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THIOCOLCHICOSIDE AS MUSCLE RELAXANT: A REVIEW

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Review Article

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ABSTRACT

Thiocolchicoside, is a synthetic sulphur derivative of colchicoside, a naturally occurring glucosidecontained in the Colchicum autumnale plant Thiocolchicoside has a selective affinity for g-amino-butyric acid (GABA) receptors and acts on themuscular contracture by activating the GABA-nergicinhibitory pathways thereby acting as a potent mus-cle relaxant Thiocolchicoside (Muscoril, Myoril, Neoflax) is a muscle relaxant with anti-inflammatory and analgesic effects. It acts as a competitive $GABA_A$ receptor antagonist and also inhibits glycine receptors with similar potency and nicotinic acetylcholine receptors to a much lesser extent. It has powerful convulsant activity and should not be used in seizure-prone individuals. Mode of action includes modulation of chemokine and prostanoid production and inhibition of neutrophil and endothelial cell adhesion molecules by which it interferes with the initiation and amplification of the joint inflammation. THC is a muscle relaxant given by oral in the treatment of arthritis in a usual dose equivalent to 8 mg first day to 12-16mg /day

KEYWORDS: *Thiocolchicoside, convulsant activity*

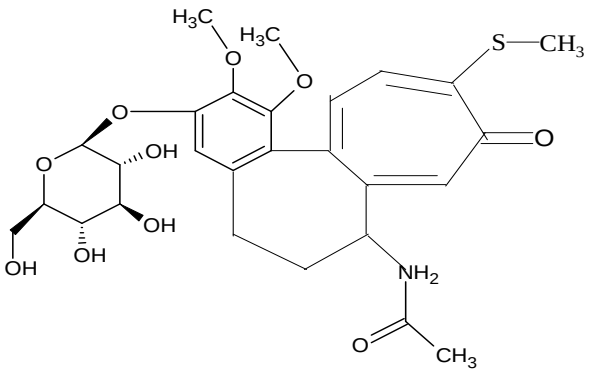
Introduction

Thiocolchicoside (THC) is used clinically for its muscle relaxant, anti-inflammatory, and analgesic properties, and it has been shown to interact with g-amino butyric acid (GABA) type A receptors (GABAARs) and strychnine-sensitive Glycine receptors in the rat central nervous system. In contrast to a proposed agonistic action at these two types of inhibitory receptors, pharmacological evidence has shown that, under certain conditions, THC manifests convulsant activity in animals and humans. .

Thiocolchicoside:

Chemically it is N-[3-(β-D-glucopyranosyloxy)-1,2-dimethoxy-10(methylthio)-9-oxo-5,6,7,9-tetrahydrobenzo [*a*] heptalen-7-yl] acetamide[1]. And has the empirical formula $C_{10}H_{21}NO_7$. THC is a muscle relaxant. Its mode of action includes modulation of chemokine and prostanoid production and inhibition of neutrophil and endothelial cell adhesion molecules by which it interferes with the initiation and amplification of the joint inflammation[1,2,3,4,5.]

Fig: [1] THC



Muscoril (Thiocolchicoside), a muscle relaxant agent with anti-inflammatory and analgesic actions, also is used topically for the treatment of muscular spasms and for rheumatologic, orthopedic, and traumatologic disorders. In this study, thiocolchicoside was formulated to use as foam to avoid contact with the afflicted area during the spreading phase. To enhance drug penetration, various enhancers were added to the base formulation.[6,7,8.]

