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SYNTHESIS AND ANALGESIC ACTIVITY OF 4-(2H-PYRIDO-(1,4) OXAZIN-4(3H)-YL SULFONYL) ANILINO-HYDROXYL AMINE

P. R. Logeshkumar[1]*, D. Bhargavi[2], M. Gayathri[2], M. Haritha[2], M. Manasa[2], K. Poornima[2] and P. Ramalakshmi[2]

[1]Professor & HOD, Department of Pharmaceutical Chemistry, Sri Krishna Chaithanya College of Pharmacy, Nimmanapalli Road, Madanapalle, Chittoor (Dt), Andhra Pradesh-517325, India.

[2]B. Pharmacy, Sri Krishna Chaithanya College of Pharmacy, Nimmanapalli Road, Madanapalle, Chittoor (Dt), Andhra Pradesh-517325, India.

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***Corresponding Author**
P. R. Logeshkumar
Professor & HOD,
Department of Pharmaceutical Chemistry,
Sri Krishna Chaithanya College of Pharmacy,
Nimmanapalli Road,
Madanapalle, Chittoor (Dt),
Andhra Pradesh-517325,
India.

ABSTRACT

Morpholine is an organic chemical compound. The heterocyclic features consists of both amine and ether functional groups. Because of the amine function group morpholine acts as a base. Morpholine is a back bone is essential in different pharmacologically active synthetic compounds. Present work summarizes the synthesis of morpholine nucleus and its derivatives. The morpholine and its compounds where synthesized in multistep reaction with more efficient process. Starting compound is available commercially. Starting compound used in this reaction is 2-aminopyridin-3-ol. Morpholine nucleus shows a broad spectrum of pharmaceuticals applications. The chemical structures of the synthesized were confirmed by means of NMR, UV and MASS spectral data. High yield and purity of the derivatives indicates lack of side reaction. In recent years various new method were developed for the synthesis of morpholine analogues. The synthesized compounds and its derivatives were then examined for antibacterial, antifungal and analgesic activities.

KEYWORDS: Morpholine, Synthesis, Pharmaceutical applications, Antibacterial, Analgesic, Antifungal activity.

INTRODUCTION

Morpholine is an organic chemical compound having the chemical formula $O(CH_2CH_2)_2NH$. This heterocycle features both amine and ether functional groups. Because of the amine, morpholine is a base; its conjugate acid is called morpholinium. For example, treating morpholine with hydrochloric acid makes the salt morpholinium chloride. The naming of morpholine is attributed to Ludwig Knorr, who incorrectly believed it to be part of the structure of morphine.

Morpholines is an open source framework that reduces the time and efforts necessary to build and change Hadoop ETL stream processing applications that extract, transform and load data into Apache Solar, HBase, HDFS, Enterprise Data Warehouses, or Analytic Online Dashboards. Want to build or facilitate ETL jobs without programming and without substantial MapReduce effort. Get the job done with a minimum amount of fuss and support costs. Here is how to get started.

A morpholine is a rich configuration file that makes it easy to define a transformation chain that consumes any kind of data from any kind of data source, processes the data and loads the results into a Hadoop component. It replaces Java programming with simple configuration steps, and correspondingly reduces the cost and integration effort associated with developing and maintaining custom ETL projects.

Morphlines is a library, embeddable in any Java codebase. A morpholine is an in-memory container of transformation commands. Commands are plugins to a morpholine that perform tasks such as loading, parsing, transforming, or otherwise processing a single record. A record is an in-memory data structure of name-value pairs with optional blob attachments or POJO attachments. The framework is extensible and integrates existing functionality and third party systems in a straightforward manner.

