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SYNTHESIS AND BIOLOGICAL ACITIVITY OF SOME THIAZINE SUBSTITUTED BENZOXAZOLES

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ABSTRACT

Some new 3,5–diaryl–4–(2–ethoxybenzoxazol–2–yl)–tetrahydro–1,4–thiazine 1,1–dioxides (**2 a–c**) and 2,5–dimethoxycarbonyl–3,5–diaryl–4–(2–ethoxybenzoxazol–2–yl)–tetrahydro–1,4–thiazine–1,1–dioxides (**2 d–f**) have been synthesized and a preliminary screening of antibacterial, antifungal, acute toxicity and antihistaminic activities was made. The structures of the synthesized compounds have been established by spectral data (IR, ^{1}H–NMR, ^{13}C–NMR).

Key words: Benzoxazoles, Thiazines, Antibacterial, Antifungal, Antihistaminic

INTRODUCTION

Heterocyclic compounds containing nitrogen and sulphur possess potential pharmacological properties[1–4]. Benzoxazoles derivatives constitute an important class of compounds possessing diverse types of biological properties[5]. In continuation of our on going research program on newer benzoxazole derivatives of biological significance, we synthesized some 3,5–diaryl–4–(2–ethoxybenzoxazol–2–yl)–tetrahydro–1,4–thiazine, 1–dioxides (**2 a–c**) and 2,5–dimethoxycarbonyl–3,5–diaryl–4–(2–ethoxybenzoxazol–2–yl)–tetrahydro–1,4–thiazine–1, 1–dioxides (**2 d–f**). A preliminary evaluation was done for their antibacterial, antifungal, acute toxicity and antihistaminic activities.

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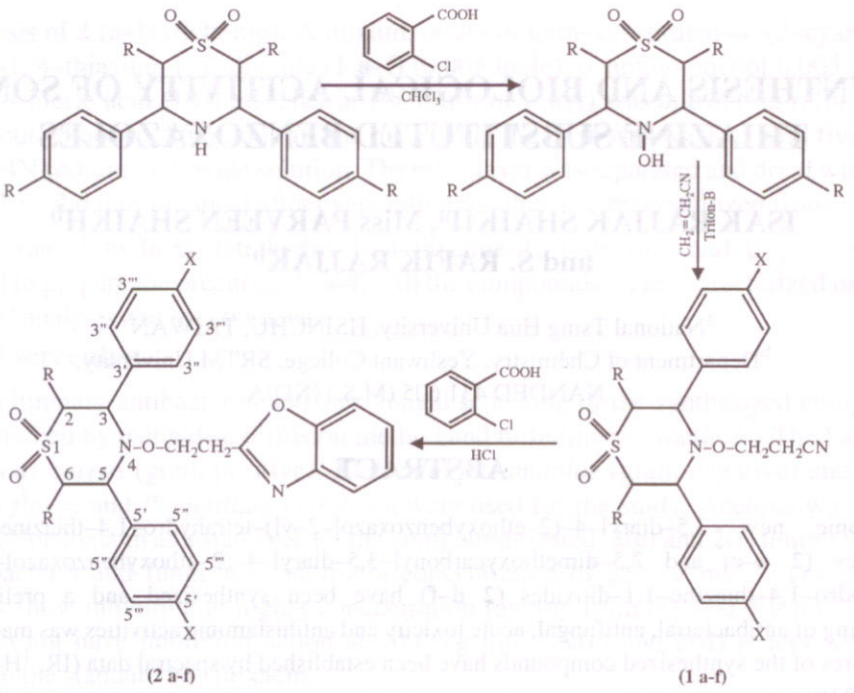
(Dedicated to Professor Rai–Shung Liu, National Tsing Hua University, Taiwan on the occasion of his 50th birthday)



Compound	R	X	Compound	R	X
2 (a)	H	H	2 (d)	$COOCH_3$	H
2 (b)	H	OCH_3	2 (e)	$COOCH_3$	OCH_3
2 (c)	H	Cl	2 (f)	$COOCH_3$	Cl

Table 1. Physical properties

Compound	Melting	Yield (%)
2 (a)	254	56
2 (b)	259	54
2 (c)	258	60
2 (d)	253	40
2 (e)	255	40
2 (f)	259	56

* All compounds gave correct C, H, N analysis.

Spectral Data

Compounds 2 a–f

IR peak at 1750–1730 cm^{-1} confirms the carbonyl group stretching vibrations in the ester group.

