

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/268007830>

New Benzimidazolo Indane-1, 3-Dione Derivatives: Synthesis and In-vitro Screening Against Helminthic Infections

Article

CITATIONS

0

READS

51

7 authors, including:



Dr. Jubie Jawahar

JSS College of Pharmacy

37 PUBLICATIONS 304 CITATIONS

SEE PROFILE



Gayathri Rajamanickam

Quest international University perak

5 PUBLICATIONS 17 CITATIONS

SEE PROFILE



ammayappan rajam Srividya

Aditya Institutes

32 PUBLICATIONS 99 CITATIONS

SEE PROFILE



Kalirajan R

JSS University

32 PUBLICATIONS 257 CITATIONS

SEE PROFILE

Some of the authors of this publication are also working on these related projects:



it is a separate project [View project](#)



genotoxicity project [View project](#)

New Benzimidazolo Indane-1, 3-Dione Derivatives: Synthesis and *In-vitro* Screening Against Helminthic Infections

S. Jubie*, R. Gayathri, A.R. Srividya^b, R. Kalirajan, S. Suresh^c, S. Sankar and K. Elango

Department of Pharmaceutical Chemistry,

^bDepartment of Pharmaceutical Biotechnology J.S.S. College of Pharmacy, Off Campus-JSS University, Mysore.

^cDepartment of Anatomy, All India Institute of Medical Sciences, New Delhi.

ABSTRACT: Novel benzimidazolo indane-1, 3-dione derivatives were synthesized and characterized by IR, ¹HNMR and Mass spectral analysis. Biological screening of synthesized compounds allowed the identification of some novel anthelmintic agents bearing indane-1, 3-dione and benzimidazole scaffolds. Some of these compounds exhibited promising anthelmintic activities.

KEYWORDS: Indane-1, 3-dione; 1, 3-dioxo-1, 2, 3 - trihydro indane-6-sulphonyl benzimidazole derivatives; electrophilic substitution; anthelmintic activity

Introduction

Indane-1, 3-dione and its derivatives are important organic compounds due to their wide range of their pharmacological and biological activities [1]. It was synthesized a hundred years ago; chemists have paid a lot of attention to this compound with dyeing properties due to its easy self condensation under both acid and basic conditions [2]. The last two decades have witnessed profound changes in indane-1, 3- dione chemistry both in quality and quantity. Indane-1, 3-dione constitutes a unique group of compounds due to its 1, 3-dicarbonyl nature. It has wide range of biological activity covering anticoagulant, bactericidal, neurotropic, antiphlogistic, radioprotective effects, zoocide, insecticide, and fungicide [3]. Specific physiochemical properties which offer wide scope for studies in the problems of theoretical organic chemistry, particularly on the basis of tautomerism, dual reactivity, electrochemical redox and corresponding quantum chemical calculations, unique properties of polycrystalline films etc [4]. In past decades, benzimidazole and its derivatives have received much attention due to their chemotherapeutic value in the development of novel anthelmintic and antimicrobial agents. The most commonly used classes of drugs to treat such infections are the benzimidazoles [5]. In this work,

we turned our interest to study the incorporation of different benzimidazoles on the indane-1, 3- dione via the sulphonyl chloride moiety, in order to afford a variety of new derivatives of our lead compound.

Results and discussion

Chemistry

The starting material compound **1**, indane-1, 3-dione was synthesized in good yield: by the reaction of diethyl phthalate with ethyl acetate. The IR spectrum of compound **1** exhibited absorption bands at 1722.4 cm⁻¹ due to C=O and 1460 cm⁻¹ due to CH₂ groups. Additional support for the structure of compound **1** was obtained by recording its ¹HNMR spectra, which exhibited a singlet at δ 3.3 due to CH₂ protons. Treatment of compound **1** with chlorosulphonic acid undergone electrophilic substitution on the aromatic ring and afforded compound **2**, indane-1, 3-dione sulphonyl chloride. The IR Spectrum of compound **2** exhibited absorption band at 1201 cm⁻¹ due to SO₂Cl stretching. The latter compound is useful intermediate for the synthesis of our titled compounds. Different compounds **a-e**, benzimidazoles obtained by the cyclocondensation of o-phenylene diamine with different acids were incorporated on compound **2**, to give the resultant novel compounds **3a-e**. The ¹HNMR spectra of these compounds showed a singlet at 2.5 ppm corresponding to the NH group of benzimidazole.