The morpholine commands were developed as part of Cloudera Search. Morphlines power ETL data flows from Flume and MapReduce and HBase and Spark into Apache Solr. Flume and Spark cover the real time case, whereas MapReduce covers the batch processing case. Since the launch of Cloudera Search morpholine development graduated into the Kite Software Development Kit (Kite SDK) in order to make the technology accessible to a wider range of users and products, beyond Search. The Kite SDK is a set of libraries, tools, examples, and documentation focused on making it easier to build systems on top of the

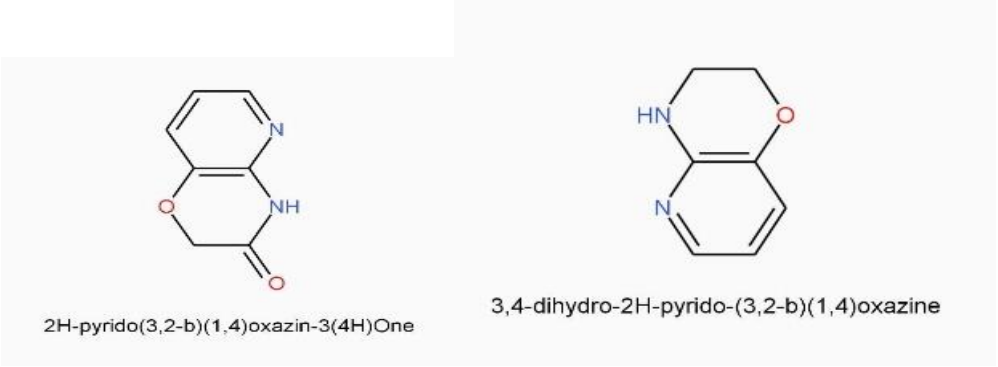
Hadoop ecosystem. The Kite SDK is hosted on GitHub and encourages involvement by the community. For example, morpholines could be embedded into Crunch, HBase, Impala, Pig, Hive, or Sqoop. Let us know where you want to take it.

MATERIALS AND METHODS

Scheme of work

Step 1: Synthesis of 2H-pyrido [3,2] [1,4] oxazin-3(4H)-one

The Chloro acetyl chloride(0.1mol) is added drop-wise to the solution of potassium carbonate (0.1 mol) and 2-amino -3-hydroxy pyridine -3-ol (0.1 mol) in THF (250 ml) at 0^0c. The resulting suspension was stirred at room temperature for 1hr. then the reaction mixture heated to reflux and maintained for 4hr. after completion of reaction, the reaction was cooled to room temperature and the inorganic solids were removed by filtration washed with THF (25 ml). filtered and washed with water (25 ml).



Potassium carbonate, chloro acetyl chloride ⟶ Tetra hydro furan,0-5^0c

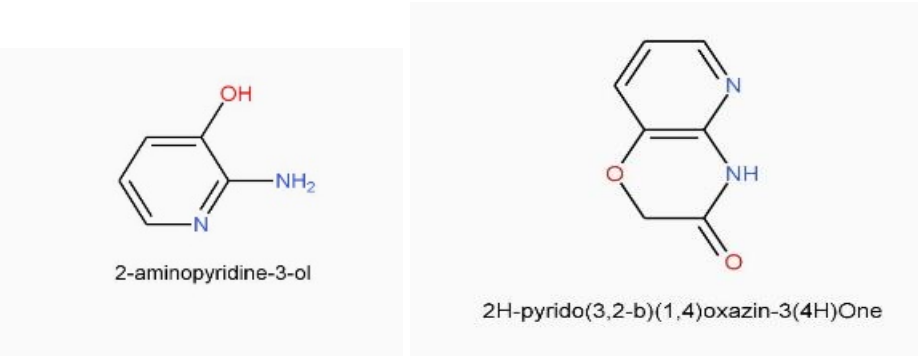
Step 2: synthesis of 3,4-dihydro-2H-pyrido[3,2-b] [1,4] oxazine

A mixture of THF 25 ml and compound-1 (0.1 mole) in 30 ml of LiAlH4 was heated with occasional stirring at 80^0c for 6 hr.

At the end of this period, the mixture was cooled and poured into ice cold water.

The separated solid was filtered.

The crude product obtained above was recrystallised from methanol -DMF solution to obtain pure compound -2.



