Synthesis, Characterization, Antibacterial and Antifungal Activities of Novel 2, 4-bis(arylamino)-5-(3-arylsydnon-4-oyl) thiazoles and 2-(N, N-disubstituted amino)-5-(3-arylsydnon-4-oyl)-4-phenylthiazoles

Dr. Jisha S P and Dr. K. N. Rajasekharan

Abstract

Several sydnone derivatives show a broad range of physiological activities, including antimicrobial, anti-inflammatory, analgesic and antipyretic properties Hence, chemists have been enthusiastically pursuing the synthesis of such derivatives. Besides, thiazoles and their derivatives exhibit various biological activities such as antimicrobial, anti-inflammatory, antiviral, antituberculosis and cytotoxic activities, among others. Consequent to these reports, the present study seeks to synthesize a series of novel thiazole derivatives that contain the sydnonyl moiety, with the aim of obtaining new biologically active compounds. In view of the continued interest in the development of simpler and more convenient synthetic routes for preparing heterocyclic systems, an efficient and useful method is reported herein to synthesize some new sydnone-substituted thiazoles.

Keywords

1-Aryl-3-(N,N'-diarylamidino)thioureas, Bromoacetylsydnones, Dendrodoine , Sydnone, Thiazole

Introduction

Sydnones are a class of compounds named after Sydney in Australia, where their synthesis and characterization were carried out initially. They are a novel catagory of mesoionic compounds having a 1,2,3-oxadiazole skeleton bearing an oxygen atom attached to the 5th position. The study of sydnones still remains a field of interest because of their electronic structure, large dipole-moment and chemical properties, and also due to their biological activities such as antitumour (Weinhein, 1992), antioxidant, anti-anginal, antimicrobial, analgesic, antileishmania and anticancer (Pilli et al., 1993). activities. The two leading research groups in this area are those of Badami (Kamble et al., 2007) and of Kallurya (Kallurya et al., 2007), and both the groups have extensively published several investigations, too numerous to cite all, on the synthesis and biological activities of sydnone derivatives.

Several sydnone derivatives show a broad range of physiological activities, including antimicrobial, anti-inflammatory, analgesic and antipyretic properties Hence, chemists have been enthusiastically pursuing the synthesis of such derivatives. Besides, thiazoles and their derivatives exhibit various biological activities such as antimicrobial, anti-inflammatory, antiviral, antituberculosis and cytotoxic activities, among others. Consequent to these reports, the present study seeks to synthesize a series of novel thiazole derivatives that contain the sydnonyl moiety, with the aim of obtaining new biologically active compounds. In view of the continued interest in the development of simpler and more convenient synthetic routes for preparing

heterocyclic systems, an efficient and useful method is reported herein to synthesize some new sydnone-substituted thiazoles.

Background and Objectives

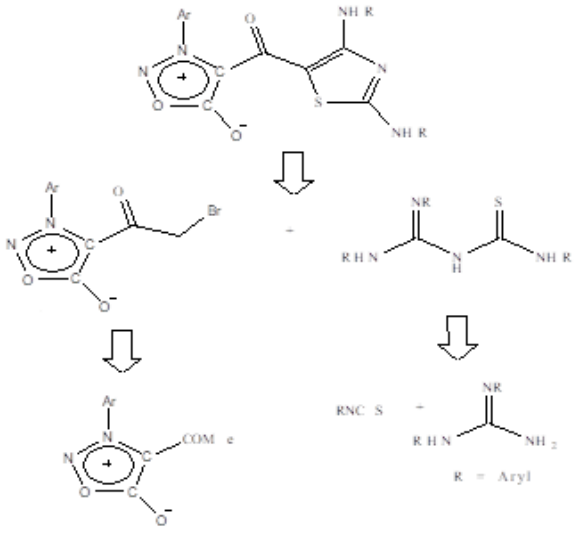
Marine natural products have attracted the attention of biologists and chemists the world over for the past five decades. As a result of the potential for new drug discovery, scientists from different disciplines, such as organic chemistry, bioorganic chemistry, pharmacology, biology and ecology have become interested in marine natural products. This interest has led to the discovery of almost 8,500 marine natural products to date and many of the compounds have shown very promising biological activity. The ocean is considered to be a great source of potential drugs. The chemical compounds, which are isolated from marine sources usually consists of nitrogen containing heterocyclic rings. Many of these may be classified as marine alkaloids due to this fact. Alkaloids have long claimed the attention of humans due to their significant bioactivity. Thus several alkaloids have found a place in western as well as in eastern systems of medicine. In fact, phytochemicals such as alkaloids have been in use from time immemorial for the treatment of illness. We have recently found excellent cancer cell cytotoxicity in hetaryl or aryl thiazolyl ketones which were designed as analogs of the cytotoxic, marine alkaloid dendrodoine. Dendrodoine is (3-N,N-dimethylamino-1,2,4-thiadiazol-5-yl)indol-3-yl ketone and incorporates a 1,2,4-thiadiazole ring; a rarity among either terrestrial or marine natural products. This interest has now led us to design and synthesise aminothiazolyl sydnonyl ketones and screen these for anti-bacterial, antifungal, antioxidant and anticancer activities. This forms the objective of the present work

