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Research Article

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Synthesis of some benzoxazole derivatives and their anti-inflammatory evaluation

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ABSTRACT

Novel series of benzo-oxazole derivatives were prepared by the condensation of 4- methyl sulfonyl acetophenone with various benzamide. The structures of the synthesized compounds were VI1-Vl3 assigned on the basis of elemental
analysis, IR, 1H NMR and mass spectroscopy. These compounds were screened for anti-inflammatory activity having asignificant anti-inflammatory activity when compared to the reference anti-inflammatory drug celecoxib using Invivo and Invitro anti-inflammatory screening

Key words: Benzo-oxazole, Carrageenan - induced rat paw edema, Anti-inflammatory activity.

INTRODUCTION

Benzo-oxazole is an aromatic organic compound with a molecular formula C7H5NO, benzene fused oxazole ring structure, and an odour similar to pyridine.Benzo-oxazole is used primarily in industry and research, and has no household use.Being a heterocyclic compound, benzo-oxazole finds use in research as a starting material for the synthesis of larger, usually bioactive structures. It is found withinthe chemical structures of pharmaceutical drugs such as Flunoxaprofen. Itsaromaticity makes it relatively stable, although as a heterocyclic, it has reactivesites which allow for functionalization. Oxazole and its derivatives are used asbuilding block for biochemicals and pharmaceutical as well as in other industrialapplications such as pesticides, dyes, fluorescent brightening agents, textileauxiliaries and plastics.**:**

General structure of benzo-oxazole

Benzo-oxazoles are an important class of heterocyclic compounds that have manyapplications in medicinal chemistry. For example, benzo-oxazole derivatives havebeen characterized as melatonin receptor agonists,17 amyloidogenesis inhibitors,18Rho kinase inhibitors,19 and antitumor agents.20 In addition to their use in medicinal chemistry, benzoxazoles are recognized as an important scaffold influorescent probes such as anion and metal cation sensors.21Benzoxazoles are an important class of heterocycles that are encountered in a number of natural products and are used in drug and agrochemical discoveryprograms, as well as for a variety of other purposes. For example, thebenzoxazole core structure is found in a variety of cytotoxic natural products, suchas the UK-1,22 AJI9561,23 and salvianen.24 Recent medicinal chemistry applicationsof benzoxazoles include the cathepsin S inhibitor,25 selective peroxisomeproliferator-activated receptor γ antagonist JTP-426467.26 Other applications ofbenzoxazoles include their use as herbicides, such as Fenoxaprop, and asfluorescent whitening agent dyes such as bisbenzoxazolylethylenes and arenesMainly there are two general methods for synthesizing 2-

substitutedbenzoxazoles, benzimidazoles, and benzothiazoles. One is the coupling of *o*-substitutedaminoaromaticswith carboxylic acid derivatives and acyl chlorides,which is either catalyzed by strong acids or microwave conditions. The other is theoxidative cyclization of Phenolic Schiff bases derived from the condensation of *o*-substitutedaminoaromatics and aldehydes. In latter reactions various oxidantshave been used. Different catalysts and different methods were also reported forthe synthesis of these heterocycles.

Pang Yi et al., 42 described the synthesis of substituted benzoxazoles by usingpalladium mediated oxidative cyclization.

Wang Shen et al., 43 described an efficient method for the synthesis of substitutedbenzimidazoles from 1,1-dibromoethenes and *o*-diaminobenzenes. The reactionemploys DABCO as the base and NMP as the solvent.developedA new and efficient method for thepreparation of benzoxazoles[4,5-*b*]pyridines from reactions of orthoesters with *o*-substituted aminoaromatics and2-amino-3-hydroxypyridine in the presence of catalytic amounts of the moisturestable, inexpensive ZrOCl2·8H2O under solvent-free conditions.

Mohammadpoor-Baltork et al., 45 described an efficient method for thepreparation of benzoxazoles, benzimidazoles and oxazolo[4,5-*b*]pyridines fromreactions of orthoesters with *o*-substituted aminoaromatics and 2-amino-3-hydroxypyridine in the presence of silica sulfuric acid under heterogeneous and solvent-free conditions.