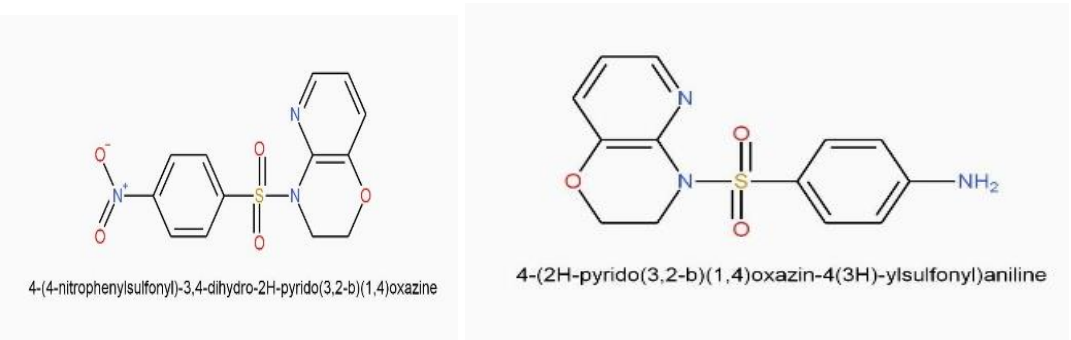
Tetra hydro furan, ⟶ Lithium aluminium hydrte, 6hr.

Step 3: synthesis of 4(4-nitrophenylsulfonyl)-3,4-dihydro-2H-pyrido[3,2-b] [1,4] oxazine

A mixture of compound -2 (0.1 mole), 4-nitro benzene sulphonyl chloride (0.1 mole), triethylamine 10ml and dichloromethane (0.1 mole) in a round bottomed flask was heated with occasional stirring for 4 hrs.

At the end of this period the mixture was poured into ice cold water.

The separated solid was filtered and dried to obtain compound -3, which are recrystallised from the methanol to obtain ccompound-3.

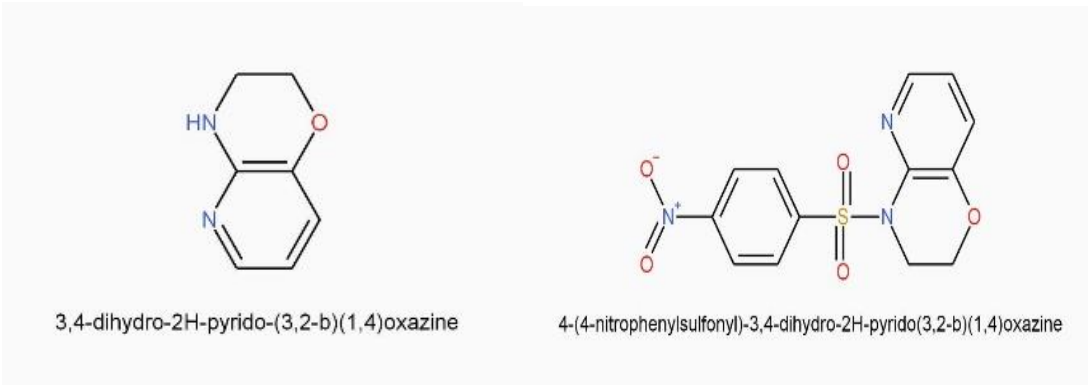


4-nitro benzene sulfonyl chloride, Tri ethylamine, ⟶ Dichloro methane, 4hr.

Step 4: Synthesis of 4-(2H-pyrido(3,2-b) (1,4) oxazin-4(3H)-sulfonyl) aniline

A mixture of compound-3 (0.1 mole) and phenyl hydrazine (0.1 mole), 50ml of acetic acid and ethanol (30 ml) was refluxed for 5hrs.

