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SYNTHESIS AND DESIGN OF A NOVEL SUBSTITUTED MORPHOLINE DERIVATIVES AND EVALUATION FOR THEIR ANALGESIC ACTIVITY

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ABSTRACT

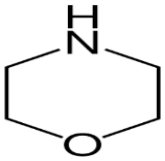
Morpholine, a six-membered heterocycle containing one nitrogen and one oxygen atom, is a moiety of great significance. It forms an important intermediate in many industrial and organic synthesis. Morpholine containing drugs are of high therapeutic value. This review discusses the synthesis of morpholines, a heterocycle that is often used in medicinal chemistry. It highlights the importance of morpholines in drug discovery and their contribution to the biological activities of bioactive molecules. This article discusses the wide range of applications of morpholine, an organic chemical compound with a six-membered ring. It covers its use in medicinal chemistry, such as in analgesics, as well as its industrial applications, such as in corrosion inhibition and as a catalyst. This review discusses the morpholine ring as a versatile synthetic building block that can be used in drug design and development. It highlights the morpholine

ring's contribution to the biological activities of bioactive molecules and its role in improving their pharmacokinetic profile.

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 generates the salt morpholinium chloride. It is a colorless liquid with a weak, ammonia- or fish-like odor. The naming of morpholine is attributed to Ludwig Knorr, who incorrectly believed it to be part of the structure of morphine. Morpholine is often produced industrially by the dehydration of diethanolamine with concentrated sulfuric acid. Alternatively, it can be made from bis(2-chloroethyl)ether in a reaction with ammonia, by which also ammonium chloride is formed. Morpholine is a common additive, in parts per million concentrations, for pH adjustment in both fossil fuel and nuclear power plant steam systems. Morpholine is used because its volatility is about the same as water, so once it is added to the water, its concentration becomes distributed rather evenly in both the water and steam phases. Its pH-adjusting qualities then become distributed throughout the steam plant to provide corrosion protection. Morpholine undergoes most chemical reactions typical for other secondary amines, though the presence of the ether oxygen withdraws electron density from the nitrogen, rendering it less nucleophilic (and less basic) than structurally similar secondary amines such as piperidine. For this reason, it forms a stable chloramine. It is commonly used to generate enamines. In nature, fruits make waxes to protect against insects and fungal contamination, but this can be lost as the fruit is cleaned. Hence a small amount of new wax, made from shellac, is applied to replace it. Morpholine is sometimes used as an emulsifier and solubility aid for this new coating. The European Union has forbidden the use of morpholine in fruit coating.

MORPHOLINE



Chemical formula – C_4H_9NO

Molar mass - $87.122 g.mol^{-1}$

Appearance - Colourless liquid

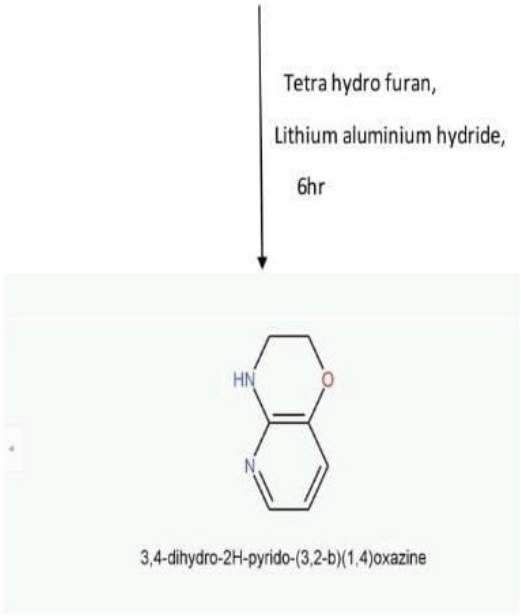
Odour	- Weak ammonia-like or fish- like
Density	- 1.007g\cm^3
Melting point	- -5^{o}C (23^{o}F;268K)
Boiling point	- 129^{o}C (264^{o}F; 402K)
Solubility	- Miscible in water
Vapor Pressure	- 6 mmHg(20^{o}C)
Acidity (pKa)	- 8.36

