantly upon administration of phenmetrazine(**1f)** and 3,5-dimethyl-2,6-diphenylmorpholine Hydrochloride (**1c)**. The observed result was found to be significantly higher compared with rats that are ingested with HFD controlled diet. This indicates that the derivatices was found to exhibit equivalent activity exhibited by phenmetrazineand its derivative. However histology report of the adipocyte was positive from the synthesized derivatives.

From the molecular docking studies as well as from in vivo study, it could be inferred that there were no differences regarding the gain in the bodyweight between the HFD control group and drugs control groups. The dietary treatment of rats with 3,5-dimethyl-2,6-diphenylmorpholine.Hydrochloride (**1c) was found to have substantially** reduced fat accumulation and caused decreased adipocytesize, which may in turn have improved lipid metabolism and attenuated compensatory hyper-insulinemia. Plasma and liver decreased significantly in rats that were given phenmetrazine**1f** and 3,5-dimethyl-2,6-diphenylmorpholine Hydrochloride **1c** than the rats with HFD controlled diet. In an agreement with in vivo results, the molecular docking results showed the least energy value with better active site binding and good ligand efficiency to the all derivatives especially for 3,5-dimethyl-2,6-diphenyl morpholine Hydrochloride 1c.Similar reports were determined from the other morpholine based derivatives which were used for determining the in vitro activity of the compounds with regards to their lipid biosynthesis **[59]** and hypolipidemic activity**[60]**.

CONCLUSION

In this proposed work we synthesised phenmetrazine and derivatives by in-situ formation of Schiff's base using various substituted keto alcohols with 1,2-amino alcohols followed by catalytic hydrogenation using ruthenium on carbon to get diols. The stereoselectivity on the isolated diols were achieved by the use of ruthenium on carbon. The diols on cyclisation by the mineral acid leads to the formation of phenmetrazine and its derivatives with remarkable yield and purity. The synthesised compounds on molecular docking studies exhibits significant binding

energy levels with better ligand efficiency with proteinPPARα (1I7G). The in-vivo study on the anti-hyperlipedemic activity of the synthesised compounds with male Wistar rats proved that the compounds isolated in this work can work as better anorectic drugs.

REFERENCES

[1] Ramachendran, J., Bradford, J., & Mclean, M. (2008). Maternal obesity and pregnancy complications: a review. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, *48*(3), 228-235

[2] Gallwitz B. *Diabetes Care 2009; 32 (Suppl. 2)*: S322 – 325.

[3] Wilson, Peter WF, et al. *Arch. Int. Med*., 2002;162(16): 1867-1872.

[4] Landsberg, Lewis, et al. *The Obesity Society and the American Society of Hypertension*." Obesity 21.1 (2013): 8-24.

[5] Calle, Eugenia E., et al. *New England Journal of Medicine* 348.17 (2003): 1625-1638.

[6] INKELES, S., & EISENBERG, D. (1981). Hyperlipidemia and coronary atherosclerosis: a review. *Medicine*, *60*(2), 110-123.

[7] Daniels, S. R., & Greer, F. R. (2008). Lipid screening and cardiovascular health in childhood. *Pediatrics*, *122*(1), 198-208.

[8] Morrell, J. S., Lofgren, I. E., Burke, J. D., & Reilly, R. A. (2012). Metabolic syndrome, obesity, and related risk factors among college men and women. *Journal of American College Health*, *60*(1), 82-89.

[9] Lichtenstein, A. H., Kennedy, E., Barrier, P., &Danford, D. (1998). Dietary fat consumption and health/discussion. *Nutrition reviews*, *56*(5), S3.

[10] Schenk S, Saberi M, Olefsky JM., *J. Clin. Invest.* 2008, 118: 2992 - 3002.

[11] Kivipelto, Miia, et al.,*Archives of neurology* 62.10 (2005): 1556-1560.

[12] Drager, Luciano F., et al. *Journal of the American College of Cardiology* 62.7 (2013): 569-576.

[13] Richard B. Rothman and Michael H. Baumann., *Am. J. Ther*. 2009; 16(4): 354 - 364.

[14] Chen, Hsin-Jen, etal.*Stroke* 37.4 (2006): 1060-1064.

[15] Curtis, Jeptha P., et al. *Archives of internal medicine* 165.1 (2005): 55-61.

[16] Hotamisligil G.S., *Nature* 2006, 444: 860 – 867.

[17] Xiaopo Zhang, Chongming Wu, Haifeng Wu, Linghui Sheng, Yan Su, Xue Zhang, Hong Luan, Guibo Sun, Xiaobo Sun, Yu Tian, YubinJi, PengGuo, and XudongXu, *Plos One*, vol. 8, no. 4, 2013.

[18] Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al. *Lancet* 376: 1670–1681.

[19] Yun, J. W. (2010). Possible anti-obesity therapeutics from nature–A review. *phytochemistry*, *71*(14-15), 1625-1641.

[20] Jensen, Michael D., et al.,*J. Am. Coll. Cardiol* (2013).

[21] Assaf, G., Cansell, G., Critcher, D., Field, S., Hayes, S., Mathew, S., &Pettman, A. (2010). Application of a process friendly morpholine synthesis to (S, S)-Reboxetine. *Tetrahedron Letters*, *51*(38), 5048-5051.

[22] Siemer Harm, Hengen Otto. 1962, *US Patent* 3,018,222.

*[23] Craddock D.*Anorectic *drugs:* use in general practice. *Drugs 1976*; *11*(38): *378 - 393*.

[24] Alan C. White, Windsor; Edwin T. Edington, Cookham. 1982; *US Patent*4,360,519.

[25] Karl zeile. 1958, *US Patent* 2835669.

[26] Tooulia, K. K., Theodosis-Nobelos, P., &Rekka, E. A. (2015). Thiomorpholine derivatives with hypolipidemic and antioxidant activity. *Archiv der Pharmazie*, *348*(9), 629-634.

[27] Ladopoulou, E. M., Matralis, A. N., Nikitakis, A., &Kourounakis, A. P. (2015). Antihyperlipidemicmorpholine derivatives with antioxidant activity: An investigation of the aromatic substitution. *Bioorganic & medicinal chemistry*, *23*(21), 7015-7023.

[28] Martel, Antonio (1957). *Can. Med., Assoc. J.* 76(2): 117-20.

[29] Hampson, J; Loraine, J.A.; Strong, J.A. (1960). *The Lancet*. **275** (7137): 1265–7.

[30] DeepaIyer and U. K. Patil (2013). *Pharm. Biol*., 2014; 52(1): 78–85.
Antony P J , Gandhi G R , Stalin A, Balakrishna K, Toppo E, Sivasankaran K , Essakiimuthu S, Al-Dhabi N A,*BiomedPharmacother*. 88 (2017) 1098-1113.

[31] Kothari S, Jain AK, Mehta SC, Tonpay SD., *ActaPoloniae Pharmaceutical Drug Research* 2011; 68(2):291-294.

[32] Mahmoud Najafian, AzadehEbrahim-Habibi, ParichehrehYaghmaei, KazemParivar, BagherLarijani.,*Iranian journal of Diabetics and lipid disorders;* 2011, Vol. 10: 1.