N. Sekar et al., 46 developed a protocol for the preparation of benzimidazoles,benzoxazoles, and benzothiazoles from reactions of aldehydes with *o*-substitutedaminoaromatics in the presence of catalytic amount of Indion 190 resin in ethanolsolvent at 70oC and obtained high yields of the products.*Chapter -2 Benzoxazole,*

John Blacker et al., 47 developed ruthenium-catalyzed hydrogen-transfer reactionsfor the conversion of alcohols and aldehydes intobenzoxazoles

K.V.Srinivasan et al., 48 described a regioselective one-pot synthesis of 2-arylbenzimidazoles, benzoxazoles and benzothiazoles and isolated high yields ofproducts under ambient conditions using the ionic liquids, 1-butylimidazoliumtetrafluoroborate ([Hbim]BF4) and 1,3-di-*n*-butylimidazolium tetrafluoroborate([bbim]BF4) as reaction media and promoters.

A. K. Chakraborti et al.,49 reported an efficient conversion of carboxylic acids tobenzothiazoles by direct condensation with 2-aminothiophenol under microwaveirradiation in the absence of solvent.

A. K. Chakraborti et al.,50 described a method for direct coupling of carboxylicacids with 2-aminophenol under microwave conditions to get 2-substitutedbenzoxazoles under metal and solvent-free conditions.

A. K. Chakraborti et al.,51 described that methanesulphonic acid has been found tobe a highly effective catalyst for a convenient and one-pot synthesis of 2-substituted benzoxazoles by the reaction of 2-aminophenol with acid chlorides.

T. Punniyamurthy et al.,52 developed a method for copper(II)-catalyzed conversionof bisaryloxime ethers to 2-arylbenzoxazoles. The reaction involves a cascade C−Hfunctionalization and C−N/C−O bond formation under oxygen atmosphere.

T. Punniyamurthy et al.,53 reported a synthesis of substituted benzimidazoles, 2-aminobenzimidazoles, 2-aminobenzothiazoles, and benzoxazoles viaintramolecular cyclization of *o*-bromoaryl derivatives using copper(II) oxidenanoparticles in DMSO under air.

P. T. Perumal et al.,54 reported that Pyridiniumchlorochromate (PCC) supportedon silica gel effects the oxidative cyclization of structurally diverse thiophenolicand Phenolic Schiff's bases, thereby providing an efficient and convenient methodfor the synthesis of a library of 2-arylbenzothiazoles and 2-arylbenzoxazoles.

M. R. Player et al.,55 developed for synthesis of benzoxazoles by using microwaveassisted dielectric heating.

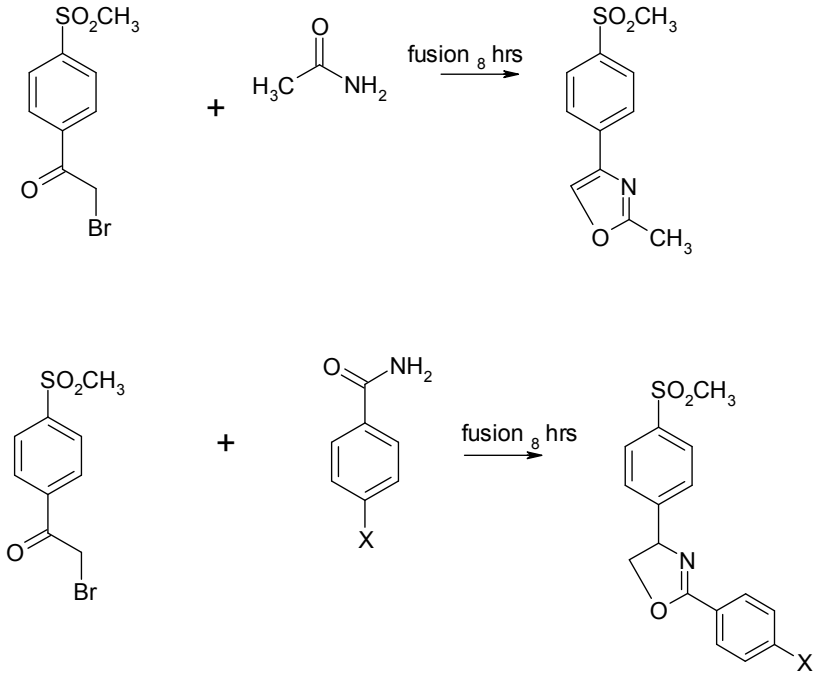
Masahiko Hayashi et al.,56 described that 2-arylbenzoxazoles were directlysynthesized from substituted 2-aminophenols and aldehydes in the presence ofactivated carbon (Darco KB) in Xylene under an oxygen atmosphere.Wang, Lei et al.,57 reported for the synthesis of benzoxazole derivatives throughthe reaction of substituted 2-aminophenols and acyl chlorides in the presence ofcatalytic amount of In(OTf)3 under solvent-free reaction conditions.S. C. Shim et al.,58 reported that 2-amino phenols react with an array of carboxylicacids in Dioxane at 180oC in the presence of tin(II)chloride to afford thecorresponding 2-substitued benzoxazole in good yields.