SYNONYMS:[9,10]

Thiocolchicoside
Tiocolchicosido
Thiocolchicosidum
Tiocolchicoside
10-Thiocolchicoside
Prestwick_875
Tiocolchicoside [DCIT]
Colchicoside, 10-thio-
Prestwick0_000539
Prestwick1_000539
Prestwick2_000539
Coltramyl
Musco-ril
Tiocolchicoside
Tiocolchicosido
Thiocolchicosidum
10-Thiocolchicoside
Prestwick_875
Tiocolchicoside [DCIT]
Colchicoside, 10-thio-
Prestwick0_000539
Prestwick1_000539
Prestwick2_000539
Thiocolchicosidum SPQR
Tiocolchicosido
Thiocolchicoside [INN:DCF]
BSPBio_000557
MLS002153865
Thiocolchicine 2-glucoside analog
SPBio_002478
BPBio1_000613
C27H33NO10S
EINECS 210-017-7
Colchicoside, 10-thio- (8CI)
AIDS131782
HMS1569L19
NSC 147755
AIDS-131782
CID72067
BRN 0072205
NSC624673
LS-9650
SMR001233221
R. 271
4-17-00-03428 (Beilstein Handbook Reference)
2-10-Di(demethoxy)-2-glucosyloxy-10-methylthiocolchicine
BRD-A11605036-001-03-2
602-41-5
Acetamide, N-(3-(beta-D-glucopyranosyloxy)-5,6,7,9-tetrahydro-1,2-dimethoxy-10-(methylthio)-9-oxobenzo(a)heptalen-7-yl)-, (S)-
N-(3-(Hexopyranosyloxy)-1,2-dimethoxy-10-(methylthio)-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl)acetamide

HISTORY:[8,9,11,12.]

Thiocolchicoside is originated from Flower Seeds of **Gloriosa superb**.

Colchicaceae.

Gloriosa superba is the national flower of Zimbabwe (where it is a protected plant). It is also the state flower of Tamil Nadu state in India, and was the national flower of Tamil Eelam and as such was displayed during Maaveerar Day.

Thiocolchicoside is a natural derivated product from colchicine & a semi-synthetic derivative of colchicoside.

THIOCOLCHICOSIDE

Description:

Thiocolchicoside is a semi-synthetic sulfur derivative of colchicoside, a naturally occurring glucoside present in the plant ***Gloriosa superb*** flower seeds in the process of producing Colchicine. It is a pale yellow powder.[13,14,15.]

Macroscopic characters:[3,5,16.]

Nature : Crystalline powder

Colour : Pale yellow to Yellow**.**

Odour : Characteristic smell.

Taste : Unpleasant taste.

Shape : Like that of colchicine with extensive hydrogen bonding determining the crystal structure.

Identity:

Purity : >95%

Strength : 4mg & 8mg

Foreign matter : not more than 2 Percent

Total ash : not more than 4 Percent

Acid-insoluble ash : not more than 1 Percent

Alcohol-soluble extractive : not less than 2.5 Percent

Loss on drying : not less than 60 Percent

Volatile Oil : not less than 0.1 Percent.

Pharmacological Study:

Thiocolchicoside binds to GABA-A and strychnine sensitive glycine receptors. Thiocolchicoside acting as a GABA-A receptor antagonist, its myorelaxant effects could be exerted at the supra-spinal level, via complex regulatory mechanisms, although a glycinergic mechanism of action cannot be excluded. The characteristics of the interaction of Thiocolchicoside with GABA-A receptors are qualitatively and quantitatively shared by its main circulating metabolite, the glucuronidated Derivative. Thiocolchicoside is rapidly absorbed after oral administration, and metabolized into 3 main metabolites. The two main circulating forms were the Thiocolchicoside aglycon and the glucuronidated derivative of Thiocolchicoside, which is active. Thiocolchicoside is well

tolerated oral administration for periods of up to 6 months.[8,13,19.]