[33] Saravanan M, Pandikumar P, Prakash Babu N, Ignacimuthu S., *Pharm. Bio. 2011;* 49(10): 1074 – 1081.

[34] Mukesh S. Sikarwar and M. B. Patil., *Indian J. Pharmacol. 2012;* 44(1):88-92.

[35] Faust I. M, Johnson P. R, Stern J. S, Hirsh J., *Am. J. Physiol. 1978*, 235: 279 – 286

[36] Ahmed I, Lakhani MS, Gillet M, et al. (2001).,*Diabetes Res. Clin. Pract*. 51:155–161.

[37] RohitGundamaraju, Kim KahHwi, Rajeev K. Singla,[1] Ravi Chandra Vemuri, and SartajBanuMulapalli., *Pharmacognosy Res. 2014* Oct-Dec; 6(4): 267 - 273.

[38] Soniya S and Deepa R., *Molecules. 2011*, 16: 8292-8304.

[39] Ganesh Kumar, Veeramachaneni, Kranthi Raj K., Bondili J S, Venkateswara Rao., *Advances in Biological Research.2016;* 10 (1): 33-36.

[40] Toppo E, Darvin S, Esakkimuthu S, Stalin A, Balakrishna K, Sivasankaran K, Pandikumar P, Essakimuthu S, Al-Dhabi N A.,*ChemBiol Interact*. 269 (2017) 9-17.

[41] Pal'chikov, V. A. (2013). Morpholines. Synthesis and biological activity. *Russian Journal of Organic Chemistry*, *49*(6), 787-814.

[42] Rana, K. A. V. I. T. A., Pandurangan, A. N. N. A. M. A. L. A. I., Singh, N. A. M. R. A. T. A., & Tiwari, A. K. (2012). A systemic review of schiff bases as an analgesic, anti-inflammatory. *Int. J. Curr. Pharm. Res*, *4*(2), 5-11.

[43] Fleck, C., Karge, E., Loy, S., Wennek-Klose, J., Listing, M., &Oelschläger, H. (2003). Local Anaesthetic Effects and Toxicity of Seven New Diethanolamine and Morpholine Derivatives of Fomocaine. *Arzneimittelforschung*, *53*(03), 221-228.

[44] Rana, K. A. V. I. T. A., Pandurangan, A. N. N. A. M. A. L. A. I., Singh, N. A. M. R. A. T. A., & Tiwari, A. K. (2012). A systemic review of schiff bases as an analgesic, anti-inflammatory. *Int. J. Curr. Pharm. Res*, *4*(2), 5-11.

[45] Hadjipetrou-Kourounakis, L., Karagounis, E., Rekka, E., &Kourounakis, P. (1989). Immunosuppression by a Novel Analgesic-Opioid Agonist. *Scandinavian journal of immunology*, *29*(4), 449-458.

[46] Balani, S. K., Ramjit, H. G., Pitzenberger, S. M., Schwartz, M. S., & Lu, A. Y. (1993). *U.S. Patent No. 5,188,950*. Washington, DC: U.S. Patent and Trademark Office.

[47] Viswanadh, N., Mujumdar, P., Sasikumar, M., Kunte, S. S., &Muthukrishnan, M. (2016). An alternate synthesis of appetite suppressant (R)-2-benzylmorpholine employing Sharpless asymmetric epoxidation strategy. *Tetrahedron Letters*, *57*(8), 861-863.

[48] Geroni, M. C., Ripamonti, M., Caruso, M., &Suarato, A. (2003). *U.S. Patent No. 6,586,428*. Washington, DC: U.S. Patent and Trademark Office.

[49] Harada, M., &Maeno, H. (1979). Biochemical characteristics of a potential antidepressant, 2-(7-indenyloxymethyl) morpholine hydrochloride (YM-08054-1). *Biochemical pharmacology*, *28*(17), 2645-2651.

[50] Zask, A., Kaplan, J., Verheijen, J. C., Richard, D. J., Curran, K., Brooijmans, N., ...& Yu, K. (2009). Morpholine derivatives greatly enhance the selectivity of mammalian target of rapamycin (mTOR) inhibitors. *Journal of medicinal chemistry*, *52*(24), 7942-7945.

[51] Barker, P. L., Bullens, S., Bunting, S., Burdick, D. J., Chan, K. S., Deisher, T., ...&Gantzos, R. (1992). Cyclic RGD peptide analogs as antiplatelet antithrombotics. *Journal of medicinal chemistry*, *35*(11), 2040-2048.

[52] Sameem, B., Saeedi, M., Mahdavi, M., Nadri, H., Moghadam, F. H., Edraki, N., ...&Amini, M. (2017). Synthesis, docking study and neuroprotective effects of some novel pyrano [3, 2-c] chromenederivatives bearing morpholine/phenylpiperazine moiety. *Bioorganic & medicinal chemistry*, *25*(15), 3980-3988.

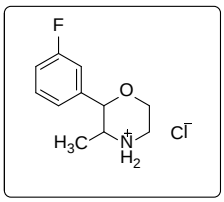
[53] Karalı, N., Gürsoy, A., Kandemirli, F., Shvets, N., Kaynak, F. B., Özbey, S., ...&Dimoglo, A. (2007). Synthesis and structure–antituberculosis activity relationship of 1H-indole-2, 3-dione derivatives. *Bioorganic & medicinal chemistry*, *15*(17), 5888-5904.

[54] Kumar, A., Srivastava, K., Kumar, S. R., Puri, S. K., & Chauhan, P. M. (2009). Synthesis of 9-anilinoacridine triazines as new class of hybrid antimalarial agents. *Bioorganic & medicinal chemistry letters*, *19*(24), 6996-6999.

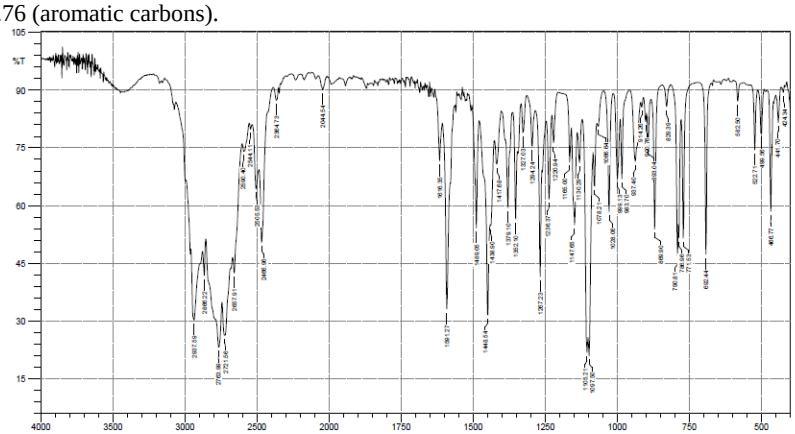
[55] Tooulia, K. K., Theodosis-Nobelos, P., &Rekka, E. A. (2015). Thiomorpholine derivatives with hypolipidemic and antioxidant activity. *Archiv der Pharmazie*, *348*(9), 629-634.
[56] Martin, W. R., Sloan, J. W., Sapira, J. D., &Jasinski, D. R. (1971). Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clinical Pharmacology & Therapeutics*, *12*(2part1), 245-258.
[57] Wijtmans, R., Vink, M. K., Schoemaker, H. E., van Delft, F. L., Blaauw, R. H., &Rutjes, F. P. (2004). Biological relevance and synthesis of C-substituted morpholine derivatives. *Synthesis*, *2004*(05), 641-662.
[58] Gard, M., & Wright, J. (2005). *The obesity epidemic: Science, morality and ideology*. Routledge.
[59] Tavridou, A., Kaklamanis, L., Megaritis, G., Kourounakis, A. P., Papalois, A., Roukounas, D., ...&Manolopoulos, V. G. (2006). Pharmacological characterization in vitro of EP2306 and EP2302, potent inhibitors of squalene synthase and lipid biosynthesis. *European journal of pharmacology*, *535*(1-3), 34-42.
[60] Chrysselis, M. C., Rekka, E. A., &Kourounakis, P. N. (2000). Hypocholesterolemic and hypolipidemic activity of some novel morpholine derivatives with antioxidant activity. *Journal of medicinal chemistry*, *43*(4), 609-612