EXPERIMENTAL SECTION

2.1. Chemistry:

All melting points are corrected and determined by the open capillary method using IA9100MK- Digital Melting Point Griffin Apparatus.. Infrared spectra were made on BRUKER Vector 22 (Japan), infrared spectrophotometers and were expressed in wavenumber (cm-1) using potassium bromide disc, at the microanalytical Center, Faculty of Science, Cairo University. The proton magnetic resonance ^{1}H-NMR and carbon magnetic resonance ^{13}C-NMR were recorded on a Bruker Avance III 400 MHz for ^{1}H and 100 MHz for ^{13}C (Bruker AG, Switzerland) with BBFO Smart Probe and Bruker 400 AEON Nitrogen-Free Magnet. Mass spectra were recorded on Fennigan MAT, SSQ 7000, Mass spectrometer, at 70 eV (EI) at the microanalytical Center, Faculty of Science, Cairo University and Waters Micromass Q-Tof Micro mass spectrometer (ESI) and Waters Acquity Ultra Performance LC with ZQ detector in ESI mode. All the compounds were named according to the IUPAC system using CS Chem. Draw Ultra version 12.0. Thin layer chromatography, using Macherey–Nagel AlugramSil G/UV254 silica gel plates and ethyl acetate-hexane as the eluting system.

Scheme



V2:X=CL
V3:X=Amino

number	Code	COX1 µm IC 50	COX2 µm IC 50
1-	Celecoxib	14.8	0.05
V1	Acetamide	3.41	.33
V2	Chloro phenyl oxazole	7.11	.69
V3	Amino phenyl oxzole	6.97	.81

2.1.1. ***General method for preparation of (4-(methyl sulfonyl)phenyl)oxazole(V1-V3)***

Amide(.145g,.898 mmol) and (methyl sulfonyl)benzoyl bromide (200 g,.749mmol) were placed in asealed tube and heated at 150^{o}C for 4 h. The reaction mixture was quenched with ethyl acetate and the residue was purified by column chromatography (gradient 100;1,20:1 hexane:dichloromethane).The Product was further Purified by Preparative-TLC(100:1,hexane:dichloromethane)to yield 0.0148 g(5%) of the Title compound as Awhite solid2-methyl-4-(4-(methyl sulfonyl)phenyl)oxazole (V1)yield 60%; mp:190-200^{o}C.^{1}H-NMR (DMSO-d_6) δ ppm:3.1(s,3H,SO_2CH_3).2.35(s,3H,CH3),7.5(s,1H,CH),7,99(d,2H,c2,6),7,76,(d,2H,c3,5).^{13}C-NMR (DMSO-d6) δ ppm:44,3(So_2CH3),138,9(C1),128,8(c2,6),128,5(c3,5),138.1(C6),oxazole ring165(c2),139,9(C4).140.1(c5) ,14,2(CH3)2-(4-chlorophenyl)-4-(4-(methyl sulonyl)phenyl)oxazole (V2)Yield 70%; mp:170-180^{o}C.^{1}H-NMR (DMSO-d_6) δ3.1(s,3H,SO2CH3)7.5(s,1H,CH),7,99(d,2H,c2,6),7,76,(d,2H,c3,5),cl benzene,7,42(d,2H,C2,6)7.33(d,2H,C3,5).^{13}C-NMR (DMSO-d6) δ ppm:44,3(So_2CH3),138,9(c1),128,8(c2,6),128,5(c3,5),138.1(C6),oxazole ring165(c2),139,9(C4).140.1(c5)benzene.129.1(c4,6),116(c1,3),162,9(c2),121.8(c5)4-(4-(4-(methyl sulfonyl)phenyl)oxazole-2 yl)benzenamine(V3)Yield 55%; mp:145-150^{o}C.^{1}H-NMR (DMS3.1(s,3H,SO2CH3)7.5(s,1H,CH),7,99(d,2H,c2,6),7,76,(d,2H,c3,5) benzene7,23(d,2H,c2,6),6,52(d,2H,c3,5),11(2H,NH2)).^{13}C-NMR(DMSO-d6) δ ppm:44,3(So2CH3),138,9(c1),128,8(c2,6),128,5(c3,5),138.1(C6),oxazolering159(c2),139,9(C4).140.1(c5)benzene.1 16.8(C2,6),128.3(c3,5),116.2(c4),148,4(c1)