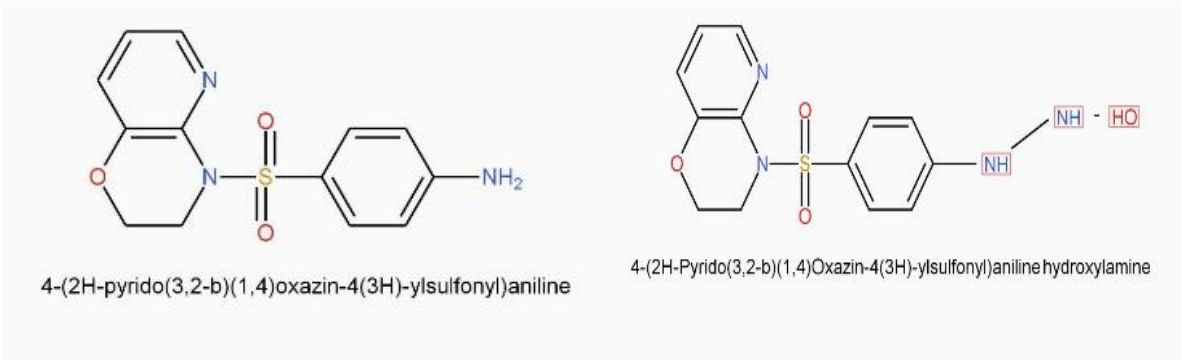
At the end of this period the mixture was cooled and poured into ice cold water.



Methanol, ⟶ Pd, 5hr.

Step 5: synthesis of 4-(2H-pyrido(3,2-b) (1,4) oxazin-4(3H)-yl sulfonyl) aniline hydroxylamine

The corresponding carboxylic acid (1 mole) was dissolved in DMF (30ml). followed by compound-4 (1mol), hexafluoro phosphate (0.1 mole) and N,N-di-isopropyl ethylamine (0.1mole). then the mixture was continued to stir for 6hr room temperature. After completion of reaction, the reaction mass poured into cold water and the suspension was stirred for 2hr at room temperature.



Carboxylic acid, DMF, ⟶ Hexa fluoro phosphate, diisopropyl ethylamine, N,N-6hr.

Physical characterization

- ✓ Molecular formula: $C_{13}H_{14}N_4SO_4$
- ✓ Molecular weight: 322gm/mole
- ✓ Soluble in Methanol, Ethanol, DMSO and DMF
- ✓ Melting point:120^0C
- ✓ Melting point were determined using Veego Digital melting point apparatus.
- ✓ The purity of synthesis compound was monitored on TLC.

Biological screening

Analgesic activity

Materials and Methods

Acute toxicity

The acute toxicity study was carried out as per OECD-425 Guidelines. Mortality in each group within 24 hrs was recorded. The animals were observed for a further 14 days for any signs for delayed toxicity. The compound has good margin of safety and did not show the lethal effects on the animals up to the doses of 500 mg/kg. Hence LD50 of morpholine derivative considered as 500mg/kg, studies were carried out with 1/10 of the LD50 dose is 50mg/kg.

Evaluation of analgesic activity

Tail immersion method

Swiss albino mice were screened by exposure to the thermal stimulus. The mice showing positive response were divided in to four groups of six animals each. The animals of Group I, II, III and IV were received DMSO (1ml/kg/p.o.), indomethacin (10 mg/kg/p.o.) and morpholine derivative i.e. (50 mg/kg) respectively. After half an hour of treatment, the tail of mice was dipped in warm water kept constant at 55±1o C up to 2cm from the tip of the tail. The time taken to withdraw the tail clearly out of water was considered as the reaction time with the cut of time being 60 sec. The observations were made at 0 min, 30 min, 60 min, 120 min, and 180 min.

Acetic acid induced writhing test

The morpholine derivative was evaluated for its analgesic activity by acetic acid induced writhing model. Swiss albino mice were divided in to four groups of six animals each. First group was served as a negative control received DMSO (1ml/kg). Second group served as positive control received indomethacin (10 mg/kg). While the third and fourth groups were administered orally with morpholine derivative. Half an hour after the administration of above drugs 0.6% v/v acetic acid (10ml/kg) i.p was given to all animals and observed for 15minutes. The number of abdominal constriction (writhing) and stretching with a jerk of the hind limb was counted for 15 minutes after administering acetic acid.

