Synthesis of 3-(substituted)-2-phenyl-5-(thiophen-2'-ylmethylidene)-3,5-dihydro-4H-imidazol-4-ones.
INTRODUCTION

The last five chapters deal with synthesis of pyrimidine derivatives of biological interest. As a part of our research program, we have also synthesized derivatives encompassing thiophenopyrimidine nucleus with a hope of getting pharmacologically lead molecules with improved biological activity, as the thiophene nucleus is known to exhibit remarkable pharmacological properties.

Thelidine\(^1\), represents molecular modification of the general ethylenediamine structure, in which the phenyl group is replaced by thiophene ring, which serves as potent antihistamine. Tiagabine\(^2\), two thiophene ring containing drug, blocks GABA reuptake action and behaves as anticonvulsant.

![Thelidine](image1)

![Tiagabine](image2)

Chalcones containing 2,5-dichlorothiophene 1 moiety have been synthesized and evaluated for antimicrobial activity\(^3\). Novel carboxylated and heteroaryl substituted chalcones\(^4\) 2 have been synthesized and reported as inhibitors of vascular cell adhesion molecule-1 expression for use in chronic inflammatory diseases.
The synthesis and evaluation of a series of 2-amino-3-(4-chlorobenzoyl)-4-[4-(alkyl/aryl)piperazin-yl]thiophene derivatives\(^5\) \(3\) and \(4\) as allosteric enhancers of the A\(_1\)-adenosine receptor have been described. Tenoxicam\(^6\) is an analogue of piroxicam with a similar profile. It is useful in the treatment of rheumatoid arthritis, osteoarthritis and related disorders.

Imidazolinones exhibit diverse biological properties\(^7\). Hence, synthesis of new imidazolinones is of considerable interest. In the recent years, the chemistry of oxazolones has received much attention due to their use as intermediates for the synthesis of some heterocyclic systems\(^8\). Imidazolinones have been reported to possess antifungal\(^9\), anti-inflammatory\(^10\), antiviral\(^11\), antitubercular\(^12\) and antihistaminic activity\(^13\).

Recently, 1,2,4-trisubstituted-5-imidazolones have been reported to possess monoamino oxidase (MAO) inhibitory and anticonvulsant activity\(^14\) and benzylidene derivatives have also been found to possess MAO inhibitory activity\(^15\-16\).
Histamine is a local hormone, found in number of animal tissues, venoms of insects, bacteria and plants. This is responsible for allergic reactions (inflammation) and excess gastric acid secretion in body. Many molecules containing imidazole$^5$ have been designed which can block histamine activity and thereby reducing the effects of histamine.

Solanki$^{18}$ et al., have been synthesized and anticancer activity of pyrazoline substituted benzylidene imidazolinones 6. Merja and Arief$^{19,20}$ et al., have reported the synthesis and biological screening of imidazolinones 7, 8 and 9.
Synthesis of some substituted imidazolinones\textsuperscript{21-22} have also been reported in the literature for their antimicrobial activity.

Antazoline\textsuperscript{23} is a compound containing imidazole and an N-benzylanilino group linked to basic nitrogen through a 2-carbon chain. It is an antihistamine drug and it can also be used, topically for eye infections. In addition to this, it acts as local anesthetic and anticholinergic. Methapyrilene, another drug with thiophene nucleus, acts as potent antihistamine\textsuperscript{24}.

Epinastine\textsuperscript{25} is another imidazole derivative which resembles tricyclic antidepressants in structure; it is a H\textsubscript{1} receptor antagonist.
Clonidine contains imidazoline ring, it stimulates alpha-2 receptor in the vasomotor center and so it is used to treat mild hypertension in human beings. Replacement of the benzenoid ring by thiophene ring in the drug forms tiamenidine, which is one-third potent as clonidine and less sedative. Moxonidine acts a stronger agonist at imidazole receptor weaker agonist at alpha-2 receptor than clonidine and it has less side effects$^{26}$.

Tioconazole$^{27}$ has been used for effective antifungal against *Torulopsis glabrata*, containing thiophene and imidazole drug.