Result and discussion

I. Synthesis of 2, 4-bis(arylamino)-5-(3-arylsydnon-4-oyl)thiazoles

Synthetic strategy and planning

Based on our long-standing interest in the synthesis of 2-aminothiazoles, we conceived the following retro synthetic strategy for the access of diaminothiazoloylsydnones .



The above retro synthetic approach revealed that the precursors needed for the synthesis of 2,4-bis(arylamino)-5-(3-arylsydnon-4-oyl)thiazoles are 3-aryl-4-bromoacetylsydnone and 1-aryl-3-(N,N'-diarylamidino)thioureas.

Synthesis of precursors

A. 1-Aryl-3-(N,N'-diarylamidino)thioureas

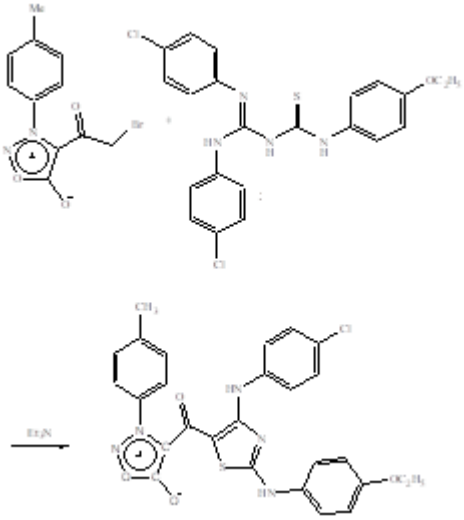
1-Aryl-3-(N,N'-diarylamidino)thioureas could be obtained from N,N'-diarylguanidines, and arylisothiocyanates. The required N,N'-diarylguanidines could be obtained by the reaction between arylcyanamide and arylamine hydrochloride. The N,N'-diarylguanidines so prepared on treatment with aryl isothiocyanates afforded 1-aryl-3-(N,N'-diarylamidino)thioureas in 70-90% yield. As we were interested in the study of anti-oxidant activity, as discussed in a subsequent section, we decided to employ alkoxyphenyl isothiocyanates such as 4-ethoxyphenyl and 4-methoxyphenyl isothiocyanates since it was expected that the incorporation of such a group would enhance the anti-oxidant activity of the present synthetic targets.

B. 4-bromoacetyl-3-arylsydnones *[Baker W, Ollis W. D. & Poole V. D. J. Chem. Soc; (1949) 307; Upadhyaya K.G, Badami B. V, Puranik G S & Biradar V N; Arch. Pharm, 313(1980)684]*