2.2.Antiinflammatory activity

BY COX Inhibitor screening assay kit

- ***Materials Needed***

1. A plate reader capable of measuring absorbance between 405-420 nm.
2. Adjustable pipettes and a repeat pipettor.
3. A source of 'UltraPure' water. Water used to prepare all EIA reagents and buffers must be deionized and free of trace organic contaminants ('UltraPure'). Use activated carbon filter cartridges or other organic scavengers. Glass distilled water (even if double distilled), HPLC-grade water, and sterile water (for injections) are not adequate for EIA. NOTE: UltraPure water is available for purchase from Cayman (Itetn No. 400000).
4. A 37°C water bath that can hold a test tube rack.
5. Disposable glass test tubes (13 mm x 100 mm).
6. Materials used for purification procedure

About This Assay

The COX (ovine) Inhibitor Screening Assay directly measures PGF2a by SnCl2 reduction of COX-derived PGH-, produced in the COX reaction. The prostanoid product is quantified via enzyme immunoassay (EIA) using a broadly specific antiserum that binds to all the major PG compounds.

This assay includes both ovine COX-1 and human recombinant COX-2 enzymes allowing the user to screen isozyme-specific inhibitors. This assay is an excellent tool which can be used for general inhibitor screening, or to eliminate false positive leads generated by less specific methods.

COX REACTION PROCEDURE

The use of both enzymes is not a requirement of the assay; one or both enzymes may be used depending on the nature of the study. TheEIA plate will allow for 36 COX reactions (in duplicate) at one dilution or 18 COX reactions (in duplicate) at two dilutions.

IMPORTANT: Please read both COX Reaction Procedure and EIA Procedure sections carefully before initiating your experiments!

COX Reagent Preparation

1. Reaction Buffer (10X) - (Item No. 460104)

Dilute 5 ml of Reaction Buffer concentrate with 45 ml of UltraPure water. This final Reaction Buffer (0.1 M Tris-HCl, pH 8.0, containing 5 mM EDTA and 2 mM phenol) is used in the COX reactions and for dilution of Heme. When stored at room temperature, this diluted Reaction Buffer is stable for at least one month. Equilibrate the diluted Reaction Buffer to 37°C before using in the COX reactions.

2. COX-1 (ovine) - (Item No. 460100)
This vial contains a solution of ovine COX-1. To avoid repeated freezing and thawing, the COX-1 should be aliquoted into several small vials and stored at -80°C. The enzyme is ready to use as supplied and should be kept on ice when thawed. There is enough COX-1 supplied to perform 40 reactions.

3. COX-2 (human recombinant) - (Item No. 460121)
This vial contains a solution of human recombinant COX-2. To avoid repeated freezing and thawing, the COX-2 should be aliquoted into several small vials and stored at -80°C. The enzyme is ready to use as supplied and should be kept on ice when thawed. There is enough COX-2 supplied to perform 40 reactions.

4. Heme - (Item No. 460102)
This vial contains a solution of Heme in dimethylsulfoxide (DMSO). Dilute 100 pi of Heme with 400 pi of IX Reaction Buffer prior to use. The diluted Heme is stable for 12 hours at room temperature.
5. Arachidonic Acid (Substrate) - (Item No. 460103)
This vial contains a solution of Arachidonic Acid in ethanol. Transfer 50 pi of the supplied Substrate to another vial, add 50 pi of Potassium Hydroxide (Item No. 460105), vortex, and dilute with 400 pi of UltraPure water to achieve a final concentration of 10 mM. Use the prepared Arachidonic Acid Solution within one hour. A 10 pi aliquot of the prepared substrate will yield a final concentration of 100 pM in the reaction.

6. Potassium Hydroxide - (Item No. 460105)
This vial contains 0.1 M Potassium Hydroxide (KOH). The reagent is ready to use as supplied.

7. Hydrochloric Acid - (Item No. 460106)
This vial contains 1 M Hydrochloric Acid (HC1). Dilute 500 pi with 4.5 ml of UltraPure water to yield a concentration of 0.1 M. This diluted HC1 is used to prepare the saturated Stannous Chloride Solution. Both HC1 solutions are stable for at least one month at room temperature.

