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2-Aminothiophenes: A Review On Synthetic Routes and Applications (Biological/Synthons)

Aman Bhalla[1]*, Preety Saini[1], Shamsher S. Bari[1]

1.Department of Chemistry & Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh - 160 014, India

ABSTRACT

Thiophene an important heterocyclic nucleus has been established as the potential scaffold entity in the largely growing chemical world of heterocyclic compounds possessing agrochemical, dyes and potent pharmacological characteristics. The present review, provide a broad view of the synthetic routes of 2-aminothiophenes and further explore their biological profiles and synthetic utility. The knowledge of various synthetic pathways and the diverse physicochemical parameters of 2-aminothiophenes draw the special attention of medicinal chemists to produce combinatorial library and carry out exhaustive efforts in the search of lead molecules.

Keywords: 2-Aminothiophene, heterocycles, biological activity, fluorescence, synthon.

*Corresponding Author Email: amanbhalla@pu.ac.in
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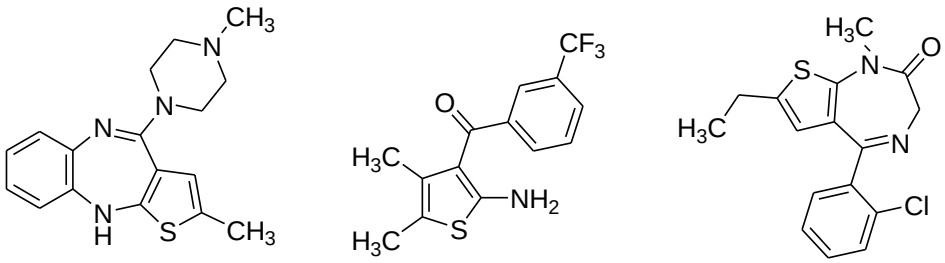
INTRODUCTION

The chemistry of heterocyclic compounds is unique as it cover over a million of known compounds and has become extensively studied research area compared to any of its sub-branch. Heterocycles with five-membered ring have always been on the forefront of attention due to their numerous uses in pharmaceuticals[1] and biologically active molecules.[2] Among the family of heterocyclic compounds sulfur-containing heterocycles viz. 2-aminothiophene and its analogues are under constant scrutiny due to their role as active pharmacophore and utility as active synthon in organic, biological and medicinal science. Many of the commercial sulfur-containing drugs available in the market such as Zyprexa, PD8173 and Clotiazepam contain 2-aminothiophene fragment as a main motif (Figure 1).[3-6]



Zyprexa **PD81723** **Clotiazepam**

Figure 1: Drugs containing 2-aminothiophene as a core moiety

2-Aminothiophene is undoubtedly the most ubiquitous member of thiophene family that occupy a distinguishing place in the field of chemical research and meet the necessary requirements to be called as "privileged structure". The chemistry of 2-aminothiophenes has maintained widespread interest in the present-day thiophene research.[7] 2-Aminothiophene and its derivatives demonstrate diverse array of biological/ pharmacological profiles and broad spectrum of applications with remarkable potency.[8,9] Considering the increasing usefulness, biological and pharmaceutical relevance as well as the diversity of structure encountered with this heterocyclic moiety interest of researchers has been rapidly growing in this class of heterocycle. Therefore, a systematic review listing important updates (synthetic, biological and synthon) on this scaffold is highly desirable.

Ample data accumulated with the chemistry of 2-aminothiophene has forced us to elaborate synthetic procedures, biological evaluation and their synthetic utility as synthon to construct varied number of derivatives with diverse applications.

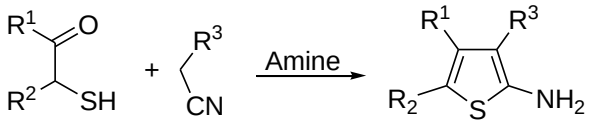
A. Synthetic routes for 2-aminothiophene

Methods used to synthesize 2-aminothiophenes can be classed under following main headings.