C. Synthesis of 2, 4-bis(arylamino)-5-(3-arylsydnon-4-oyl)thiazoles

The reaction between 1-aryl-3-(N,N'-diarylamidino)thioureas and 4-bromoacetyl-3-arylsydnones was conducted in DMF at 60-70°C in presence of Et_3N. The results of the reaction of 1-[N,N'-di(4-chlorophenyl)amidino]-3-(4-ethoxyphenyl)thiourea with 4-bromoacetyl-3-(4-methylphenyl)sydnone is described now as a typical example. Work up subsequent to the reaction and purification of the crude product so obtained by crystallisation provided a deep red crystalline solid. The molecular formula was found to be $C_{27}H_{22}ClN_5O_4S$, based on the elemental analysis. The IR (KBr) spectrum of the compound presently obtained shows ν_{N-H} stretching bands at 3261 and 3121 cm^{-1}. A strong peak at 1745 cm^{-1} is indicative of the presence of the sydnonyl moiety, since the band is assigned to the ν_{C-O} band of the sydnone ring carbonyl group. Another peak at 1645 cm^{-1} arises from a conjugated carbonyl group. A moderate to strong band at 819 cm^{-1} due to aryl C-H bending band indicates the presence of 1,4-disubstituted benzene rings in the compound. The ^1H NMR spectrum (400 MHz) shows a singlet at δ 2.47 is due to hydrogens of the methyl group of a methylphenyl group. The triplet at δ 1.42 and a quartet at δ 4.04 are indicative of an ethoxyphenyl group. is due to the $–CH_2$ hydrogens of ethoxy group. A doublet at δ 6.92 is attributable to the aryl hydrogens ortho to the ethoxy group. The aryl hydrogen region shows two complex multiplets in the range δ 7.28-7.41 and δ 7.42-7.56 arising from six aromatic hydrogens. The signal due to the rest of the aryl hydrogens seems to be submerged in the chloroform peak that appears in this area. Two broad peaks at δ 7.74 and at δ 11.22 are attributed to two –NH-groups. The FAB MS shows a strong M^+ peak at 548, which confirms the molecular mass of the compound to be 547, compatible with the data from elemental analysis. The ^{13}C NMR spectrum of the compound shows peaks at δ 55.70 and 63.75 indicating the presence of $–OCH_2-CH_3$ group. The above data supports the

formulation of the product obtained above as 4-(4-chlorophenylamino)-2-(4-ethoxyphenylamino)-5-[3-(4-methylphenyl)sydnon-4-oyl]thiazole**.**



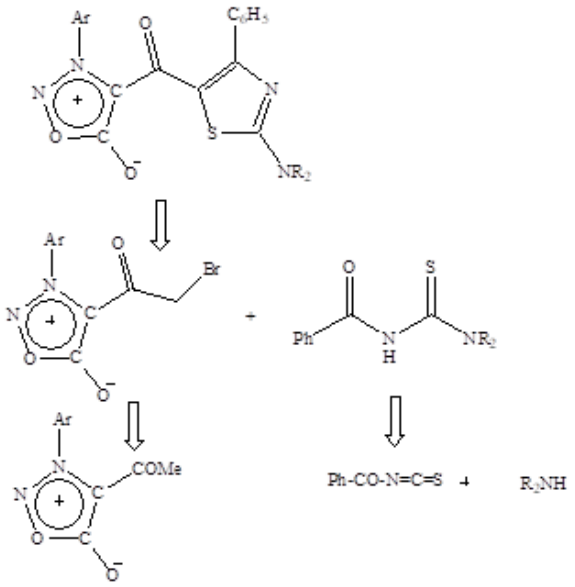
We also synthesized three other examples of this class of sydnonoylthiazoles. Thus we have now shown that 2,4-(bisarylamino)-5-(3-arylsydnon-4-oyl)thiazoles could be obtained from 1-aryl-3-(N,N-diphenylamidino)thioureas in 69-74% yield. The different 2,4-bis(arylamino)-5-(3-arylsydnon-4-oyl)thiazoles synthesized are tabulated below.

Table 1.0. Synthesized 2,4-bis(arylamino)-5-(3-arylsydnon-4-oyl)thiazoles 1a-d

Thaizole	Ar^1	Ar^2	Ar^3
1a	4-ethoxyphenyl	4-chlorophenyl	phenyl
1b	4-ethoxyphenyl	4-chlorophenyl	4-methylphenyl
1c	4-methoxyphenyl	4-methylphenyl	4-methoxyphenyl
1d	4-ethoxyphenyl	Phenyl	4-methoxyphenyl

II. Synthesis of 2-(N,N-disubstituted amino)-5-(3-arylsydnon-4-oyl)-4-phenylthiazoles

For the synthesis of 2-(N,N-disubstituted amino)-5-(3-arylsydnon-4-oyl)-4-phenyl thiazoles, we have chosen the route that employs imidoylthioureas and α-haloketones as the resource materials. This selection is based on the following retrosynthetic analysis.



