RESUME

The thesis describes the work related to synthesis, structure elucidation stereochemistry and biological assay (anticancer and antimicrobial screening) grouped in three parts with six chapters as long alkyl chain substituted-s-triazolo-thiadiazepines, long alkyl chain substituted-benzopyrano-s-triazolo-thiadiazepines, long alkyl chain substituted-s-triazolo-thiadiazoles, 2-aryl-3-N-long alkyl chain substituted-thiazolidin-4-ones/thiazan-4-one, 2-aryl-2-methyl-3-N-long alkyl chain substituted-thiazolidin-4-one and biological screening: study for anticancer and antimicrobial activity.

The techniques used for structure elucidation are $^1$H-NMR, $^{13}$C-NMR, APT,NOE, 2DNMR (COSY, HETCOR) including DCI-MS, IR and FTIR.

PART ONE

1,2,4-TRIAZOLO[3,4-b][1,3,4]THIAZIDAZEPINES/THIDIAZOLEs

CHAPTER I. Long alkyl chain substituted-s-Triazolo-Thiazidiazepines

4-Amino-5-mercapto-1,2,4-triazoles and their N-bridged heterocyclic derivatives have received much attention during recent years on account of their wide spectrum biological potentialities. The 1,2,4-triazole nucleus has been incorporated into a wide variety of therapeutically interesting drugs including $H_1/H_2$-Histamine receptor blockers, cholinesterase active agents, CNS stimulants, antianxiety agents and sedatives. Also 1,3,4-thiadiazepine derivatives are associated with a varied range of biological activities such as anticancer, anti-IIIV, anticholinergic, antidepressant, anaesthetic, calcium antagonist choloretics and ACE inhibitory activity. Prompted by these
observations and as part of our continuing programme in the search of biologically active compounds with sulphur and nitrogen containing heterocycles, we have undertaken the synthesis of two novel compounds, 2-(4-chlorophenyl)-4-[2-(4-chlorophenyl)ethenyl]-7-(9-decenyl)-2,3-dihydro-1,2,4-triazolo[3,4-b][1,3,4]thiadiazepine (4) and 2,4-bis(4-chlorophenyl)-7-(9-decenyl)-2,3-dihydro-1,2,4-triazolo[3,4-b][1,3,4]thiadiazepine (7) by the reaction of 4-amino-3-(9-decenyl)-5-mercapto-1,2,4-triazole (1) with (i) 1,5-bis(4-chlorophenyl)pent-1,4-dien-3-one (2) and (ii) 4,4'-dichlorochalcone (5). In each of the above synthesis, a Michael adduct of (2)/(5) and the s-triazole (1) were also obtained. The reaction of (1) with 1,3-bis(2-thienyl)propen-1-one (8) furnished only the Michael adduct (9) as the sole product. (Scheme 1)

The structures of these compounds were established on the basis of spectral studies such as IR, DCI-MS, EI-MS, $^1$H-NMR, and $^{13}$C-NMR spectra.
Syntheses of (3), (4); (6), (7) and (9)

(i) (1) : 1,5-bis(4-chlorophenyl)pent-1,4-dien-3-one(2) (molar ratio, 1:1), dry benzene, reflux 32 h
(ii) (1) : 4,4'-dichloroalchocne (5) (molar ratio, 1:1), dry benzene, reflux 26 h.
(iii) (1) : 1,3-bis(2-thienyl)propen-1-one (6) (molar ratio, 1:1), dry benzene, reflux 30 h.

SCHEME 1
CHAPTER II. Long alkyl chain substituted-Benzopyrano-s-Triazolo- 
Thiadiazepines

As part of our programme in search of biologically active compounds and in 
continuation of the work described in previous chapter, we extended our work on the 
reaction of the s-triazole (1) with exocyclic \( \alpha,\beta \)-unsaturated enone systems and 
synthesised two novel compounds, 2,3-bis(4-chlorophenyl)-11-(9-decenyl)-2a,3-
dihydro[1]benzopyrano[3,4-e]-2a-dihydro-1,2,4-triazolo[3,4-b][1,3,4]thiadiazep-
ine (12) and 2,3-bis(phenyl)-11-(9-decenyl)-2a,3-dihydro[1]benzopyrano[3,4-e]- 
2a-dihydro-1,2,4-triazolo[3,4-b][1,3,4]thiadiazepine (15) by the reaction of the s-
triazole (1) with \( E-3-(4\text{-chlorobenzylidene})-4'-\text{chloro flavanone (10)} \) and \( E-3-
benzylidene flavanone (13) \) in dry benzene using \( p\text{-TsOH} \) as catalyst. An adduct, 2-
(4-chlorophenyl)-3-[3-(9-decenyl)-4-amino-5-(4-chlorobenzylthio)-1,2,4-triazolyl]- 
2,3-dihydro-4-benzopyrone (11) in the former and 2-(phenyl)-3-[3-(9-decenyl)-4-
amino-5-(benzylthio)-1,2,4-triazolyl]-2,3-dihydro-4-benzopyrone (14) in the latter 
was also obtained in good yields(Scheme 2).
The structures of these compounds were confirmed by IR, DCI-MS, \(^1\)H-NMR, \(^{13}\)C-NMR, COSY and HETCOR spectral studies. The configurations at the three stereogenic centres C-2, C-3 and C-1' in compounds (11) and (14) were established on the basis of the inspection of models and the values of coupling constants.