Synthesis Of Thiocolchicoside:[20.] (A) In a flask at room temperature under inert atmosphere, 3-demethylthiocolchicine (201 mg, 0.5 mmol) and 2,3,4,6-tetra-O-acetyl-α, D-glycopyranosyl fluoride (263 mg, 0.75 mmol) are suspended in anhydrous CH_3 CN (10 ml). The reaction mixture is added with 1,1,3,3-tetramethylguanidine (188 µl, 1,5 mmol). Following the addition of the base, the reagents are dissolved and the solution is colored in red. Ether BF3 (502 pl, 8 mmol) is added and the mixture becomes lighter in color.The reaction is continued with magnetic stirring and checked by TLC using a MeOH--CH_2 Cl_2 1:9 system. After 20 minutes the starting product is completely transformed. A $KHCO_3$ saturated solution is added and the phases are partitioned; the aqueous phase is extracted with AcOEt (3×10 ml). The combined organic phases are washed with a $KHSO_4$ saturated solution and a NaCl saturated solution. The mixture is dried over $MgSO_4$, filtered and the solvent is evaporated off, to obtain a solid crude product (562 mg) which is dissolved in ethanol (4 ml). 1N NAOH (2 ml) is added, with magnetic stirring. The progress of the reaction is checked by TLC: (MeOH--CH_2 Cl_2 /1:9). The reaction is complete within 3 hours. Thiocolchicoside (272 mg, 0.48 mmol) crystallizes directly from the reaction medium (97% yield).

(B) Exogenously supplied 3-demethylthiocolchicine was converted into 3-*O*-glucosyl thiocolchicine (thiocolchicoside) by a cell suspension culture of *Centella asiatica*. Around 30% of 3-demethylthiocolchicine (136 µM) was glucosylated after an 11-day incubation period. *In vitro* glucosylation by cell-free extracts demonstrated that theenzymatic reaction required specifically uridine diphosphate-D -glucose (UDPG1c)as a high energy glucose donor. Various endogenous phenolic compounds were assayed for their effect on the glucosyltransferase reaction.[19]

(C)Synthesis of colchicoside and thiocolchicoside:[22]

01g of 3-demethylcolchicine was dissolved in water and dioxane mixture and added to three neck round bottom flask in basic medium of TEA under nitrogen atmosphere. Subsequently 06g of a- acetobromoglucose was dissolved in dioxane and added to reaction mixture. This mass was kept agitated under the identical conditions over 24-48h. The temperature of the reaction was maintained at 0±5oC. Monitoring of the progress of the reaction was done by TLC using the mobile phase as mentioned earlier. Post reaction the mass was washed with sodium bicarbonate solutions and then with chloroform. The converted product was exchanged with methanolic chloroform. It was then dried with Na2SO4 and concentrated under reduced pressure in rotary evaporator. As a result the brownish syrupy mass was obtained. It was then dissolved in methanol and deprotected, using 1% sodium hydroxide solution as an exothermic reaction. Finally the product was recovered with 10% methanolic chloroform. Resulting mass was dried under reduced pressure and the off white colchicoside was thus recovered was 02g. On crystallization it yielded 1.5g of pure colchicoside of 99% assay. To assess its purity it was then taken as 01g, dissolved in 04g of water, and added to three necked round bottom flask at 20±30oC. 0.5g of NaSCH3 was added over the period of 15-20 minutes. Reaction was monitored with the mobile phase of CHCl3: AcOH: H2O (7:2:1). On completion of the reaction it was exchanged with 10% methanolic chloroform until the entire product was recovered. The solution was dried in rotary evaporator under reduced pressure to get syrupy brownish residue. It was then made to solubilise with methanol and kept in the freezer for crystallization overnight. Recovered

crystallized product was 1.5g of fast yellow color. Its specification was as per USP. Figure 1 and 2 may be referred as synthetic schemes.

Analysis: The drug was analyzed by the polarimeter for its SOR, purity by HPLC and confirmation of the structure by 300 MHz 1HNMR.

Side Effect of Thiocolchicoside: [23, 24, 25:] Side effect of skeletal muscle relaxants may include: sedation, drowsiness, blurred or double vision, constipation or diarrhea, dizziness and drowsiness, nervousness and confusion, dry mouth, dyspepsia (chronic or recurrent pain in the upper abdomen, upper abdominal fullness, and feeling full earlier than expected when eating), fatigue, headache, heartburn, hiccups and nausea, insomnia, stomach cramps, trembling, vomiting, and weakness; and possible dependence following long-term use, Photosensitivity reactions.