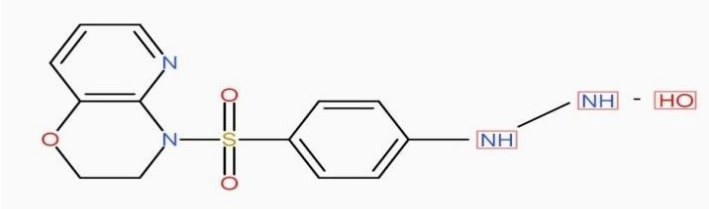
% Protection = 1- (Experimental/control) x 100

Statistical analysis

One way analysis of variance (ANOVA) by Dunnett's method was employed using Graph pad instat 3.0 software for statistical analysis of the data. A probability value of < 0.01 was considered statistically significant. Values in the text and tables are represented as Mean ± SEM.

Spectral analysis

IUPAC Name



4-(2H-pyrido (3,2-b) (1,4) oxazin-4(3H)-yl sulfonyl) anilino hydroxylamine

IR interpretation

I.R. spectral data (KBr discs) (in cm^{-1})	
N-H str.	3460.63
C=N str.	1508.06
=C-H str.	3523.31
C-N str.	1343.91

^{1}HNMR interpretation

^{1}HNMR Spectral data Absorption position (in PPM)	
6.34 – 7.21	m, 19H, ArH
1.16	d, 3H, CH3
2.35	s, 3H, CH3
3.10, 2.85	d, 2H, CH2
3.14	q, 1H, CH
4.0	s, 2H, NH
4.12	d, 1H, CH
4.13	t, 1H, CH

RESULTS AND DISCUSSION

Synthesis

The present study report the synthesis of morpholine derivatives electrophilic substitution of 2-aminopyridine 3-ol in THF & chloro acetyl chloride was carried out stepwise at different temperature by various hydroxyl amine. The final morpholine derivative was synthesized. compound 4 was replaced by hydroxyl amine. Since the report regarding this compound suggest morpholine possesses a good bioactive moiety.

Physical characterization

Melting points of the synthesized compound was taken in open capillary tubes and was uncorrected and were found to be in the range 110-120˚C.

TLC was performed using precoated silica gel plates of 0.25mm thickness. Eluents used were chloroform, methanol (3:7) spots were visualised in U.V. light.

At room temperature solubility of newly synthesized compounds were determined by various organic solvents and it was found that all compounds were freely soluble in Methanol, Ethanol, DMSO and DMF.

Structural confirmation

The Infra red spectroscopy was performed with KBr on perkin FT-IR instrument. Presence of stretching in the range 700 cm-1 to 3900 cm-1 indicating the presence of NH functional group. Stretching between 1500 cm-1 to 1600 cm-1 indicates the presence of C=N characteristics. CN stretching between at 1300 cm-1 to 1400 cm-1.

^{1}H NMR spectroscopy was recorded on Bruker 400 MZs Advance. 1H NMR the chemical shifts were reported as parts per million downfield from tetra methyl silane and solvent used as DMSO. Presence of chemical shift in the range 6.34-7.21 (m, 19H, ArH), 2.85-3.10 (d, 2H, CH2).

Analgesic activity

Tail immersion method

The analgesic effect of Morpholine derivative (50 mg/kg) were studied by using tail immersion method and it was compared with the Group I. The morpholine derivative shows significant and almost equal to that of the positive control at 60 minute of post treatment.

Table 1: The analgesic activity of Morpholine derivative by tail immersion method.

Groups	Treatment	Dose (mg/kg)	Post treatment reaction time in seconds				
			0 min	30 min	60 min	120 min	180 min
1	DMSO	1ml	2.5± 0.094	2.5± 0.094	2.75± 0.094	2.5± 0.094	2.75± 0.094
2	Indomethacin	10	2.75± 1.08	7.12± 1.08*	7.75± 1.08*	8.20± 1.08*	8.75± 1.08*
3	Morpholine derivative	50	2.50± 1.01	6.30± 1.01*	6.73± 1.01*	7.80± 1.01*	8.20± 1.01*

Values are expressed as mean ± SEM (N=6), P<0.01* considered significant with respect to the control group.