Supplementary Material-IR, NMR and Mass SPECTRUM

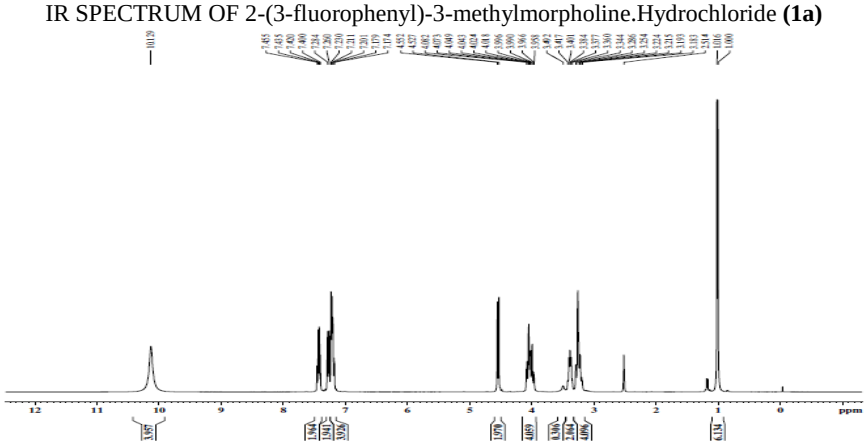
Structural Elucidation of 2-(3-fluorophenyl)-3-methylmorpholine.Hydrochloride (1a)



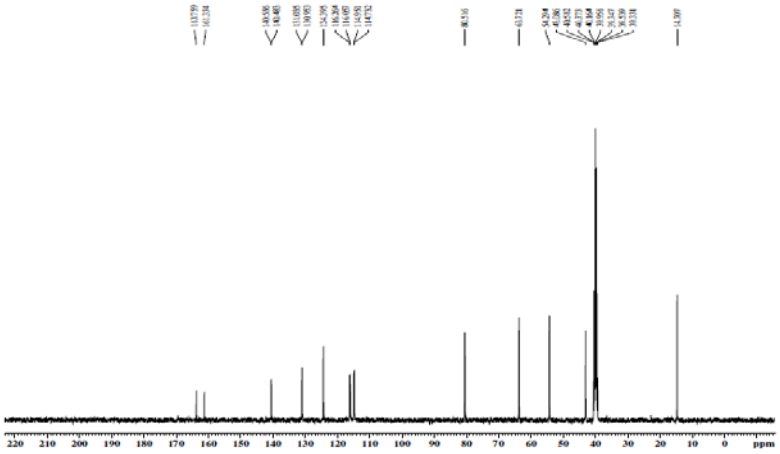
White crystalline solid; Melting Range: 228 °C – 229 °C; IR(cm^{-1}) (KBr): C-H (arom) str. At 2938, C-H (alipha.) str. at 2866, $^{+}$N-H_2str. at 2764, benzenoid bands at 1591 and 1449, C-N str. at 1385, at 1105, C-H out of plane bending of mono substituted phenyl ring at 870,791 and 692. ^{1}H-NMR (DMSO-d6, 400 MHz) (δH): 1.00-1.02 (3H, d, CH-$\underline{CH_3}$), 3.18-3.29 (2H, m,-N-$\underline{CH_2}$-CH_2), 3.34-3.42 (2H, m, -O-$\underline{CH_2}$-CH_2), 3.96-4.08(1H, m, -H2N-CH-CH3), 4.53- 4.55 (1H, d, O-CH), 7.17-7.45 (4H,m, H arom.). 10.13 (2H, s, +N-H2); ^{13}C- NMR (DMSO-d6, 100 MHz) (δC): 14.71 (CH-$\underline{C}H_3$), 43.09 (-N-$\underline{C}H_2$-CH_2), 54.29 (N-$\underline{C}$H-CH), 63.72 (-O-$\underline{C}H_2$-CH_2), 80.52 (O-$\underline{C}$H-CH), 114.73-163.76 (aromatic carbons).



IR SPECTRUM OF 2-(3-fluorophenyl)-3-methylmorpholine.Hydrochloride **(1a)**

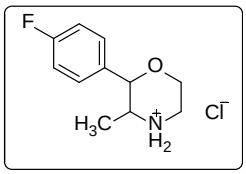


^{1}H NMR SPECTRUM OF 2-(3-fluorophenyl)-3-methylmorpholine.Hydrochloride (**1a)**

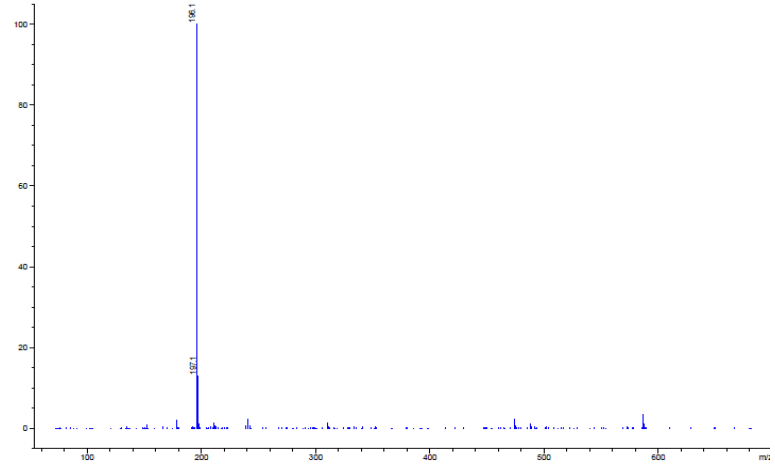


^{13}C NMR SPECTRUM OF2-(3-fluorophenyl)-3-methylmorpholine.Hydrochloride (**1a**)