A series of imidazolylmethylthiophenes$^{28}$ 11 have been prepared and evaluated as ligands for the $\alpha_2$ adrenoceptor. These compounds were tested in two animal models that are predictive of analgesic activity in humans. The 3-thienyl compounds were generally the most potent, particularly those with substitution in
the 4th-position. A subset of the most active compounds was further evaluated for adverse cardiovascular effects in the anesthetic rat model. In addition, it binds well at the $\alpha_{2D}$ adrenoreceptor, in the rat abdominal irritant test (RAIT).

1-[2-(Diarylmethoxy)ethyl]-2-methyl-5-nitroimidazoles\textsuperscript{12} 12 (DAMNI's) is a novel family of HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTI's) active at submicromolar concentration. Replacement of one phenyl ring of 1-[2-(diphenylmethoxy)ethyl]-2-methyl-5-nitroimidazole with heterocyclic rings, such as 2-thienyl or 3-pyridinyl, led to novel DAMNIs with increased activity. In HIV-1 WT cell-based assay the racemic 1-{2-[a-(thiophen-2-yl)phenylmethoxy]ethyl}-2-methyl-5-nitroimidazole showed potent activity.

These research findings on the efficacy of the imidazole and thiophene analogs encourages us to take up the synthesis of these compounds with a view to exploit their biological potency. Therefore, in present work we have synthesized 2-phenyl-4-(thiophen-2'-ylmethylene)oxazol-5(4H)-one 1 by Erlenmayer condensation. Which was then treated with substituted primary aryl amines and substituted hydrazides to get good biodynamic leads encompassing thiophene and imidazole moieties.

All the synthesized compounds were characterized by elemental analyses, IR, $^1$H NMR and mass spectral data. The sequence of reactions carried out in this chapter is depicted in the Scheme-VI.
Scheme VI

A = \begin{align*}
R & = \text{Ph} \\
2a & = 3-\text{NO}_2 \\
2b & = 4-\text{NO}_2 \\
2c & = 4-\text{CH}_3 \\
2d & = 3-\text{Cl} \\
2e & = 4-\text{Cl} \\
2f & = 4-F,3-\text{Cl} \\
2g & = 4-\text{OH} \\
2h & = 4-\text{COOH} \\
5a & = 4-\text{H} \\
5b & = 4-\text{OCH}_3 \\
5c & = 2-\text{Cl} \\
\end{align*}

B = \begin{align*}
\text{H}_2\text{C} & = \text{CH}_2 \\
3 & = 4-\text{OCH}_3 \\
4 & = 4-\text{H} \\
\end{align*}

C = \begin{align*}
\text{C}=\text{O} & = 4-\text{H} \\
\text{C} & = 4-\text{H} \\
\text{C} & = 4-\text{H} \\
\end{align*}

D = \begin{align*}
\text{NC} & = 4-\text{H} \\
\text{NC} & = 4-\text{H} \\
\text{NC} & = 4-\text{H} \\
\end{align*}

E = \begin{align*}
\text{NC} & = 4-\text{H} \\
\text{NC} & = 4-\text{H} \\
\text{NC} & = 4-\text{H} \\
\end{align*}

i = D\text{ry Pyridine}
PRESENT WORK

Mixture of thiophene-2-carbaldehyde, benzoylglycine, in presence of acetic anhydride was taken in conical flask, heated for a while in presence of sodium acetate and then refluxed on water bath till the completion of the reaction. The reaction mixture was kept overnight and decomposed in ice cold ethanol and recrystallized from benzene.

\[
\begin{align*}
\text{C}_7\text{H}_4\text{CHO} + \text{C}_7\text{H}_5\text{N}=\text{C}(\text{CH}_3\text{CO}_2\text{O}) & \quad \text{CH}_3\text{COONa} \quad \text{(I)}^\text{\textdegree} \text{\textcircled{C}O} \\
\text{C}_7\text{H}_4\text{N}=\text{C}(\text{CH}_3\text{CO}_2\text{O}) & \quad \text{O}=\text{\textcircled{C}}\text{O} \\
\text{C}_7\text{H}_5\text{N}=\text{C}(\text{CH}_3\text{CO}_2\text{O}) & \quad \text{O}=\text{\textcircled{C}}\text{O} \\
\end{align*}
\]

The IR spectrum of the compound 2-phenyl-4-(thiophen-2'-ylmethylene)oxazol-5(4\text{H})-one 1 exhibited an absorption band at 1784cm\(^{-1}\) which is a characteristics of lactone carbonyl and another band at 1640cm\(^{-1}\) due to C=N. \(^1\text{H}\) NMR spectrum of compound 1 was taken in CDCl\(_3\), spectrum exhibited two doublets and one triplet at \(\delta\) 8.2, 7.7 and 7.1 respectively for the protons of thiophene ring. A multiplet at \(\delta\) 7.6 to 7.5 for the five aromatic protons and one proton of allyl group was also observed in \(^1\text{H}\)NMR spectrum.