Therapuetic Uses:[7,26]

Thiocolchicoside is a muscle-relaxant(skeletal) agent used for the treatment of orthopedic, traumatic and rheumatologic disorders.Anti-inflammatory & Analgesic properties.Used in combination with glafenine and meprobamate to tranquilize patients undergoing hysterosalpingography. In the treatment of painful muscle spasms. Muscle relaxant Thiocolchicoside acts both in contractures of central origin and in those of reflex type, rheumatic and traumatic. Spastic sequelae of hemiparesis, Parkinson's disease and latrogenic Parkinson symptoms, particularly the neurodyslectic syndrome. Acute and chronic lumbar and sciatic pain, cervico-brachial neuralgia, persistent torticollis, post-traumatic and post-operative pain.

MARKETED FORMULATIONS:[27]

Brand Names

- Adalgur (Thiocolchicoside and Paracetamol)
  Teofarma, Spain
- Adeleks
  Mustafa Nevzat, Turkey
- Biocolchid
  Biogalenic, Venezuela
- Colthiozid
  Pharmy, France
- Coltramyl
  Aventis, Peru; Roussel, Vietnam; Sanofi-Aventis, France; Sanofi-Aventis, Malta; Sanofi-Aventis, Oman; Theraplix, Tunisia; Winthrop, Tunisia
- Coltrax
  Sanofi-Aventis, Brazil; Sanofi-Aventis, Venezuela
- Colval
  Valmor, Venezuela
- Decontril
  B&G, Italy
- Dynaxon
  Winthrop, Turkey
- Eusilen
  Cofasa, Venezuela
- Haliver
  Velka, Greece
- Lampral
  Biotech, Venezuela
- Miorel
  Daiichi Sankyo, France
- Miotens
  Dompé, Italy
- Muscoflex
  Bilim, Turkey; Epifarma, Italy

- Muscoril Trauma (Thiocolchicoside and Escin)
  Sanofi-Aventis, Italy
- Muscoril
  BB Farma, Italy; Pharmazena, Italy; Programmi Sanitari, Italy; Sanofi Synthelabo-F, Italy; Sanofi-aventis, Czech Republic; Sanofi-aventis, Ecuador; Sanofi-aventis, Poland; Sanofi-aventis, Turkey; Sanofi-Synthelabo, Greece
- Musco-Ril
  Sanofi-aventis, Greece
- Myolax
  ADWYA, Tunisia
- Myoplège
  Genévrier, France
- Myoril
  Sanofi-Aventis, India
- Neoflax
  Menarini, Costa Rica; Menarini, Dominican Republic; Menarini, Guatemala; Menarini, Honduras; Menarini, Nicaragua; Menarini, Panama; Menarini, El Salvador
- Neuroflax
  Aventis, Peru
- Recoside
  ARIS, Turkey
- Relaxil
  Opalia, Tunisia
- Relmus
  Sanofi-Aventis - Produtos farmacêuticos, S.A., Portugal
- Sciomir
  CT, Italy
- Strialisin
  MDM, Italy
- TDP(Thiocolchicoside and Diclofenac)
  Aamorb, India
- Teraside
  Krugher, Italy
- Thiocolchicoside Almus
  Almus, France
- Thiocolchicoside Alter
  Alter, France

Dosages Of Thiocolchicoside: Oral :Adult: Initially,16mg daily. Intramuscular; Muscular spasms Adult: upto 8mg daily.[29]

Contraindications: [24,29]

It is contraindicated to pregnant women, lactating mother and also peoples about to undergo surgery and having ulcer to stomachs. Should not be used during pregnancy and lactation. Should not be given to children. Avoid in people who develop hypersensitivity to it (Skidmore-Roth, 2001).

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32. http://druginfosys.com/Drug.aspx?drugCode=1062&drugName=Thiocolchicoside&typs=12

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