Acetic acid induced writhing

The analgesic effect of Morpholine derivatives (50 mg/kg) were studied by acetic acid induced writhing method. The morpholine derivative shown significant (p<0.01) reduction in the number of writhes induced by acetic acid when compared to Group I, which served as negative control.

Table 2: The analgesic activity of Morpholine derivative by acetic acid induced writhing response in mice.

Groups	Treatment	Dose (mg/kg)	Mean number of writhing(15 mints)	Percentage of protection
1	DMSO	1 ml	47.00± 1.238	0
2	Indomethacin	10	9.16 ± 0.477 *	80.51
3	Morpholine derivative	50	13.2 ± 0.87 *	71.91

Values are expressed as mean ± SEM (N=6), P<0.01* significant with respect to the control group.

DISCUSSION

Acetic acid induced writhing and Tail immersion methods are used to study the action on the peripheral nervous system. The analgesic effect of morpholine derivative was studied using the above said methods and it was compared with the Group I (DMSO 1ml/kg). Our results showed that acetone extract possessed good analgesic activity than alcoholic extract. The activity of morpholine derivative is significant and is equipotent to that of the positive control at 60 minute of post treatment. Increase in the immersion time of the tail in hot water suggests that the extracts probably inhibit the production of substance p and bradykinin. Acetic acid which causes nociception by liberating endogenous substances including histamine, serotonin, bradykinin and prostaglandin, which may stimulates pain. Therefore the morpholine derivative might inhibit the synthesis and release of these endogenous substances.

REFERENCES

1. Nurcan berber, “synthesis of certain new morpholine derivatives bearing a thiazide moiety‘’, journal of science, 2019; 23, 4: 554-558.

2. Entesar o. Altamiemi, ‘’synthesis and characterization of some new morpholine derivatives‘’, Baghdad science journal, 2016; 2, 13: 253-265.
3. Loganath velupillai, prashanth p dixit, M.s. shingare, D.v.mane ‘’synthesis and biological evaluation of (35)-3-[4-methoxy benzyl] morpholine derivatives from L- tyrosine ‘’, indo American journal of pharmaceutical sciences, 2, 3: 722-730.
4. Santosh Kumar Srivastava, javeed ahmad war, Savitri devi Srivastava ‘’design, synthesis, and molecular docking studies of some morpholine linked thiazolidinone hybrid molecules ‘’, European journal of chemistry, 7, 3: 271-279.
5. Loganathan velupillai, prashanth p dixit, M.s. shingare, D.v.mane, choudhari B.R, ‘’synthesis and biological evaluation of some novel fused ring pyridine morpholine benzene, sulphonamide derivatives‘’, world journal of pharmacy and pharmaceutical sciences, 2015; 4, 8: 1413-1422.
6. Anna Pratima G. Nikalji, matin patel, yogini Ranade, Rishikesh Deshpande and dansukh rajani, ‘’design and synthesis of novel N- substituted morpholine benzamide derivatives as antimicrobial agents’’, pelagia research library, 2012; 3, 4: 462-469.
7. Varinder k-Aggarwal, Muhammad yar, Eoghan M. mc garrigle, ‘’an annulation reaction for the synthesis of morpholines, thiomorpholines, and piperazines from beta-heteroatom amino compounds and vinyl sulfonium salts’’, angewandte chemie. Int. Ed, 2008; 47: 3784-3786.
8. Muhammad taha, syed adnan ali shah, Muhammad affi, manar zulkeflec, sadia suttan, abdul wadood fazal Rahim, not hadiani ismali, ‘’morpholine hydrazine scaffold: synthesis, anticancer activity and docking studies’’, Chinese chemical letters, 2017; 28: 607-611.
9. Wei-ke su*, chen-feng zhou, Jian-Jun li, " morpholine triflate promoted one -four - component synthesis of dihydropyrano [2,3-c] pyrazoles, chinese chemical letters, 2016; 27: 1686-1690.
10. edjlali, ladan*, babazadeh, mirzaagha, Hosseinzadehkhanmini, Rahim, new strategy for the synthesis of morpholine cores: synthesis from N-propargyl amines iran journal of chemistry. chem. eng, 2017; 36, 3: 1-13.