2-Phenyl-4-(thiophen-2'-ylmethylene)oxazol-5(4\text{H})-one 1 was mixed with 4-nitro aniline in a dry conical flask and refluxed for 8 hours in dry pyridine. The completion of the reaction was monitored by TLC. Excess pyridine was removed by distillation under reduced pressure. The content was cooled to room temperature and diluted by adding little ice cold water. The separation of product
was achieved by neutralization with dilute hydrochloric acid and then product was filtered, dried and recrystallized using ethanol to give pure $2a$.

The IR spectrum of $2b$ exhibited shift of lactone carbonyl peak from 1784 cm$^{-1}$ to 1633 cm$^{-1}$ which confirmed the formation of imidazole ring. The compounds $2b$-i were prepared by similar procedure with varying reaction time using various substituted anilines such as

- 2-Nitroaniline and 4-Nitroaniline.
- 4-Methylaniline.
- 3-Chloroaniline, 4-chloroaniline and 3-chloro-4-flouroaniline.
- 4-Aminophenol.
- 4-Aminobenzoic acid.

The IR spectrum of the compound 3-(3-chloro-4-fluorophenyl)-2-phenyl-5-(thiophen-2'-ylmethylidene)-3,5-dihydro-4H-imidazol-4-one $2f$ exhibited an absorption band at 1690 and 1655 cm$^{-1}$ due to C=O and C=N respectively. $^1$H NMR spectrum of compound $2f$ exhibited a multiplet in the region δ 8.1 to 7.1 for protons of thiophene ring, eight aromatic protons of two phenyl rings and one proton of allyl group. The mass spectrum of the compound $2f$ showed molecular ion peak at m/z 382.
Mass fragmentation of compound 2f

Molecular formula: C_{20}H_{12}ClFN_{2}OS  
Molecular weight: 382

![Mass fragmentation diagram with peaks and molecular ions](image_url)
Experiment MIR_ATRACH.XPM
Path of File D:\STAFF\GURU
Instrument Type Tensor 27
Resolution 4

Sample Name TM 4
Date of Measurement 11/05/2009
Sample Form SOLID
Sample Scans 16
+Q1: Exp 1, 0.913 to 1.022 min from Sample 10 (FOX) of 30APR08-01.wiff (Turbo Spray), subtracted (0.223 to 0.550 min), Smooth... Max. 3.3e7 cps.
EXPERIMENTAL

2-Phenyl-4-(thiophen-2'-ylmethylene)oxazol-5(4H)-one 1
(Erlenmayer condensation)

Thiophene-2-carbaldehyde (1.12g, 0.01mol), benzoyleglycine (5.37g, 0.03mol) acetic anhydride (9.18ml, 0.09mol) and sodium acetate (2.46g, 0.03mol) were taken in 250ml conical flask and heated on electric hot plate with constant stirring. As soon as the mixture liquefied completely, the flask was transferred to water bath and heated for 2 hours. Then 10 ml of ethanol was added slowly to the contents of the flask and allowed the mixture to stand overnight. The solid obtained was filtered, washed with cold ethanol and recrystallized from benzene.

Solid; (52%); golden yellow; m.p. 158 °C;
IR (KBr) v (cm⁻¹); 1784 (O-C=O); 
¹H
NMR DMSO δ; 8.1 to 7.1 (m, 9H, Ar-H);
Elemental analysis. Calculated, (%) for C₉H₆NO₂S: C, 65.87; H, 3.55; N, 5.49;
Found: C, 65.85; H, 3.50; N, 5.41.

3-(m-Nitrophenyl)-2-phenyl-5-(thiophen-2'-ylmethylidene)-3,5-dihydro-4H-imidazol-4-one 2a

Mixture of thiophene azolactone (1.27g, 0.005mol) and 3-nitroaniline (0.69g, 0.005mol) were refluxed in dry pyridine for 8 hours monitoring the completion of reaction by TLC. After that, excess solvent was removed by distillation under reduced pressure. The content were cooled to room temperature and diluted by adding little ice cold water. It was then neutralized with dilute
hydrochloric acid, to get 2a which was filtered, dried and recrystallized by using benzene. Similarly compounds 2b-2h and 3-6 were prepared by same procedure.