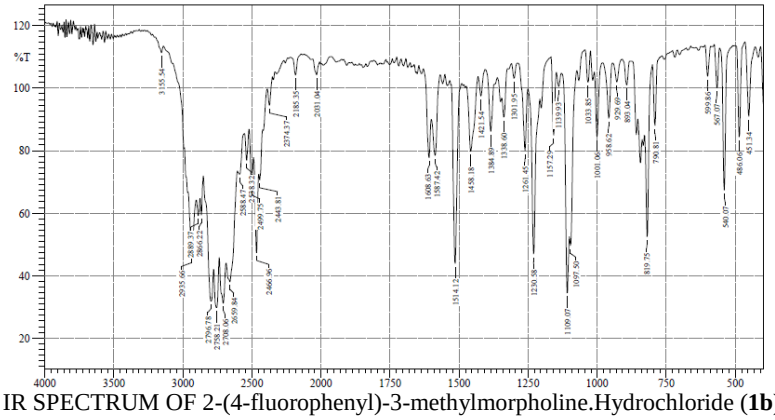
Structural Elucidation of 2-(4-fluorophenyl)-3-methylmorpholine.Hydrochloride (1b)



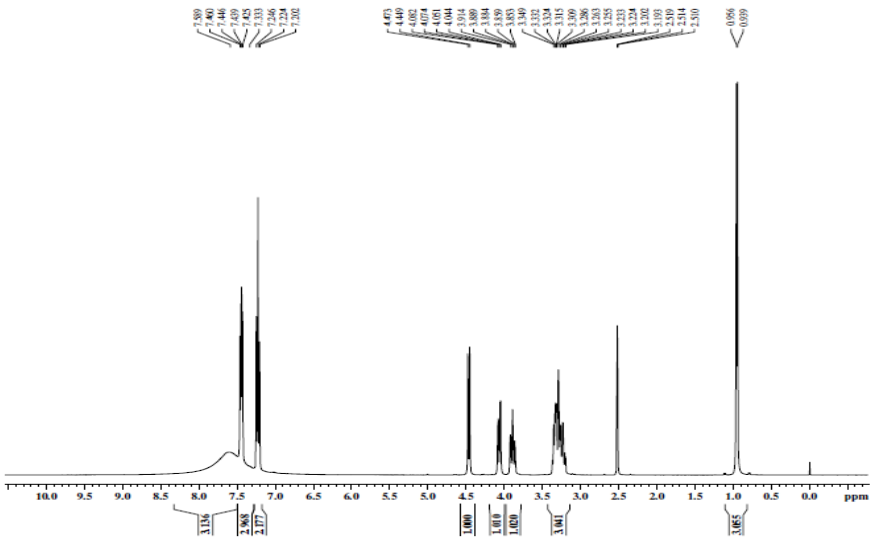
White crystalline solid; Melting Range: 175 °C - 176 °C; IR(cm^{-1}) (KBr): C-H (arom) str. At 2936, C-H (alipha.) str. at 2866, $^{+}$N-H$_2$str. at 2758, benzenoid bands at 1609 and 1458, C-N str. at 1385, C-O str. at 1109, C-H out of plane bending of mono substituted phenyl ring at 820. ^{1}H-NMR (DMSO-d6, 400 MHz) (δH): 0.94-0.96 (3H, d, CH-C<u>H</u>$_3$), 3.19-3.29 (2H, m,-N-C<u>H</u>$_2$-CH$_2$), 3.31-3.91 (2H, m, -O-C<u>H</u>$_2$-CH$_2$), 4.04-4.08(1H, m, -H2N-C<u>H</u>-CH$_3$), 4.45- 4.47 (1H, d, O-C<u>H</u>), 7.20-7.46 (4H,m, H arom.), 7.59 (2H, s, $^{+}$N-H$_2$); ^{13}C- NMR (DMSO-d6, 100 MHz) (δC) : 14.86 (CH-<u>C</u>H$_3$), 43.35 (-N-<u>C</u>H$_2$-CH$_2$), 54.49 (N-<u>C</u>H-CH), 64.06 (-O-<u>C</u>H$_2$-CH$_2$), 80.72 (O-<u>C</u>H-CH), 115.73-165.56 (aromatic carbons). ESI-MS: m/z 196 (M+H, 100%); Elemental analysis for C$_{11}$H$_{14}$FNO.HCl, calculated: C, 57.14; H, 6.57 and N, 6.02. Found: C, 57.02; H, 6.53 and N, 6.05.



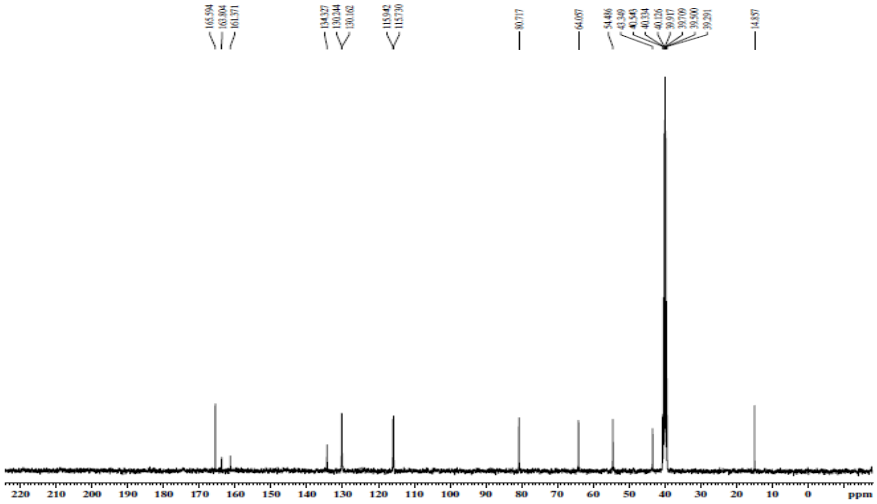
MASS SPECTRUM OF 2-(4-fluorophenyl)-3-methylmorpholine.Hydrochloride (**1b**)



IR SPECTRUM OF 2-(4-fluorophenyl)-3-methylmorpholine.Hydrochloride (**1b**)

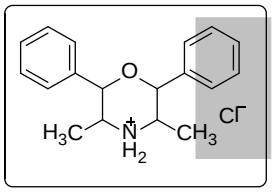


NMR SPECTRUM OF 2-(4-fluorophenyl)-3-methylmorpholine.Hydrochloride (**1b**)

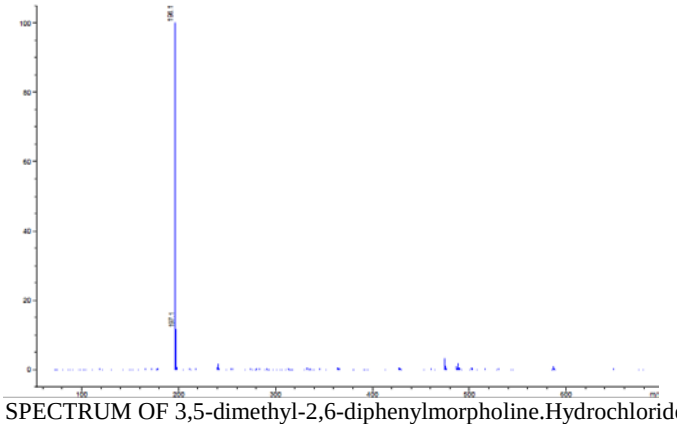


^{13}C SPECTRUM OF 2-(4-fluorophenyl)-3-methylmorpholine.Hydrochloride (**1b**)