\[ \text{Scheme 2} \]
CHAPTER III. Long alkyl chain substituted-s-Triazolo-Thiadiazoles

1,2,4-Triazole and its derivatives have been found to play vital role in medicine, agriculture and industry. The fused ring systems such as s-triazolo[3,4-b][1,3,4]thiadiazoles have varied range of biological activities as antibacterial, antifungal, antiinflammatory, antihypertensive, analgesic and anthelmintic agents. These findings have tempted us to undertake this problem on the synthesis of three new compounds, (i) 2-(4-methoxyphenyl)-5-(9-decenyl)-2,3-dihydro-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (17) (ii) 2-(4-chlorophenyl)-5-(9-decenyl)-2,3-dihydro-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (19) and (iii) 2-(2-thienyl)-5-(9-decenyl)-2,3-dihydro-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (21) from (i) p-anisaldehyde, (ii) p-chlorobenzaldehyde and (iii) thiophen-2-aldehyde respectively using 4-amino-3-(9-decenyl)-5-mercapto-1,2,4-triazole (1) in the presence of a catalytic amount of p-TsOH. In each reaction, the corresponding Schiff bases (16), (18), and (20) have also been obtained. The reaction of furfuraldehyde with the triazole (1) yielded only the Schiff base (22) (Scheme 3).

The structure of these compounds were established on the basis of spectral studies of IR, DCI-MS, $^1$H-NMR and $^{13}$C-NMR spectra.
SCHEME 3
PART TWO

2,3-DISUBSTITUTED THIAZOLIDIN-4-ONES/THIAZAN-4-ONES

CHAPTER IV. 2-Aryl-3-N-Long alkyl chain substituted-Thiazolidin-4-ones/Thiazan-4-one,

The interest in substituted thiazolidin-4-ones and thiazan-4-ones in particular for medical application is increasing strongly. The thiazolidin-4-ones, their derivatives and analogues have been found to exhibit usually high \textit{in vitro} activity against \textit{Mycobacterium tuberculosis}, highly potent and selective anti-Platelet Activating Factor activity and broad spectrum activity against various diseases. Because 4-thiazolidinones substituted in the 2-position were proven to be biologically very potent and selective and in anticipation that by incorporating a long chain alkylthioether moiety to thiazolidin-4-one ring, the biological activity may be enhanced due to lipophilization of the resulting molecule, we have undertaken this problem. It consists of the synthesis of the following four novel compounds, (i) 2-(3-nitrophenyl)-3-[11-(carboxymethylthio)undecanamido]thiazolidin-4-one (26), (ii) 2-(3-nitrophenyl)-5-(methyl)-3-(10-undecanamido)thiazolidin-4-one (27) and 2-(3-nitrophenyl)-5-(methyl)-3-[11-\{1-carboxyethylthio\}undecanamido]thiazolidin-4-one (28), (iii) 2-(3-nitrophenyl)-3-[11-(2-carboxyethylthio)undecanamido]thiazan-4-one (30) from \textit{m}-nitrobenzaldehyde-10-undecenohydrazone (24) using mercaptoacetic acid in (i), 2-mercapto-propionic acid in (ii) and 3-mercaptopropionic acid in (iii) in dry benzene. An adduct, (25) in the former and (29) in the latter was also obtained in good yields. (Scheme 1)

The compounds (24), (25) and (29) were found to exist in to be in its two forms, synperiplanar (major) and antiperiplanar (minor) as represented
in Fig. 1. The structure and stereochemistry of these compounds were established on the basis of IR, DCI-MS, $^1$H-NMR, $^{13}$C-NMR, NOE experiments, COSY and HETCOR spectral studies.