* For correspondence: S. Jubie,

E-mail: jubiejawahar@gmail.com

Biology

The synthesized compounds demonstrated paralysis as well as death of adult earthworm (*Pheretima posthuma*) in time as compared to piperazine citrate. The more interesting result could be observed in the treatment of compound **3b** and Compound **3c** especially at the concentration of 25 mg/ml exhibited significant activities. The results are mentioned in Table 1.

Experimental

Chemistry

Indane- 1,3-dione (**1**) and benzimidazoles (**a-e**) were prepared according to the literature methods [3, 6]. Melting

points were taken in open glass capillary using Veego VMP-1 melting point apparatus and are uncorrected. The identification and purity of the synthesized compounds were checked by thin layer chromatography using silica gel G as an adsorbent. The spots were detected by exposure to iodine vapor. Infrared spectra of compounds were recorded on Shimadzu FT-IR spectrometer model using KBr pellet technique. Proton (^1H) NMR spectra of compounds were recorded on Bruker DRX-300 (300 MHz FT-NMR) using DMSO- d_6 as solvent and TMS as an Internal standard. Mass spectra were obtained using Shimadzu LCMS 2010A.

Table 1 Anthelmintic activity of indane-1, 3-dione derivatives

Compound	Conc (mg/mL)	Time taken for Paralysis (Mean \pm SEM)	Time taken for Death (Mean \pm SEM)
3a	25	25.07 \pm 0.0577	32.83 \pm 0.5823
	50	22.05 \pm 0.2449	28.75 \pm 0.2500
	100	15.43 \pm 0.1282	20.85 \pm 0.1408
3b	25	20.5 \pm 0.2963	28.55 \pm 0.1176
	50	17.5 \pm 0.1155	20.38 \pm 0.1138
	100	11.58 \pm 0.1302	18.5 \pm 0.1302
3c	25	19.2 \pm 0.0872	32.9 \pm 0.4655
	50	14.6 \pm 0.1352	23.63 \pm 0.3084
	100	11.1 \pm 0.1054	20.25 \pm 0.09916
3d	25	15.6 \pm 0.1291	21.5 \pm 0.2236
	50	15.47 \pm 0.1022	18.2 \pm 0.7664
	100	12.56 \pm 0.1408	13.42 \pm 0.08724
3e	25	19.3 \pm 0.07303	25.47 \pm 0.1256
	50	15.4 \pm 0.0802	15.52 \pm 0.1276
	100	13.5 \pm 0.1155	11.45 \pm 0.0991

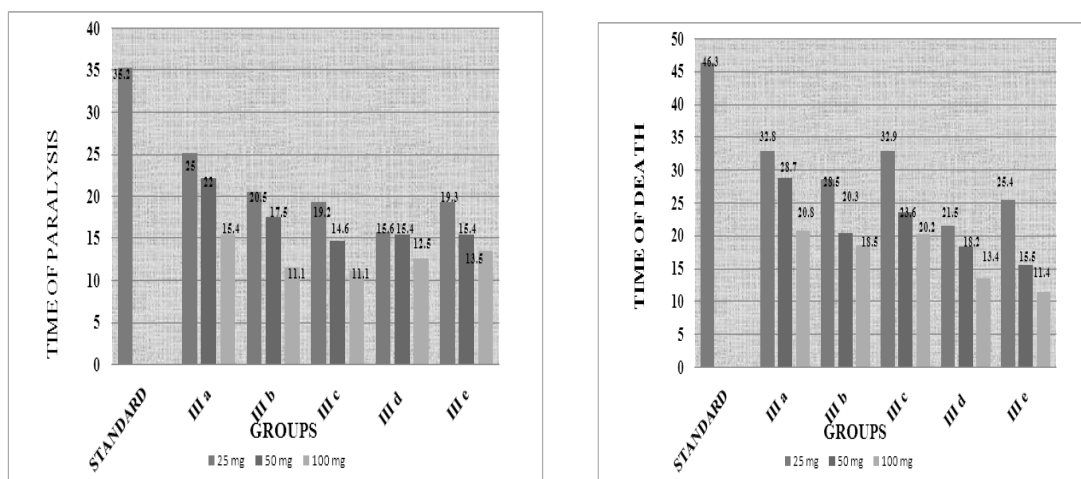


Fig. 1 Graph showing difference in time of paralysis & time of death in anthelmintic activity