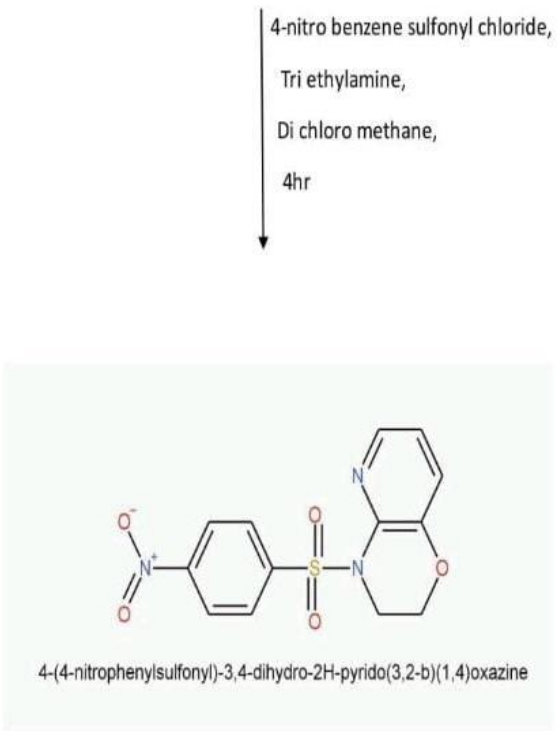
SCHEME AND MATERIALS METHOD

2-aminopyridine-3-ol

Potassium carbonate,
Chloro acetyl chloride,
Tetra hydro furan,
0-5°C, 4hr.

2H-pyrido(3,2-b)(1,4)oxazin-3(4H)One


Tetra hydro furan,
Lithium aluminium hydride,
6hr
HN
O
N
3,4-dihydro-2H-pyrido-(3,2-b)(1,4)oxazine


4-nitro benzene sulfonyl chloride,
Tri ethylamine,
Di chloro methane,
4hr
N
O
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N
S
N
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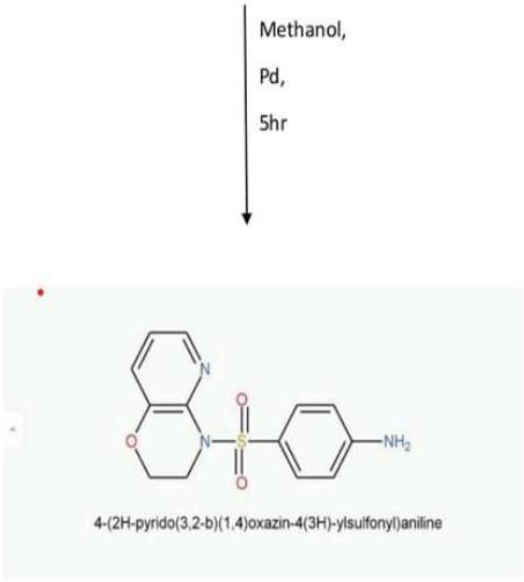
4-(4-nitrophenylsulfonyl)-3,4-dihydro-2H-pyrido(3,2-b)(1,4)oxazine



STEP-1

[2H-pyrido(3,2-b)(1,4)oxazin-3(4H)-one]

- The chloroacetyl chloride (0.1.mole) is added drop-wise to the solution of potassium carbonate (0.1.mole) and 2-amino-3-hydroxypyridine-3-ol (0.1.mole) in THF (250 ml) at 0^{o}C. The resulting suspension was stirred at room temperature for 1 hour.
- Then the reaction mixture heated to reflux and maintained for 4hr. After the completion of reaction, the reaction was cooled to room temperature and the inorganic solids were removed by filtration washed with THF (25ml). Filtered and washed with water (25ml).

STEP-2

- A mixture of THF 25ml (0.1mole) in 30ml of LiAlH4 was heated with occasional stirring at 80^{o}C for 6 hours.
- At the end of this period, the mixure was cooled and poured into ice cold water.
- The separated solid was filtered.
- The crude product obtained above was recrystallized from methanol-DMF solution to obtain pure compound-2.

STEP-3

- A mixture of compound-2 (0.1mole) 4-nitrobenzene sulphonyl chloride (0.1mole), trimethylamine 10ml and dichloromethane (0.1mole) in a round bottom flask was heated with occasional stirring for 4 hours.
- At the end of this period the mixture was poured into cold ice water. The separated solid was filtered and dried to obtain compound-3, which are recrystallized from hot methanol to obtain compound-3.