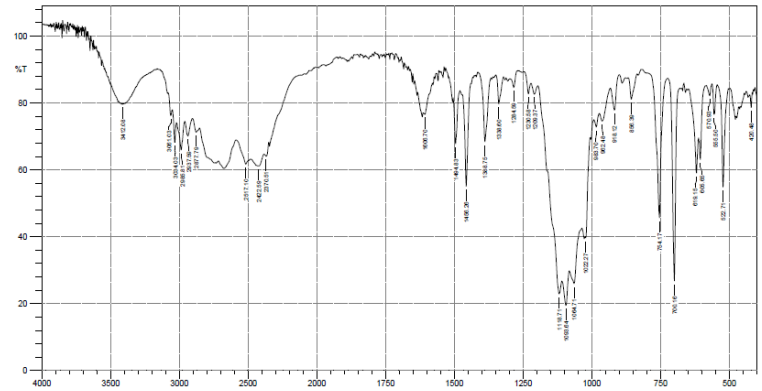
Structure elucidation of 3,5-dimethyl-2,6-diphenylmorpholine.Hydrochloride (1c)



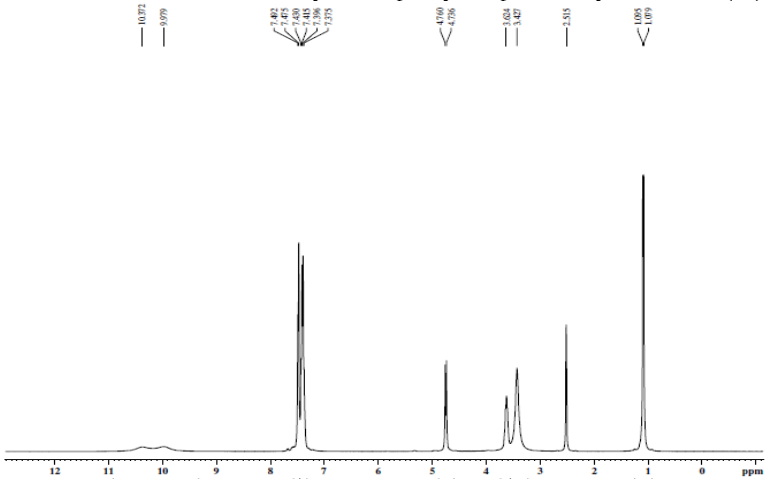
White crystalline solid; Melting Range: 248 °C - 250 °C; IR(cm^{-1}) (KBr): C-H (arom) str. At 3032, C-H (alipha.) str. at 2868, +N-H str. at 2623, benzenoid bands at 1495 and 1454, C-N str. at 1381, C-O str. at 1090, C-H out of plane bending of mono substitutedphenyl ring at 756 and 700. ^{1}H-NMR (DMSO-d6, 400 MHz) (δH) : 1.08-1.09 (6H, d, CH-C<u>H</u>$_3$), 3.62(2H, m, -N-C<u>H</u>-CH$_3$), 4.74- 4.76 (2H, d, O-C<u>H</u>), 7.37-7.49 (10H,m, H arom.), 9.98 (1H, s, N-H), 10.37 (1H, s, $^{+}$N-H); ^{13}C- NMR (DMSO-d6, 100 MHz) (δC): 14.50 (CH-<u>C</u>H$_3$), 54.98 (N-<u>C</u>H-CH$_3$), 81.14 (O-<u>C</u>H-CH$_3$), 128.13-137.62 (aromaticcarbons). ESI-MS: m/z 268 (M+H, 100%); Elementalanalysis for $C_{18}H_{21}NO.HCl$, calculated: C, 71.22; H, 7.28 and N, 4.57. Found: C, 71.16; H, 7.30 and N, 4.61.



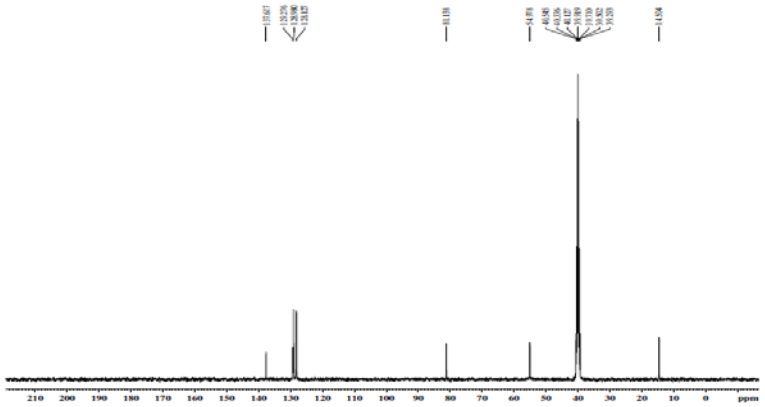
MASS SPECTRUM OF 3,5-dimethyl-2,6-diphenylmorpholine.Hydrochloride (**1c**)



IR SPECTRUM OF 3,5-dimethyl-2,6-diphenylmorpholine.Hydrochloride (**1c**)

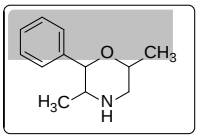


^{1}H NMR SPECTRUM OF 3,5-dimethyl-2,6-diphenylmorpholine.Hydrochloride (**1c**)

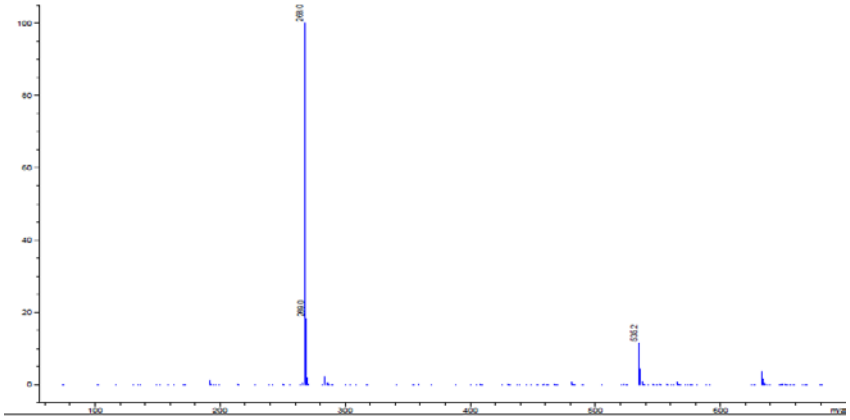


C^{13} NMR SPECTRUM OF 3,5-dimethyl-2,6-diphenylmorpholine.Hydrochloride (**1c**)