Synthesis of 1, 3-dioxo-1, 2, 3 –trihydro indane -6-sulphonylchloride (2)

Indane-1, 3- dione (0.03 mole, 4.86 g) was added portionwise to chlorosulphonic acid (0.27 mole, 17.9 mL) at 0°C. After being stirred for 10 h at room temperature, the reaction solution was added to ice-water and then filtered. The resulting solid was washed with water and recrystallized from dry dioxan-benzene mixture to give white crystals **2** to yield (90%), mp 140-142 ° C; R_f (benzene/acetone 3:1) 0.39; IR (KBr) 1712 (C=O), 1201.6 (SO₂Cl), 1464 (cyclopentane C-H), 1363 (SO₂), 597.9 (Cl), 742 (Ar C-H) cm⁻¹; ¹H-NMR (DMSO-d₆, 300 MHz) δ 6.8 (m, 3H, Ar-H), 2.5 (s, 2H, CH₂). ms: m/z = found 246.35 (M+).

General Procedure for the synthesis of compounds (3)

1,3-dioxo-indane- 6- sulphonyl chloride (0.01 mole, 2.4 g) was dissolved in dry dimethyl sulphoxide (20 mL) followed by addition of benzimidazole derivatives (0.02 mole) and the mixture was kept under stirring at room temperature for 10 h. The resulting mixture was then poured into water (50 mL) to give a foamy precipitate and recrystallized from hot water.

2, 3-dioxo -1, 2, 3, 4-tetrahydroquinoxaline-6-sulphonylbenzimidazole

This compound was obtained as a white solid (57%), mp >360°C; R_f (chloroform/methanol 9:1) 0.45; IR (KBr): 1712 (C=O), 1610 (C=N), 1458 (cyclopentane C-H), 1363 (SO₂), 742 (Ar C-H) cm⁻¹; ¹H-NMR (DMSO-d₆, 300 MHz) δ: 3.3 (s, 2H, CH₂), 7.1-7.2(m, 3H, Ar-H), 7.5-7.9(m, 4H, Ar-H benzimidazole), 5.3(d, 1H, CH benzimidazole), 2.5(d, 1H, NH benzimidazole); ms: m/z = found 328.50 (M+).

2, 3-dioxo-1, 2, 3, 4-tetrahydroquinoxaline-6-sulphonyl (2-methyl) benzimidazole

This compound was obtained as a white solid (58%), mp >360°C; R_f (chloroform/methanol 9:1) 0.34; IR (KBr): 1712(C=O), 1610 (C=N), 1458 (cyclopentane C-H), 1363 (SO₂), 742 (Ar C-H) cm⁻¹; ¹H-NMR (DMSO-d₆) δ: 3.3 (s, 2H, CH₂), 7.2-7.3 (m, 3H, Ar-H), 7.5-7.8 (m, 4H, Ar-H benzimidazole), 2.6 (d, 1H, NH benzimidazole), 2.3 (t, 3H, CH₃ benzimidazole), 2.5 (m, 1H, CH benzimidazole); ms: m/z = found 343.45 (M+).

2, 3-dioxo -1, 2, 3, 4-tetrahydroquinoxaline-6-sulphonyl (2-ethyl) benzimidazole

This compound was obtained as a white solid (47%), mp >360°C; R_f (chloroform/methanol 9:1) 0.27; IR (KBr) 1718(C=O), 1650 (C=N), 1440 (cyclopentane CH), 1367 (SO₂), 754 (Ar C-H) cm⁻¹; ¹H-NMR (DMSO-d₆) δ: 3.5 (s, 2H, CH₂), 3.8 (m, 1H, CH benzimidazole), 6.8 (m, 3H, Ar-H), 7.8 (m, 4H, Ar-H benzimidazole), 4.1 (d, 1H, NH

benzimidazole), 2.1 (t, 3H, CH₃ benzimidazole); ms: m/z = found 356.73(M+).