As indicated above, the retro synthetic analysis suggested that 1-benzoyl-3-[N,N-(disubstituted)]thioureas and 3-aryl-4-bromoacetylsydnones could serve as plausible starting materials.

Synthesis of precursors

A. Synthesis of acylthioureas

The acylthioureas required for the present work were prepared by a modification of the synthesis of such compounds developed earlier in our laboratory. In this method, a phase transfer catalysed, room temperature reaction is used for obtaining benzoyl isothiocyanate from benzoyl chloride and KCNS. The benzoyl isothiocyanate obtained was reacted without isolation with several secondary amines.

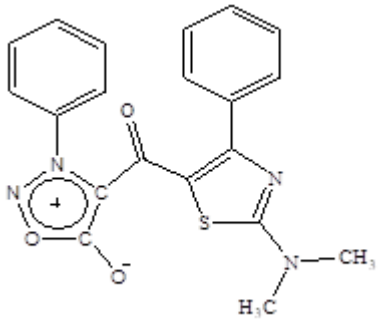
The secondary amines used in the present study are N,N-dimethylamine, N-methyl, N-phenylamine, piperidine, pyrrolidine and morpholine. Their reaction with benzoyl isothiocyanate led to the preparation of the N-benzoyl-N',N'-dimethylthiourea, N-benzoyl-N',N'-methylphenylthiourea, 1-(N-benzoylthiocarbamoyl)piperidine, 1-(N-benzoylthiocarbamoyl)pyrrolidine and 1-(N-benzoylthiocarbamoyl)morpholine . The latter three compounds may also be considered as acylthioureas and named trivially as 1-benzoyl-3-(N,N-pentamethylene)thiourea, 1-benzoyl-3-(N,N-tetramethylene)thiourea and 1-benzoyl-3-[N',N'-(3-oxapentamethylene)]thiourea respectively. These names will be used here after. The details of the preparation of these thioureas are included in experimental section.

B 4-bromoacetyl-3-arylsydnones *[Baker W, Ollis W. D. & Poole V. D. J. Chem. Soc; (1949) 307; Upadhyaya K.G, Badami B. V, Puranik G S & Biradar V N; Arch. Pharm, 313(1980)684]*

C. Synthesis of 2-[N,N-(disubstituted)amino]-5-(3-arylsydnon-4-oyl)- 4-phenylthiazoles

The reaction of N-benzoyl-N',N'-dimethylthiourea and 4-bromoacetyl-3-phenylsydnone , each at 0.05mmol level, was carried out in DMF at 85^0C, in the absence of triethylamine. Work up and purification by crystallization yielded a reddish brown compound which has a molecular formula $C_{20}H_{16}N_4O_3S$. A strong peak

at 1774 cm^{-1} in the IR spectrum of the compound is attributed a C=O group in sydnone and another at 1597 cm^{-1} arises from a conjugated C=O group. Bands due to benzene ring C-H bending vibrations are seen at 692 and 755 cm^{-1}. The broad peak centered at 3433 cm^{-1} in this and the other IR spectra was due to moisture present in the KBr used to make pellets. The ^1H NMR spectrum (300 MHz) shows a singlet due to six hydrogen at δ 3.59. The aromatic region shows a set of three multiplets, together accounting for ten aryl hydrogens. These multiplets were seen at δ 7.35-7.42, 7.45-7.52 and 7.67-7.78. The FAB mass spectrum indicates that the molecular mass of the compound to be 392. On the basis of these spectral evidences, the compound now obtained was formulated as 2-[N,N-(dimethyl)amino]-4-phenyl-5-(3-phenylsydnon-4-oyl)thiazole**.**



Thus, we have now found that 2-[N,N-(disubstituted)amino]-4-phenyl-5-(3-arylsydnon-4-oyl)thiazoles can be obtained from 1-acyl-3-[N,N-(disubstituted)]thioureas in 80-85% yield. We next established the generality of the reaction sequence by using several other 1-acyl-3-[N,N-(disubstituted)]thioureas to obtain the following 5-(3-arylsydnon-4-oyl)-2-[N,N-(disubstituted)amino]-4-phenylthiazoles**.**