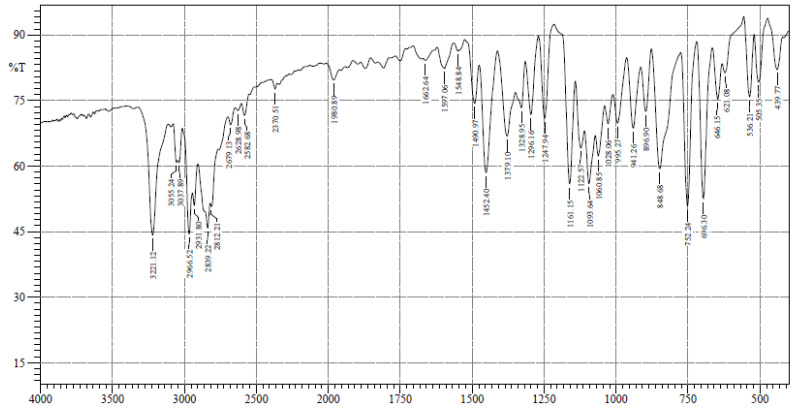
Structure elucidation of 3,6-dimethyl-2-phenylmorpholine (1d)



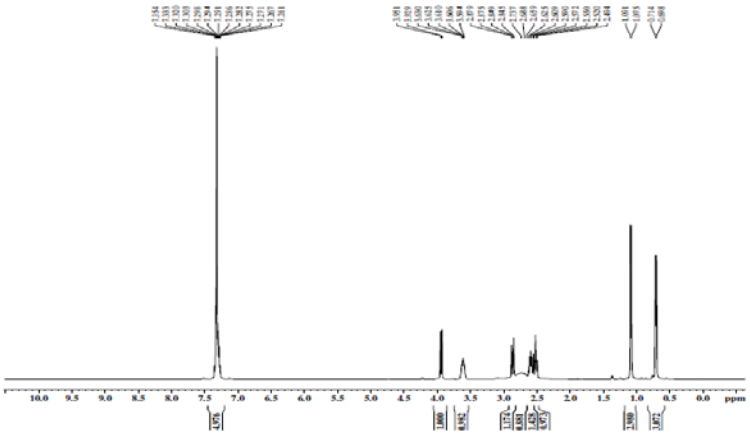
White crystalline solid, Melting Range: 58 °C - 59 °C IR(cm^{-1}) (KBr): C-H (arom) str. at 3221, C-H (alipha.) str. at 2966, benzenoid bands at 1597 and 1452, C-N str. at 1379,C-O str. at 1161, C-H out of plane bending of mono substituted phenyl ring at 752 and 696. ^{1}H-NMR (DMSO-d6, 400 MHz) (δH) : 0.70-0.71 (3H, d,O- CH-$\underline{CH_3}$), 2.49-2.62 (2H, m,-N-$\underline{CH_2}$-CH_2), 2.69 (1H, b s, N-$\underline{H}$), 2.84-2.88 (1H, m,-N-$\underline{CH}$-CH_3), 3.59-3.63 (1H, t, -O-C$\underline{H}$-CH_3), 3.93- 3.95 (1H, d, O-C$\underline{H}$), 7.17-7.45 (4H,m, H arom.), ^{13}C- NMR (DMSO-d6, 100 MHz) (δC): 18.01 (N-CH-$\underline{C}H_3$), 19.39 (O-CH-$\underline{C}H_3$); 53.04 (-N-$\underline{C}H_2$-CH), 55.72 (N-$\underline{C}$H-CH), 72.84 (-O-$\underline{C}H_2$-CH-CH_3), 85.85 (O-$\underline{C}$H-CH), 127.95-141.01 (aromatic carbons). ESI-MS: m/z 192 (M+H, 100%); Elemental analysis for $C_{12}H_{17}NO$, calculated: C, 73.47; H, 8.92 and N, 7.30 Found: C, 75.35; H, 8.96 and N, 7.32



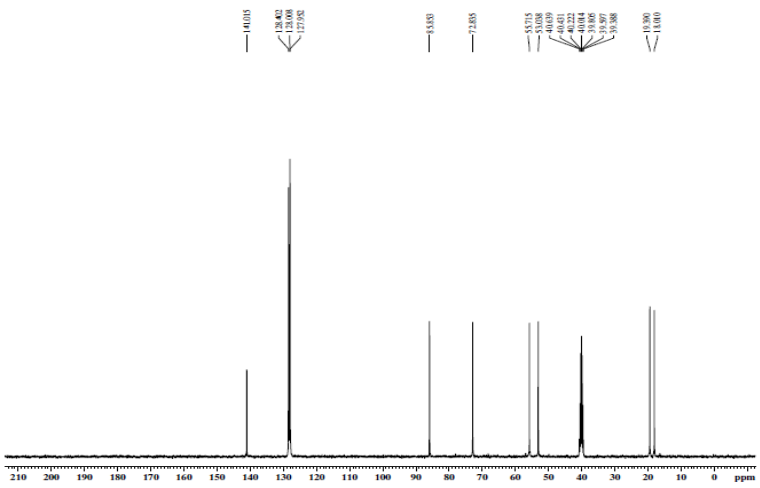
MASS SPECTRUM OF 3,6-dimethyl-2-phenylmorpholine (**1d**)



IR SPECTRUM OF 3,6-dimethyl-2-phenylmorpholine (**1d**)

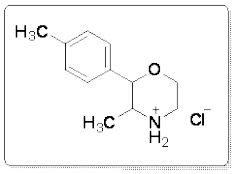


^{1}H NMR SPECTRUM OF 3,6-dimethyl-2-phenylmorpholine (**1d**)

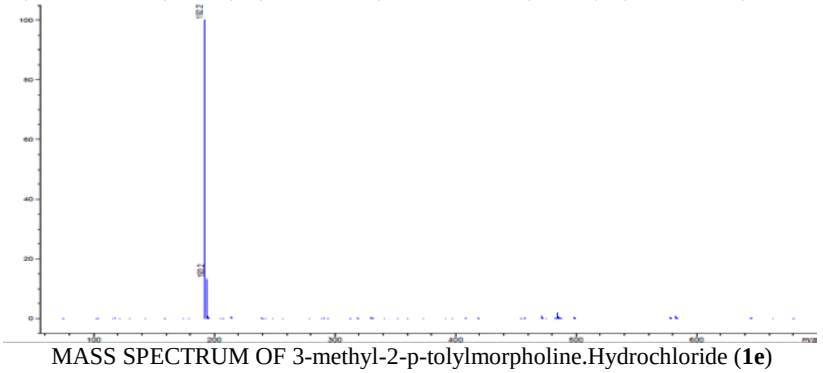


^{13}C SPECTRUM OF 3,6-dimethyl-2-phenylmorpholine (**1d**)