2, 3-dioxo-1, 2, 3, 4-tetrahydroquinoxaline-6-sulphonyl (2-propyl) benzimidazole

This compound was obtained as a white solid (46%), mp >360°C; R_f (chloroform/methanol 9:1) 0.23; IR (KBr): 1712(C=O), 1651 (C=N), 1448(cyclopentane C-H), 1370(SO₂), 750 (Ar C-H) cm⁻¹; ¹H-NMR (DMSO-d₆) δ: 3.8(s, 2H, CH₂), 3.8 (m, 1H, CH benzimidazole), 6.5 (m, 3H, Ar-H), 7.2 (m, 4H, Ar-H benzimidazole), 4.1 (d, 1H, NH benzimidazole), 1.6 (m, 2H, CH₂-CH₂-CH₃), 1.4(m, 2H, CH₂-CH₃), 2.1 (t, 3H, CH₃ benzimidazole); ms: m/z = found 371.45 (M+).

2, 3-dioxo-1, 2, 3, 4-tetrahydroquinoxaline-6-sulphonyl (2-acetyl) benzimidazole

This compound was obtained as a white solid (42%), mp >360°C; R_f (chloroform/methanol 9:1) 0.22; IR (KBr) 1712(C=O), 1657 (C=N), 1456 (cyclopentane C-H), 1370(SO₂), 758(Ar C-H) cm⁻¹; ¹H-NMR (DMSO-d₆) δ: 3.8(s, 2H, CH₂), 4.2 (m, 1H, CH benzimidazole), 6.8 (m, 3H, Ar-H), 7.0 (m, 4H, Ar-H benzimidazole), 4.1(d, 1H, NH benzimidazole), 2.1(t, 3H, CH₃ benzimidazole); ms: m/z = found 370.14 (M+).

Biology**Anthelmintic activity**

The anthelmintic assay was carried as per the method of Ajaiyeoba et al [7] with minor modifications [8]. The assay was performed on adult earthworm (*Pheretima posthuma*) owing to its anatomical and physiological resemblance with the intestinal roundworm parasites of human beings. Because of easy availability, earthworm has been used extensively for preliminary *in vitro* evaluation of anthelmintic compounds. The drug is insoluble in water hence it was made as suspension with water for injection using 0.05% carboxy methyl cellulose as suspending agent. Three concentrations (25, 50 and 100 mg/mL) of each compound were prepared. Piperazine citrate (25 mg/mL) was used as reference standard and distilled water as control. Time for paralysis was noted when no movement of any sort could be observed except when the worms were shaken vigorously. Time for death of worms was recorded after ascertaining that worms neither moved when shaken vigorously nor when dipped in warm water (50°C).

References

- [1] Jubie, S.; Meena, S.; Ramseshu, K.V.; Jawahar, N.; Vijayakumar.; *Ind J Chem.* **2010**, 49 B, 1261.
- [2] Roberto, H.; Belen, B.; Fructuoso, B.; Avelino, M.; *Tetrahedron Lett.* **2007**, 47, 6437.

- [3] Meena, S.; Shankar, D.; Ramseshu, K.V.; Giles, D.; Ind J Chem. **2006**, 45 B, 1572.
- [4] Giles, D.; Prakash, M.S.; Ramseshu, K.V.; E J Chem. **2007**, 4,328.
- [5] Akbar, M. ; Naser, M. ; Mansourch, M. J Heterocycl Chem. **2010**, 47, 77.
- [6] Ashutosh, K.B.; Hasanali, K.P.R.S.; Manish P.P.; H.D.P. Indian J heterocycl Chem. **2003**, 13, 187.
- [7] Ajaiyeoba, E.O.; Onocha, P.A.; Olarenwaju, O.T.; Pharm Bio. **2001**, 39, 217.
- [8] Satish, B.K.; Ravindra, A.F.; Int J Pharm Tech Res. **2009**,1,68.