Table 2.0. Synthesized 2-[N,N-(disubstituted)amino]-5-(3-arylsydnon-4-oyl)-4-phenylthiazoles 2a-p

2	-RR^1	Ar
a	-NMe_2	phenyl
b	-NMePh	
c	Piperidinyl	
d	Pyrrolidinyl	
e	Morpholinyl	
f	-NMe_2	4-methylphenyl
g	-NMePh	
h	Pyrrolidinyl	
i	Piperidinyl	
j	Morpholinyl	
k	-NMe_2	4-methoxyphenyl
l	-NEt_2	
m	-NMePh	

n	Morpholinyl	
o	Pyrrolidinyl	
p	Piperidinyl	

Bioactivity Studies of sydnonoylthiazoles

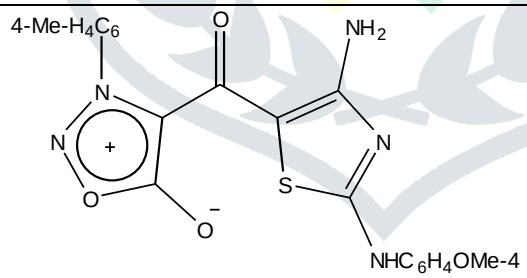
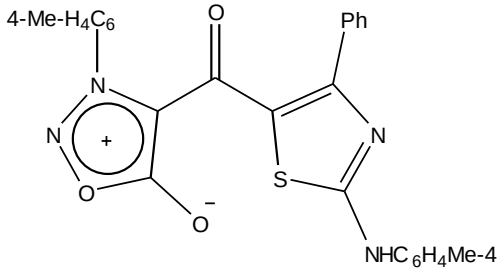
I. Anti-bacterial activity of sydnonoylthiazoles

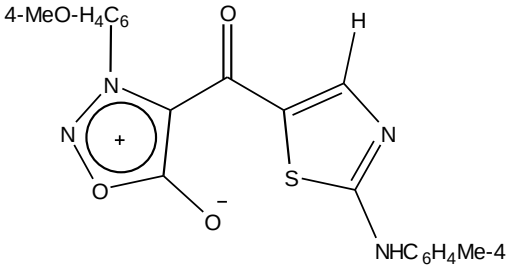
The chemotherapeutic agents in current use vary in their scope of antibacterial activity. Some are limited by their spectrum of activity, being effective against only one group of microorganism. Others exhibit broad-spectrum activity against a range of microorganisms. The drug susceptibilities of many pathogenic microorganisms are known, but it is usually necessary to test several agents to determine the drug of choice.

A standard filter paper disc-agar diffusion procedure known by Kirby-Bauer method (Kurzer and Sanderson, 1960), is frequently used to determine the drug susceptibility of microorganisms isolated from environment or tissues. This method allows for the rapid determination of the efficiency of a drug by measuring the diameter of the zone of inhibition that results from diffusion of the agent into the medium surrounding the disc.

The newly synthesized compounds have presently been screened for antibacterial activity against two typical Gram-negative *Escherichia coli* and Gram positive *Lactobacillus* each. As a reference standard, penicillin-G was used. The data are presented in tabular form in Table III. 2.

Table. 3. Antibacterial activity of active sydnonoylthiazoles

Comp No:	Thiazoles	Inhibition Zone (mm)	
		Lactobacillus	*E. coli*
16g		1mm	-
42f		-	2.8mm

45h		1.5mm	1.4mm
	Penicillin-G (Standard)	4 mm	4.5 mm

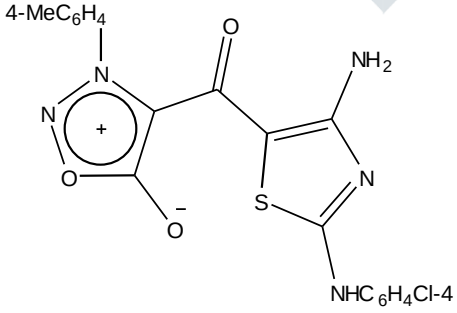
On the basis of the above antibacterial activity in which most of the newly synthesized sydnonoylthiazole derivatives were screened, we had expected to draw some inferences regarding the relation between antibacterial activity and structural features of the compounds that have been screened. There are three structural variables in all compounds that have examined for their antibacterial activity. The first one of these is the nature of the heterocyclic moiety attached to the C-5 of the thiazole, the second is the substituent attached to C-4 and the third is the substituent present in C-2 position of the thiazole nucleus. However, we could not attempt any generalization since the thiazoles had no, or very poor, activity. Nevertheless, it was observed that the presence of 4-$CH_3C_6H_4NH$- and 4-CH_3O-C_6H_4NH- substitution at the thiazole C2 carbon as well as on the aryl ring of the sydnon N3 nitrogen favored the appearance of antibacterial activity, however unremarkable it is.