STEP-4

- A mixture of compound-3 (0.1mole) and phenyl hydrazine (0.1mole), 50ml of acetic acid and ethanol (30ml) was refluxed for 5 hours.
- At the end of this period the mixture was cooled and poured into ice cold water.

STEP-5

- The corresponding carboxylic acid (1mole) was dissolved in DMF (30ml). Followed by compound-4 (1mole) and N, N-diisopropyl ethyl amine (0.1mole). Then the mixture was continued to sit for 6 hours at room temperature. After completion of reaction, the reaction mass poured into cold water and the suspension was stirred for 2 hours at room temperature.

CHEMICALS

Choloroacetyl chloride, potassium carbonate, 2-amino-3-hyrdroxypyridine-3-ol, lithium aluminium hydride ($LiAlH_4$), dimethyl formamide (DMF), methanol, 4-nitrobenzene sulphonyl chloride, trimethylamine, dichloromethane, phenylhydrazine, acetic acid, carboxylic acid, N,N-diisopropyl ethylamine, tetrahydrofuran (THF).

APPARATUS

Round bottom flask, Reflex condenser, Measuring cylinder, Beakers, Funnel, Petri plate, Glass rods, Water bath, Weghing balance, Tripod stand.

PHYSICAL CHARACTERIZATION

Chemical formula – C_4H_9NO

Molar mass - 87.122g.mol^{-1}

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Odour - Weak ammonia-like or fish- like

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Vapor Pressure - 6 mmHg(20^{o}C)

Acidity (pKa) - 8.36

BIOLOGICAL ACTIVITY

ANALGESIC ACTIVITY

An analgesic drug, also called simply an analgesic, antalgic, pain reliever, or painkiller, is any member of the group of drugs used for pain management. Analgesics are conceptually distinct from anesthetics, which temporarily reduce, and in some instances eliminate, sensation, although analgesia and anesthesia are neurophysiologically overlapping and thus various drugs have both analgesic and anesthetic effects. Analgesic choice is also determined by the type of pain: For neuropathic pain, recent research has suggested that classes of drugs that are not normally considered analgesics, such as tricyclic antidepressants and anticonvulsants may be considered as an alternative. Various analgesics, such as many NSAIDs, are available over the counter in most countries, whereas various others are prescription drugs owing to the substantial risks and high chances of overdose, misuse, and addiction in the absence of medical supervision.

Classification

Analgesics are typically classified based on their mechanism of action.

NSAIDs

Nonsteroidal anti-inflammatory drugs (usually abbreviated to NSAIDs), are a drug class that groups together drugs that decrease pain[10] and lower fever, and, in higher doses, decrease inflammation.[11] The most prominent members of this group of drugs—aspirin, ibuprofen and naproxen, and Diclofenac—are all available over the counter in most countries.

COX-2 inhibitors

These drugs have been derived from NSAIDs. The cyclooxygenase enzyme inhibited by NSAIDs was discovered to have at least two different versions: COX1 and COX2. Research suggested most of the adverse effects of NSAIDs to be mediated by blocking the COX1 (constitutive) enzyme, with the analgesic effects being mediated by the COX2 (inducible) enzyme. Thus, the COX2 inhibitors were developed to inhibit only the COX2 enzyme (traditional NSAIDs block both versions in general). These drugs (such as rofecoxib, celecoxib, and etoricoxib) are equally effective analgesics when compared with NSAIDs, but cause less gastrointestinal hemorrhage in particular.

After widespread adoption of the COX-2 inhibitors, it was discovered that most of the drugs in this class increase the risk of cardiovascular events by 40% on average. This led to the withdrawal of rofecoxib and valdecoxib, and warnings on others. Etoricoxib seems relatively safe, with the risk of thrombotic events similar to that of non-coxib NSAID diclofenac.

Opioids

Morphine, the archetypal opioid, and other opioids (e.g., codeine, oxycodone, hydrocodone, dihydromorphine, pethidine) all exert a similar influence on the cerebral opioid receptor system. Buprenorphine is a partial agonist of the μ-opioid receptor, and tramadol is a serotonin norepinephrine reuptake inhibitor (SNRI) with weak μ-opioid receptor agonist properties. Tramadol is structurally closer to venlafaxine than to codeine and delivers analgesia by not only delivering "opioid-like" effects (through mild agonism of the mu receptor) but also by acting as a weak but fast-acting serotonin releasing agent and norepinephrine reuptake inhibitor. Tapentadol, with some structural similarities to tramadol, presents what is believed to be a novel drug working through two (and possibly three) different modes of action in the fashion of both a traditional opioid and as an SNRI. The effects of serotonin and norepinephrine on pain, while not completely understood, have

had causal links established and drugs in the SNRI class are commonly used in conjunction with opioids (especially tapentadol and tramadol) with greater success in pain relief.