3-(p-Nitrophenyl)-2-phenyl-5-(thiophen-2'-ylmethylidene)-3,5-dihydro-4H-imidazol-4-one 2b

Solid; (58%); m.p. 205 °C; IR (KBr) v (cm⁻¹); 1654 (C=O); Elemental analysis.
Calculated, (%) for C₁₀H₈N₂O₂S: C, 63.99; H, 3.49; N, 11.19; Found: C, 63.90; H, 3.44; N, 11.17.

3-(p-Methylphenyl)-2-phenyl-5-(thiophen-2'-ylmethylidene)-3,5-dihydro-4H-imidazol-4-one 2c

Solid; (65%); m.p. 217 °C; IR (KBr) v (cm⁻¹); 1633 (C=O); Elemental analysis.
Calculated, (%) for C₂₀H₁₃N₃O₃S: C, 63.99; H, 3.49; N, 11.19. Found: C, 63.91; H, 3.42; N, 11.11.
3-(m-Chlorophenyl)-2-phenyl-5-(thiophen-2'-ylmethylidene)-3,5-dihydro-4H-imidazol-4-one 2d

Solid; (47%); m.p. 218 °C; IR (KBr) ν (cm⁻¹); 1642 (C=O); Elemental analysis. Calculated, (%) for C20H13CIN2OS: C, 65.84; H, 3.59; N, 7.68. Found: C, 65.78; H, 3.56; N, 7.62.

3-(p-Chlorophenyl)-2-phenyl-5-(thiophen-2'-ylmethylidene)-3,5-dihydro-4H-imidazol-4-one 2e

Solid; (55%); m.p. 224 °C; IR (KBr) ν (cm⁻¹); 1696 (C=O); Elemental analysis. Calculated, (%) for C20H13ClN2OS: C, 65.84; H, 3.59; N, 7.68. Found: C, 65.79; H, 3.57; N, 7.64.

3-(3-Chloro-4-fluorophenyl)-2-phenyl-5-(thiophen-2'-ylmethylidene)-3,5-dihydro-4H-imidazol-4-one 2f

Solid; (45%); m.p. 245 °C; IR (KBr) ν (cm⁻¹); 1645 (C=O); ¹H NMR δ: 10.1 to 7.1 (m, 12H, Ar-H); Elemental analysis. Calculated, (%) for C20H12ClFN2OS: C, 62.75; H, 3.16; N, 7.32. Found: C, 62.70; H, 3.11; N, 7.22.
3-((p-Hydroxyphenyl)-2-phenyl-5-(thiophen-2'-ylmethylidene)-3,5-dihydro-4H-imidazol-4-one 2g

Solid; (41%); m.p. 232 °C; IR (KBr) ν (cm⁻¹); 3310 (OH), 1649 (C=O); Elemental analysis. Calculated, (%) for C₂₀H₁₄N₂O₂S: C, 69.35; H, 4.07; N, 8.09. Found: C, 69.26; H, 4.00; N, 8.01.

3-((p-Carboxyphenyl)-2-phenyl-5-(thiophen-2'-ylmethylidene)-3,5-dihydro-4H-imidazol-4-one 2h

Solid; (45%); m.p. 244 °C; IR (KBr) ν (cm⁻¹); 3329 (OH), 1679 (C=O); Elemental analysis. Calculated, (%) for C₂₁H₁₄N₂O₃S: C, 67.37; H, 3.77; N, 7.48. Found: C, 67.31; H, 3.72; N, 7.44.