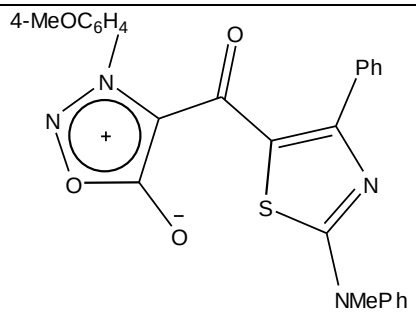
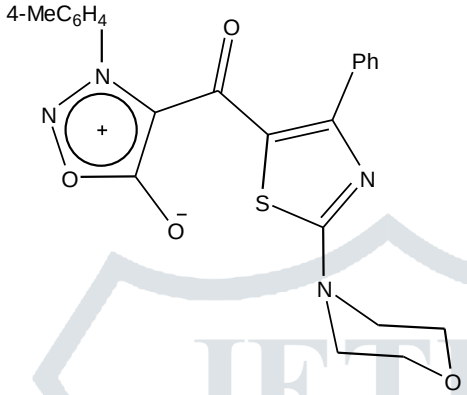
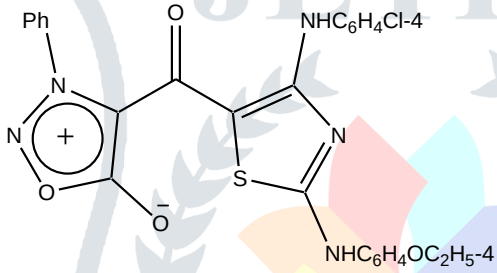
II Anti fungal activity of sydnonoylthiazoles

Antifungal activity of compounds were studied by the disc diffusion method against the organisms ***Trichoderma*** **and** ***Aspergillus niger*****.** The media used for antifungal activity was known as sabourauds at agar media. The activity was assayed at a sample concentration of 50µg/mL using DMF. Ketaconazole at 50 µg/mL was used as the standard.

The antifungal activity of the active sydnonoylthiazoles are given below in Table. 4.

Table. 4. Antifungal activity of active sydnonoylthiazoles

Comp No:	Thiazoles	Inhibition Zone (mm)	
		Trichoderma	*Aspergillus*
16h		-	2.7mm

38m		-	1.3mm
38j		0.8mm	-
36a		-	2.2mm
	Standard (Ketaconazole)	4.5 mm	5.5 mm

Based on the antifungal activity assay of twenty of the newly synthesized sydnonoylthiazoles, it was observed that the presence of a 4-Cl-C_6H_4- substitutent at the thiazole C2 amino group, or both at the thiazole C2 and C4 amino groups, favored the manifestation of some antifungal activity. None of the 4-unsubstituted 2-aminothiazoles were active. Overall, the anti-fungal activity of the 2-aminothiazoles was very minimal.

D. Conclusions

In conclusion**,** from 1-aryl-3-(N-nitroamidino)thioureas**,** we have synthesized four novel 2,4-bis(arylamino)-5-(3-arylsydnon-4-oyl)thiazoles **1a-d** in 69-74% yield by the reaction with 1-aryl-3-[N,N-diphenylamidino)thioureas and 4-bromoacetyl-3-arylsydnones **,** sixteen novel 2-(N,N-disubstituted amino)-5-(3-arylsydnon-4-oyl)-4-phenylthiazoles **2a-p** on treating 4-bromoacetyl-3-arylsydnones with 1-acyl-3-(disubstituted)thioureas in 80-85% yield. We have characterized all the synthesized. The antibacterial and antifungal activities of all the synthesized sydnonoylthiazoles were studied and we could identify minimal activity among these.

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