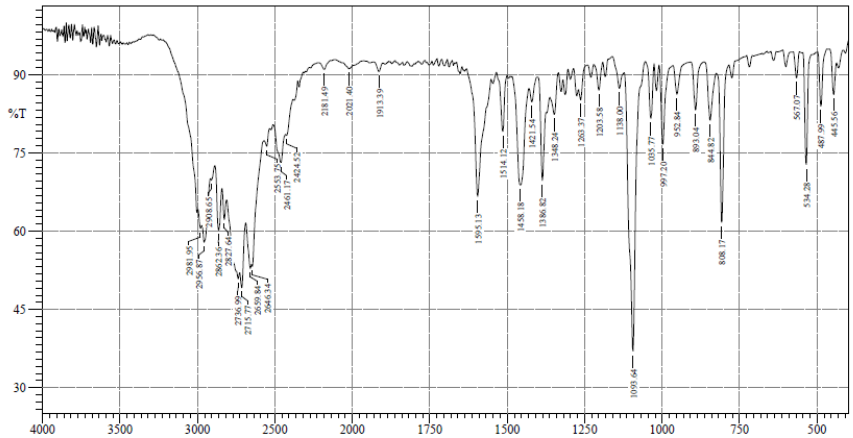
Structure elucidation of 3-methyl-2-p-tolylmorpholine.Hydrochloride (1e)



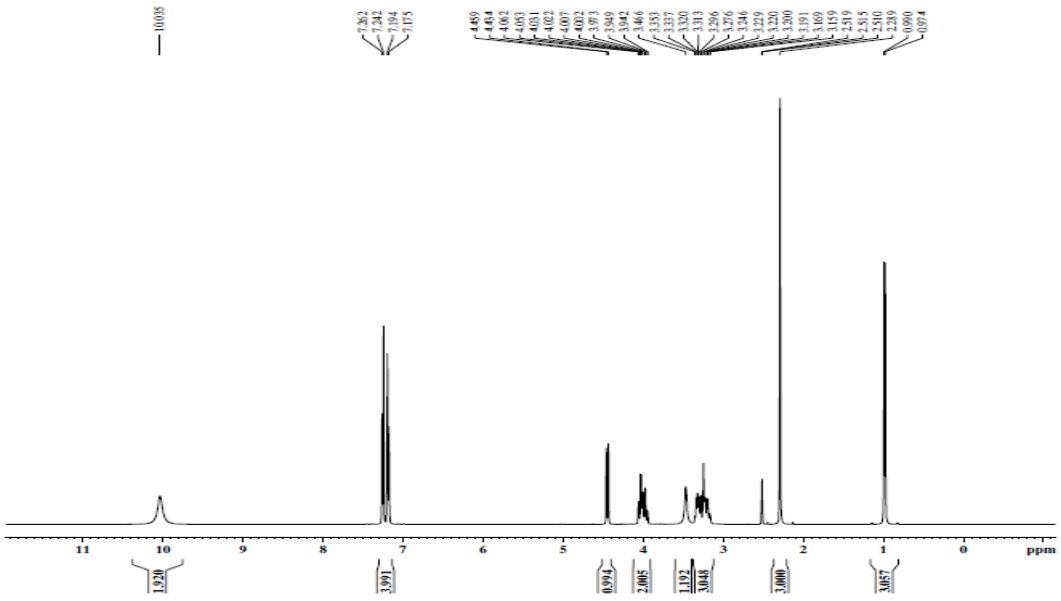
White crystalline solid; Melting Range: 225 °C - 226 °C; IR(cm^{-1}) (KBr): C-H (arom) str. At 2982, C-H (alipha.) str. at 2862, $^{+}$N-H_2str. at 2716, benzenoid bands at 1593 and 1458, C-N str. at 1387, C-O str. at 1094, C-H out of plane bending of mono substituted phenyl ring at 808. ^{1}H-NMR (DMSO-d6, 400 MHz) (δH) : 0.97-0.99 (3H, d, CH-C<u>H</u>$_3$), 2.4 (3H, s, C-C<u>H</u>$_3$), 3.16-3.35 (2H, m,-N-C<u>H</u>$_2$-CH$_2$), 3.47 (1H, m, -H$_2$N-C<u>H</u>-CH$_3$) 3.94-4.43 (2H, m, -O-C<u>H</u>$_2$-CH$_2$), 4.43- 4.45 (1H, d, O-C<u>H</u>), 7.17-7.26 (4H,m, H arom.), 10.03 (2H, s, $^{+}$N-H$_2$); ^{13}C- NMR (DMSO-d6, 100 MHz) (δC) : 14.85 (CH-C<u>H</u>$_3$), 21.24 (C-CH$_3$) 43.18 (-N-C<u>H</u>$_2$-CH$_2$), 54.58 (N-C<u>H</u>-CH), 63.71 (-O-C<u>H</u>$_2$-CH$_2$), 81.14 (O-C<u>H</u>-CH), 127.8 - 138.55 (aromatic carbons). ESI-MS: m/z 192 (M+H, 100%); Elemental analysis for $C_{12}H_{17}NO.HCl$, calculated: C, 63.35; H, 8.00 and N, 6.17 Found: C, 63.29; H, 7.97 and N, 6.15.



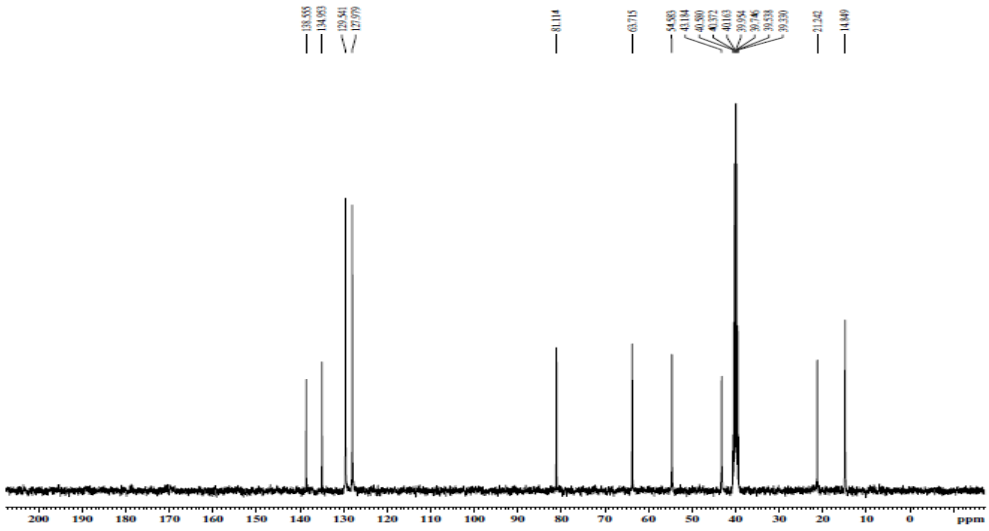
MASS SPECTRUM OF 3-methyl-2-p-tolylmorpholine.Hydrochloride (**1e**)



IR SPECTRUM OF 3-methyl-2-p-tolylmorpholine.Hydrochloride (**1e**)

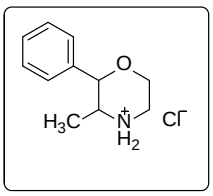


^{1}H NMR SPECTRUM OF 3-methyl-2-p-tolylmorpholine.Hydrochloride (**1e**)