Dosing of all opioids may be limited by opioid toxicity (confusion, respiratory depression, myoclonic jerks and pinpoint pupils), seizures (tramadol), but opioid-tolerant individuals usually have higher dose ceilings than patients without tolerance. Opioids, while very effective analgesics, may have some unpleasant side-effects. Patients starting morphine may experience nausea and vomiting (generally relieved by a short course of antiemetics such as phenergan). Pruritus (itching) may require switching to a different opioid. Constipation occurs in almost all patients on opioids, and laxatives (lactulose, macrogol-containing or co-danthramer) are typically co-prescribed.

When used appropriately, opioids and other central analgesics are safe and effective; however, risks such as addiction and the body's becoming used to the drug (tolerance) can occur. The effect of tolerance means that frequent use of the drug may result in its diminished effect. When safe to do so, the dosage may need to be increased to maintain effectiveness against tolerance, which may be of particular concern regarding patients with chronic pain and requiring an analgesic over long periods. Opioid tolerance is often addressed with opioid rotation therapy in which a patient is routinely switched between two or more non-cross-tolerant opioid medications in order to prevent exceeding safe dosages in the attempt to achieve an adequate analgesic effect.

Opioid tolerance should not be confused with opioid-induced hyperalgesia. The symptoms of these two conditions can appear very similar but the mechanism of action is different. Opioid-induced hyperalgesia is when exposure to opioids increases the sensation of pain (hyperalgesia) and can even make non-painful stimuli painful (allodynia).

Alcohol

Alcohol has biological, mental, and social effects which influence the consequences of using alcohol for pain. Moderate use of alcohol can lessen certain types of pain in certain circumstances.

The majority of its analgesic effects come from antagonizing NMDA receptors, similarly to ketamine, thus decreasing the activity of the primary excitatory (signal boosting)

neurotransmitter, glutamate. It also functions as an analgesic to a lesser degree by increasing the activity of the primary inhibitory (signal reducing) neurotransmitter, GABA.

Attempting to use alcohol to treat pain has also been observed to lead to negative outcomes including excessive drinking and alcohol use disorder.

Cannabis

Medical cannabis, or *medical marijuana*, refers to cannabis or its cannabinoids used to treat disease or improve symptoms. There is evidence suggesting that cannabis can be used to treat chronic pain and muscle spasms, with some trials indicating improved relief of neuropathic pain over opioids.

Combinations

Analgesics are frequently used in combination, such as the paracetamol and codeine preparations found in many non-prescription pain relievers. They can also be found in combination with vasoconstrictor drugs such as pseudoephedrine for sinus-related preparations, or with antihistamine drugs for people with allergies.

While the use of paracetamol, aspirin, ibuprofen, naproxen, and other NSAIDS concurrently with weak to mid-range opiates (up to about the hydrocodone level) has been said to show beneficial synergistic effects by combating pain at multiple sites of action, several combination analgesic products have been shown to have few efficacy benefits when compared to similar doses of their individual components. Moreover, these combination analgesics can often result in significant adverse events, including accidental overdoses, most often due to confusion that arises from the multiple (and often non-acting) components of these combinations.

Alternative medicine

There is some evidence that some treatments using alternative medicine can relieve some types of pain more effectively than placebo. The available research concludes that more research would be necessary to better understand the use of alternative medicine.

Other drugs

Nefopam—a monoamine reuptake inhibitor, and calcium and sodium channel modulator—is also approved for the treatment of moderate to severe pain in some countries.

Flupirtine is a centrally acting K^+ channel opener with weak NMDA antagonist properties. It was used in Europe for moderate to strong pain, as well as its migraine-treating and muscle-relaxant properties. It has no significant anticholinergic properties, and is believed to be devoid of any activity on dopamine, serotonin, or histamine receptors. It is not addictive, and tolerance usually does not develop. However, tolerance may develop in some cases.