![Chemical structures](image)

**Fig. 1**

(24) $R = \text{CH} = \text{CH}_2$  
(25) $R = \text{(CH}_2)_2\text{S} - \text{CH}_2 - \text{COOH}$  
(29) $R = \text{(CH}_2)_2\text{S} - \text{CH}_2 - \text{CH}_2 - \text{COOH}$

(26) $R = \text{(CH}_2)_2\text{S} - \text{CH}_2 - \text{COOH}, \ R' = \text{H}$  
(27) $R = \text{CH} = \text{CH}_2, \ R' = \text{CH}_3$  
(28) $R = \text{(CH}_2)_2\text{S} - \text{CH}_3 - \text{COOH}, \ R' = \text{CH}_3$
Synthesis of: (25) - (30)

(i) (24) : H₂S.CH₂.COOH (molar ratio, 1:3), dry benzene, reflux, 16 h.
(ii) (24) : H₂S.CH(CH₃).COOH (molar ratio, 1:3), dry benzene, reflux, 22 h.
(iii) (24) : H₂S.(CH₂)₂.COOH (molar ratio, 1:3), dry benzene, reflux, 26 h.

SCHEME 1
CHAPTER V. 2-Aryl-2-Methyl-3-N-Long alkyl chain substituted-Thiazolidin-4-one

As part of our programme in search of biologically active compounds with sulphur and nitrogen containing heterocycles and in continuation of the above mentioned work, we have undertaken this problem on the synthesis of 2-(4-chlorophenyl-2-methyl-3-[11-(carboxymethyl/2-carboxyethylthio)undecanamido]thiazolidin-4-ones/thiazan-4-one from p-chloroacetophenone-10-undeceno-hydrazone (31) using (i) mercaptoacetic acid and (ii) 3-mercapto propionic acid. An adduct, (32) in the former and (35) as the sole product in the latter was also obtained in good yields. (Scheme 1)

The structures of these compounds were established by IR, DCI-MS, \(^1\)H-NMR, \(^1\)C-NMR, NOE experiments, COSY and HETCOR spectral studies. Here again the compounds (31), (32) and (35) were found to exist in its two forms, synperiplanar (major) and antiperiplanar (minor) as represented in Fig. 2

![Chemical Structures](image-url)
Synthesis of (32) - (35)

(i) (31) : HS.CH₂.COOH (molar ratio, 1:3), dry benzene, reflux, 24h.
(ii) (31) : HS.(CH₂)₂.COOH (molar ratio, 1:3), dry benzene, reflux, 28h.
PART THREE

SCREENING FOR BIOLOGICAL ACTIVITY

CHAPTER VI. Study for Anticancer and Antimicrobial Activities

(A) ANTICANCER ACTIVITY

The compounds (I), (4), (7), (9), (12), (16), (17), (20), (21), (22), (24), (26), (27), (30), (31) and (32) have been evaluated for anticancer activity first in the 3-cell lines of three types of human cancers: breast (MCF7), Lung (NCI-H460) and CNS (SF-268) at one concentration as the one dose primary anticancer assay. Out of the sixteen compounds screened, only one compound, (27) was found to be active. This compound was then screened for cytotoxic activity at five different concentrations against 60 cell lines of nine types of human cancers: leukaemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast. This compound showed anticancer activity only at higher concentration, 1x 10^-4. Noteworthy results was obtained in the case of non-small lung cancer, melanoma and renal where the reduction in growth is 75, 74 and 70 and 77% respectively.

(B) ANTIMICROBIAL ACTIVITY

A total of 10 compounds were tested against two Gram +ve bacteria (Staphylococcus aureus, Bacillus subtilis) and two Gram -ve bacteria (Escherichia coli, Pseudomonas aeruginosa) and a yeast, Candida albicans. Varying level of antimicrobial activity was detected against one or more test organisms. Solvent control (DMSO) showed non-significant inhibition to test microorganisms. Antimicrobial activity against Gram -ve bacteria was deduced in all compounds. However such activity could be detected only in four compounds against Gram +ve bacteria. The
compounds (25), (26), (30) and (31) demonstrated activity against both Gram +ve and Gram -ve bacteria.

The compounds exhibited antimicrobial activity in the concentration range 200 μg to 500 μg/100 μl. Two compounds, (30) and (31) also demonstrated antifungal (anticandidal) activity. Overall broad spectrum antimicrobial activity i.e. active against Gram +ve and Gram -ve was deduced in (25), (26), (30) and (31). These compounds may be directly explored in the preparation of topical antiinfective agents. However, further exploration requires detailed study on exact MIC values and least toxicity to host cell and system.