2-(5-Allyl-2-methoxyphenoxy)-N-[5-oxo-2-phenyl-4-(thiophen-2'-ylmethylene)-4,5-dihydro-1H-imidazol-1-yl]acetamide 3

Solid; (55%); m.p. 210 °C; IR (KBr) ν (cm⁻¹); 1659 (C=O); Elemental analysis. Calculated, (%) for C₂₆H₂₃N₃O₄S: C, 65.94; H, 4.90; N, 8.87. Found: C, 65.90; H, 4.76; N, 8.48.
N-[5-oxo-2-phenyl-4-(thiophen-2'-ylmethylene)-4,5-dihydro-1H-imidazol-1-yl]isonicotinamide 4

Solid; (50%); m.p. 210 °C; IR (KBr) ν (cm\(^{-1}\)); 3194 (NH), 1635 (C=O);
Elemental analysis. Calculated, (%) for C\(_{20}\)H\(_{14}\)N\(_4\)O\(_2\)S: C, 64.16; H, 3.77; N, 14.96. Found: C, 64.10; H, 3.72; N, 14.90.

5-Cyano-1-methyl-2-[5-oxo-2-phenyl-4-(thiophen-2'-ylmethylene)-4,5-dihydro-1H-imidazol-1-ylamino]-4-phenyl-1,6-dihydropyrimidine-6-one 5a

Solid; (35%); m.p. 175 °C; IR (KBr) ν (cm\(^{-1}\)); 3215 (NH), 2201 (CN), 1635 (C=O); Elemental analysis. Calculated, (%) for C\(_{26}\)H\(_{18}\)N\(_6\)O\(_2\)S: C, 65.26; H, 3.79; N, 17.56. Found: C, 65.21; H, 3.74; N, 17.51.

5-Cyano-1-methyl-2-[5-oxo-2-phenyl-4-(thiophen-2'-ylmethylene)-4,5-dihydro-1H-imidazol-1-ylamino]-4-anisyl-1,6-dihydropyrimidine-6-one 5b

Solid; (45%); m.p. 194 °C; IR (KBr) ν (cm\(^{-1}\)); 3289 (NH), 2223 (CN), 1664 (C=O); Elemental analysis. Calculated, (%) for C\(_{27}\)H\(_{20}\)N\(_6\)O\(_3\)S: C, 63.77; H, 3.96; N, 16.53. Found: C, 63.71; H, 3.90; N, 16.46.
5-Cyano-1-methyl-2-[5-oxo-2-phenyl-4-(thiophen-2'-ylmethylene)-4,5-dihydro-1H-imidazol-1-ylamino]-4-(p-chlorophenyl)-1,6-dihydropyrimidine-6-one 5c

Solid; (40%); m.p. 204°C; IR (KBr) v (cm⁻¹); 3293 (NH), 2201 (CN), 1610 (C=O), Elemental analysis. Calculated, (%) for C₂₆H₁₇ClN₆O₂S: C, 60.88; H, 3.34; N, 16.38. Found: C, 60.80; H, 3.30; N, 16.32.

2-(4-Acetanidophenoxy)-N-[5-oxo-2-phenyl-4-(thiophen-2'-ylmethylene)-4,5-dihydro-1H-imidazol-1-yl]acetamide 6

Solid; (45%); m.p. 124°C; IR (KBr) v (cm⁻¹); 3210 (NH), 1645 (C=O); Elemental analysis. Calculated, (%) for C₂₄H₂₀N₄O₄S: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.57; H, 4.31; N, 12.12.
Table VI: Physical and analytical data of newly synthesized compounds

<table>
<thead>
<tr>
<th>Comp</th>
<th>M.P. (°C)</th>
<th>Anal. Calcd. (Found %)</th>
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<tr>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>1</td>
<td>158</td>
<td>65.87 (65.85)</td>
</tr>
<tr>
<td>2a</td>
<td>205</td>
<td>63.99 (63.90)</td>
</tr>
<tr>
<td>2b</td>
<td>217</td>
<td>63.99 (63.91)</td>
</tr>
<tr>
<td>2c</td>
<td>209</td>
<td>73.23 (73.17)</td>
</tr>
<tr>
<td>2d</td>
<td>218</td>
<td>65.84 (65.78)</td>
</tr>
<tr>
<td>2e</td>
<td>224</td>
<td>65.84 (65.79)</td>
</tr>
<tr>
<td>2f</td>
<td>245</td>
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</tr>
<tr>
<td>2g</td>
<td>232</td>
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<td>2h</td>
<td>244</td>
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<td>210</td>
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<td>5a</td>
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<td>6</td>
<td>124</td>
<td>62.60 (62.57)</td>
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</table>

Some of the selected compounds have been tested for antibacterial, antifungal, anti-TB and anticancer activities and results have been discussed in Chapter-VIII.
REFERENCES