Ziconotide, a blocker of potent N-type voltage-gated calcium channels, is administered intrathecally for the relief of severe, usually cancer-related pain.

Adjuvants

Certain drugs that have been introduced for uses other than analgesics are also used in pain management. Both first-generation (such as amitriptyline) and newer antidepressants (such as duloxetine) are used alongside NSAIDs and opioids for pain involving nerve damage and similar problems. Other agents directly potentiate the effects of analgesics, such as using hydroxyzine, promethazine, carisoprodol, or tripelennamine to increase the pain-killing ability of a given dose of opioid analgesic.

Adjuvant analgesics, also called atypical analgesics, include orphenadrine, mexiletine, pregabalin, gabapentin, cyclobenzaprine, hyoscine (scopolamine), and other drugs possessing anticonvulsant, anticholinergic, and/or antispasmodic properties, as well as many other drugs with CNS actions. These drugs are used along with analgesics to modulate and/or modify the action of opioids when used against pain, especially of neuropathic origin.

Dextromethorphan has been noted to slow the development of and reverse tolerance to opioids, as well as to exert additional analgesia by acting upon NMDA receptors, as does ketamine. Some analgesics such as methadone and ketobemidone and perhaps piritramide have intrinsic NMDA action.

The anticonvulsant carbamazepine is used to treat neuropathic pain. Similarly, the gabapentinoids gabapentin and pregabalin are prescribed for neuropathic pain, and phenibut is available without prescription. Gabapentinoids work as $\alpha_2\delta$-subunit blockers of voltage-gated calcium channels, and tend to have other mechanisms of action as well. Gabapentinoids are all anticonvulsants, which are most commonly used for neuropathic pain, as their mechanism of action tends to inhibit pain sensation originating from the nervous system.

Uses

- Topical nonsteroidal anti-inflammatory drugs provide pain relief in common conditions such as muscle sprains and overuse injuries. Since the side effects are also lesser, topical preparations could be preferred over oral medications in these conditions.

- Topical analgesia is generally recommended to avoid systemic side-effects. Painful joints, for example, may be treated with an ibuprofen- or diclofenac-containing gel (The labeling for topical diclofenac has been updated to warn about drug-induced hepatotoxicity.); capsaicin also is used topically. Lidocaine, an anesthetic, and steroids may be injected into joints for longer-term pain relief. Lidocaine is also used for painful mouth sores and to numb areas for dental work and minor medical procedures. In February 2007 the FDA notified consumers and healthcare professionals of the potential hazards of topical anesthetics entering the bloodstream when applied in large doses to the skin without medical supervision. These topical anesthetics contain anesthetic drugs such as lidocaine, tetracaine, benzocaine, and prilocaine in a cream, ointment, or gel.

PRINCIPLE OF ANALGESIC ACTIVITY

Pain is an unpleasant sensory and emotional experience that results from actual (e.g. trauma) (or) potential tissue damage. Pain can be purely nociceptive, purely neuropathic, or mixed. Nociceptive pain is caused by damage to soft tissues and bones by disease or trauma.

The analgesia produced by opioids is most effective for acute or chronic nociceptive pain, but can be helpful for some types of neuropathic pain. In addition to the antinociceptive effect, opioids alter the perception of pain, making it less unpleasant.

Analgesics can inhibit the sensation of pain by inhibiting transmission of non-nociceptive impulses along primary afferents (eg, local anesthetics) or by altering the perception of pain (eg, opioids).

RESULTS AND DISCUSSION

Synthesis: The present study report the synthesis of morpholine derivatives nucleophillic substitution of phenylhydrazine with 1-(H-morpholine-2yl) ethanone was carried out stepwise at different temperature. The first step involves substitution of 1-(H- morpholine-2yl) ethanone and the next by polyphosphoric acid. The final morpholine derivative in the

synthesized compound 3 was replaced by morpholine. Since the report regarding this compound suggest a morpholine posses 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 95-105℃.

TLC was performed using precoated silica gel plates of 0.25mm thickness. Eluents used were Acetic acid: n-butanol: Water (7:2:1) spots were visualized 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, DMF.

CONCLUSION

The synthesized compound was subjected to biological evaluation. The compound were evaluated for analgesic studies revealed that the substitution of different aromatic amines to parent morpholine nucleus show the moderate activity.

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