^{1}H–NMR : Two different methylenic protons in the side chain linking the thiazine moiety with the benzoxazole molecule at C–2 provided two characteristic triplets at δ 2.40 and 3.61. The aromatic protons gave the multiplet in the range of 7.2–7.4 δ. The methoxy protons of the anisyl substituted thiazine derivative gave a characteristic singlet at δ 3.8. In **2 (b)** and **2 (e)**, two sets of singlets are observed for the aryl groups at around 6.8 and 7.21 to 7.5 ppm. In most of the para–methoxy compounds, the ortho–protons with respective methoxy group are absorbed in the up field region around 6.8–6.9 ppm. In compounds **2 (c)** and **2 (f)**, since the benzoxazole aromatic signals are merged with the para–chloro phenyl signals, it is difficult to distinguish the signals of ortho–protons and meta–protons with respect to chlorine substituents in para chloro phenyl groups present at C–3 and C–5 positions of the six membered heterocyclic moiety. Hence, the observed multiplet rather than two sets of signals in the region of around 7.2–7.5 ppm is characteristic for aryl protons. The assignments for the rest of the signals have been made on the basis of comparison with the di– and tetra– substituted N–hydroxy thiazines and 4–(2–cyanoethoxy) di– and tetra–substituted tetrahydrothiaine–1, 1–dioxide[6].

^{13}C–NMR: 163 ppm is for the C^b of the benzoxazole. This deshielding absorption of benoxazole may be due to the influence of $–CH_2CH_2O$ moiety. Absorptions at 110, 114, 119, 133 and 143 ppm are due to the rest of the carbons present in the benzoxazole moiety. Absorptions observed at 127–129 ppm are because of the aryl carbons at C–3, C–5 ipso carbon (140.20 ppm) in the downfield region than that of the rest of the aromatic carbons. Peaks at 159.67 and 159.01 ppm in **2 (b)** and **2 (e)** respectively are characteristic of methoxy group having ipso carbons at C–5 and C–7.

The assignment of the thiazine ring carbons along with the side chain is made on the methylenic carbon on the basis of comparison of the signals with that for 1,4–thiazine–1,1–dioxide and its N–hydroxy analogues (starting materials).

The thiazine ring carbons and side chain methylenic carbons in **2 (a)** and **2 (d)** are observed at around 55, 69 and 27 ppm. The signals at 67 ppm is characteristic for side chain methylenic carbon connected to oxygen and a signal resonating at 20 ppm is assigned to another side chain methylenic carbon attached to benzoxazole moiety. In addition, a signal observed at 53–54 ppm in **2 (b)** and **2 (e)** is characteristic for methoxy carbon at C–3 and C–5 positions of aromatic compounds.

EXPERIMENTAL

The melting points were determined on a MEL–Temp apparatus by open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Perkin Elmer–597 spectrometer. ^{1}H–NMR spectra were recorded on a Bruker WH200 spectrophotometer in $CDCl_3$ using TMS as an internal standard. The purity of the compounds was checked by the thin layer chromatography (TLC) on silica gel plate.

Synthesis of 2 (a–f) (Scheme): A mixture of di– or tetra–substituted–4–(2–cyanoethoxy–tetrahydro–1, 4–thiazine–1, 1–dioxide (**1 a–f**) (0.005 mole), o–amino phenol 0.005 mole) and dilute hydrochloric acid (10.0 mL HCl in 100.0 mL of water) was allowed to reflux in an oil bath for about 18 hours. After cooling, the material in the flask was washed with five 25.0 mL portions of 4N sodium hydroxide solution. The ether layer was separated and dried with calcium chloride. The solid thus obtained after evaporation of ether was recrystallized from ethanol.

Firstly, the N–hydroxy–tetrahydro–1, 4–thiazine–1, 1–dioxide and their nitriles were synthesized to prepare the precursor **1** (**a–f**). All the compounds were characterized on the basis of elemental analysis and spectra data.

Biological screening

The preliminary antibacterial and anti–fungal screening of the synthesized compounds (**2 a–f**) were studied by using disc diffusion method and turbidimetric method[7]. The bacteria viz. *Stahylococcus aureus* (gram positive), *Klebsiella pneumoniae* (gram negative) and the fungi *Aspergillus flavus* and *Penicillium inclobium* were used for the study. Acetone was used as a control and Norfloxacin as a standard. Of the compounds tested, **2(c)** and **2(f)** inhibit the growth of tested bacteria and fungi at a minimum concentration of 25 %g mL^{-1}. The rest of the compounds show inhibition at higher concentration ranging from 50–200 %g mL^{-1} and **2(a)** and **2(d)** do not have inhibition action at 200 %g mL^{-1}. **2(c)** and **2(d)** is less active when compared to the standard Norfloxacin.

Acute toxicity studies

Acute toxicity studies were carried out for the compounds **2(c)** and **2(f)** using five groups of albino mice for each compound and each group comprised of 10 animals. The LD_{50} values of the active compounds were found to be > 1000 mg kg^{-1} body weight. All the compounds were found to be nontoxic to mice up to 1000 mg kg^{-1} p.o. dose.

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