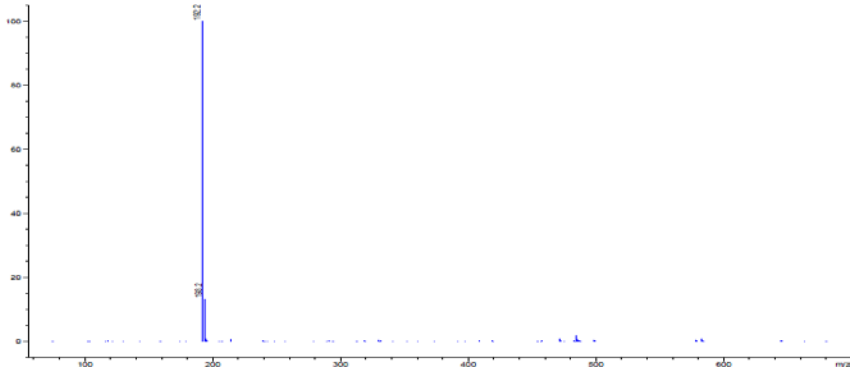


^{13}C SPECTRUM OF 3-methyl-2-p-tolylmorpholine.Hydrochloride (**1e**)

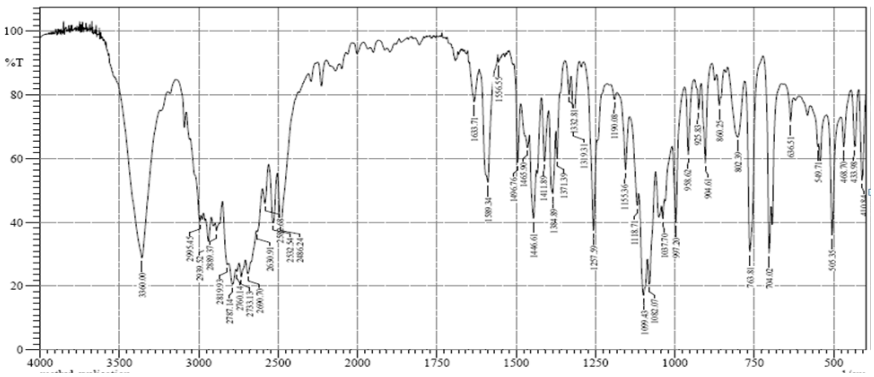
Structure elucidation of 3-methyl-2-PhenylmorpholineHydrochloride (1f)



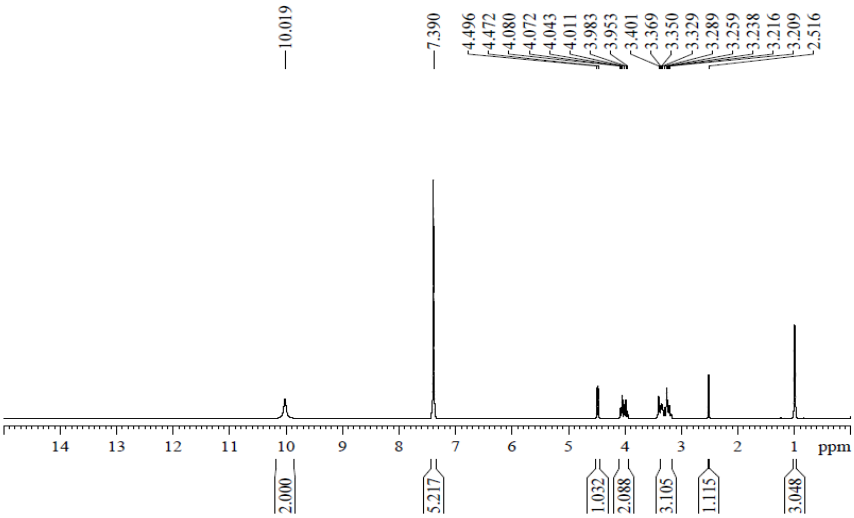
White crystalline solid; Melting Range: 182 °C - 183 °C; IR(cm^{-1}) (KBr):.C-H (arom) str. At 3360, C-H (alipha.) str. at 2787, $^{+}$N-H str. at 2582 and 2533, benzenoid bands at 1634 and 1589, C-N str. at 1385, C-O str. at 1258, C-H out of plane bending of mono substitutedphenyl ring at 764 and 704. ^{1}H-NMR (DMSO-d6, 400 MHz) (δH) : 0.98 (3H, d, CH-$\underline{CH_3}$), 2.52 (1H, d,-N-$\underline{CH}$-CH_2), 3.21-3.37 (2H, d of d, -N-$\underline{CH_2}$-CH_2), 3.98-4.08(2H, d of d, -O-C$\underline{H_2}$-CH_3), 4.47- 4.49 (1H, d, O-C$\underline{H}$-$\underline{CH}$), 7.39 (5H,m, H arom.), 10.02 (1H, s, $^{+}$N-H_2); ^{13}C- NMR (DMSO-d6, 100 MHz) (δC) : 14.84 (CH-$\underline{C}H_3$), 43.18 (-N-$\underline{C}$H-CH_2), 54.55 (-O-$\underline{C}H_2$-CH_2), 63.75 (N-$\underline{C}$H-CH),81.33(-O-$\underline{C}$H-CH_3), 128.09-137.86 (aromatic carbons). ESI-MS: m/z 178 (M+H, 100%); Elemental analysis for $C_{11}H_{15}NO.HCl$, calculated: C, 61.87; H, 7.58 and N, 6.52. Found: C, 61.82; H, 7.55 and N, 6.55.



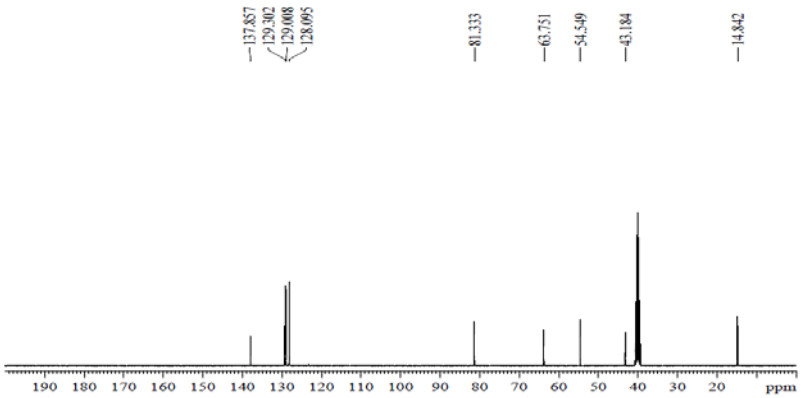
MASS SPECTRUM OF 3-methyl-2-PhenylmorpholineHydrochloride (**1f**)



IR SPECTRUM OF 3-methyl-2-PhenylmorpholineHydrochloride (**1f**)



^{1}H NMR SPECTRUM OF 3-methyl-2-PhenylmorpholineHydrochloride (**1f**)



^{13}C SPECTRUM OF 3-methyl-2-PhenylmorpholineHydrochloride (**1f**)