8. Stannous Chloride - (Item No. 460107)
This vial contains crystalline Stannous Chloride. Add 5 ml of 0.1 M HC1 and vortex to produce a saturated solution of Stannous Chloride. (This saturated Stannous Chloride Solution may be cloudy.) This solution is stable for eight hours at room temperature. If not performing all of the COX reactions in one day, weigh 125 mg of Stannous Chloride into another vial and add 2.5 ml of 0.1 M HC1. 100 pi of saturated Stannous Chloride is required for each reaction. NOTE: Stannous Chloride is used to reduce PGEI2, produced in the COX reaction, to a more stable PC, PGF2ccPerforming COX Reactions

Pipetting Hints
• It is recommended that a repeating pipettor be used to deliver Arachidonic Acid to the test tubes. This saves time and helps to maintain more precise incubation times.
• Use different tips to pipette the buffer, enzyme, Heme, inhibitor, and Arachidonic Acid.
• Before pipetting each reagent, equilibrate the pipette tip in that reagent (i.e., slowly fill the tip and gently expel the contents, repeat several times).
• Do not expose the pipette tip to the reagent(s) already in the test tube.

5. COX-2 Inhibitor tubes - add 950 pi of Reaction Buffer, 10 pi of Heme, and 10 pi of COX-2 to six test tubes.
6. Add 20 pi of inhibitor to the COX-1 and -2 inhibitor tubes and 20 pi of Reaction Buffer or solvent to the 100% Initial Activity tubes and vortex.
7. Incubate for 10 minutes at 37°C. NOTE: The incubation of the enzymes with the inhibitor can be between 10 and 20 minutes without affecting enzyme stability, but the incubation time MUST be the same for all samples in an individual experiment.
8. Initiate the reaction by adding 10 pi of Arachidonic Acid to all the test tubes. Vortex and incubate for another two minutes at 37°C.
9. Add 50 pi of 1 M HC1 to each test tube to stop enzyme catalysis. Remove test tubes from the water bath, add 100 pi of the saturated Stannous Chloride Solution to each test tube and vortex. Incubate for five minutes at room temperature. The reaction mixture will be cloudyCalculations

Preparation of the Data
The following procedure is recommended for preparation of the data prior to graphical analysis.

NOTE: If the plate reader has not subtracted the absorbance readings of the blank wells from the absorbance readings of the rest of the plate, be sure to do that now.

1. Average the absorbance readings from the NSB wells.
2. Average the absorbance readings from the B0 wells.
3. Subtract the NSB average from the B0 average. This is the corrected B0 or corrected maximum binding.
4. Calculate the %B/B0 (% Sample or Standard Bound/Maximum Bound) for the remaining wells. To do this, subtract the average NSB absorbance from the Si absorbance and divide by the corrected B0 (from Step 3). Multiply by 100 to obtain %B/Bq. Repeat for S2-S8 and all sample wells.

NOTE: The total activity (TA) values are not used in the standard curve calculations. Rather, they are used as a diagnostic tool; the corrected Bg divided by the actual TA (10X measured absorbance) will give the % Bound. This value should closely approximate the % Bound that can be calculated from the Sample Data (see page 25). Erratic absorbance values and a low (or no) % Bound could indicate the presence of organic solvents in the buffer or other technical problems (see page 31 for Troubleshooting).

If you have purified your samples (see Interference, page 29), the final sample concentrations can be determined Plot the Standard Curve

Plot %B/B0 for standards S1-S8 versus Prostaglandin concentration using linear (y) and log (x) axes and perform a 4-parameter logistic fit.

Alternative Plot - The data can also be lineraized using a logit transformation. The equation for this conversion is shown below. NOTE: Do not use %B/Bg in this calculation.

logit (B/B0) = In [B/B0/(l - B/B0)]

Plot the data as logit (B/B0) versus log concentrations and perform a linear regression fit.

RESULTS AND DISCUSSION

3.1. Chemistry

The synthetic approaches adopted to obtain the target compounds v1-v3 were depicted in scheme 1.The structures of the newly synthesized compounds were established on the basis of their elemental analyses and spectral data bromoacetophenonea was the key starting material for the new oxazole dervatives V1-V3 .They were synthesized in good yields upon the fusion of amide b and bromoacetophenone a for 8 hrs The H1-NMR of Theses copounds showing 8.1 (CH)

3.2. Anti-inflammatory screening

All the 3 newly synthesized compounds(10mg|ml)were screened for anti-inflammatory activity using Cox1,Cox2

CONCLUSION

The newly synthesized compounds V1-V3presented here differed in their corresponding anti-inflammatory activity depending on the type of the derivative hybridized to the benzo oxazole moiety. The derivative having the electron withdrawing Cl group at the p-position of benzene ring attached at the 2-position of oxazole ring showed the highest activity.

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