(i) The Gewald Reaction

2-Aminothiophene was discovered for the first time in 1910 by Benary[10] by treatment of 4-chloro-2-cyano-3-oxobutanoate with potassium hydrosulfide. Following Benary's pioneering work, Karl Gewald and his collaborators established the most elegant and promising set of interrelated synthetic routes (Version 1, 2, 3 and 4) for synthesizing 2-aminothiophenes.

In the first version, Gewald[11] devised 2-component reaction between α-mercaptoaldehyde or α -mercaptoketone **1** and an activated nitrile **2** with an *in situ* generated mercapto compound in the presence of an amine acting as basic catalyst in a suitable solvent such as *N*,*N*-dimethylformamide, dioxane, water, ethanol or methanol to yield 2-aminothiophenes **3** (Scheme 1).

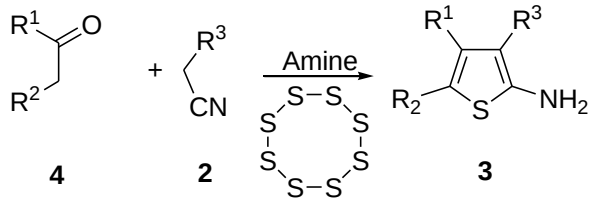


1 **2** **3**

R^1, R^2 = H, alkyl, aryl, cycloalkyl, hetaryl
R^3 = CN, COOMe, COOEt, COPh, CO-hetaryl, $CONH_2$

Scheme 1: Synthesis of 2-aminothiophenes *via* the first version of Gewal reaction

In the second version, Gewald *et al.*[12] reported 3-component reaction between an aldehyde, a ketone or a 1,3-dicarbonyl compound **4**, an activated nitrile **2** and sulfur under the same reaction conditions as followed in the first version to furnish 2-aminothiophenes **3** (Scheme 2).

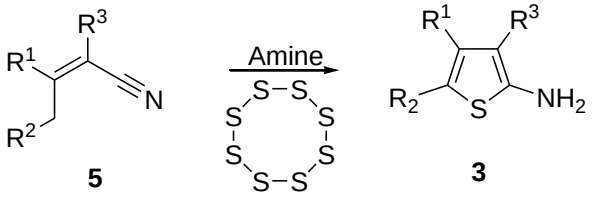


4 **2** **3**

R^1, R^2 = H, alkyl, aryl, cycloalkyl, hetaryl
R^3 = CN, COOMe, COOEt, COPh, CO-hetaryl, $CONH_2$

Scheme 2: Synthesis of 2-aminothiophenes *via* the second version of Gewald reaction

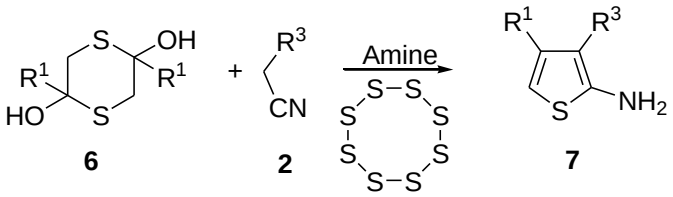
In the third version, Gewald and Schinke[13] reported a two step-2-component synthetic procedure for the synthesis of 2-aminothiophenes **3** with an initial preparation of α,β-unsaturated nitrile **5** from an aldehyde, a ketone or 1,3-dicarbonyl compound **4** which upon treatment with sulfur and amine under same reaction conditions as those of first and second version afforded target compound **3** (Scheme 3).



R^1, R^2 = H, alkyl, aryl, cycloalkyl, hetaryl
R^3 = CN, COOMe, COOEt, COPh, CO-hetaryl, $CONH_2$

Scheme 3: Synthesis of 2-aminothiophenes *via* the third version of Gewald reaction

In the fourth version[14] of Gewald reaction α -sulfonylcarbonyl compound (substituted 1,4-dithiane-2,5-diol) **6** undergo reaction with α-activated acetonitrile **2** under the same reaction condition as that of the first version to yield compound **7** (Scheme 4).



R^1 = H, alkyl
R^3 = CN, COOMe, COOEt, COPh, CO-hetaryl, $CONH_2$

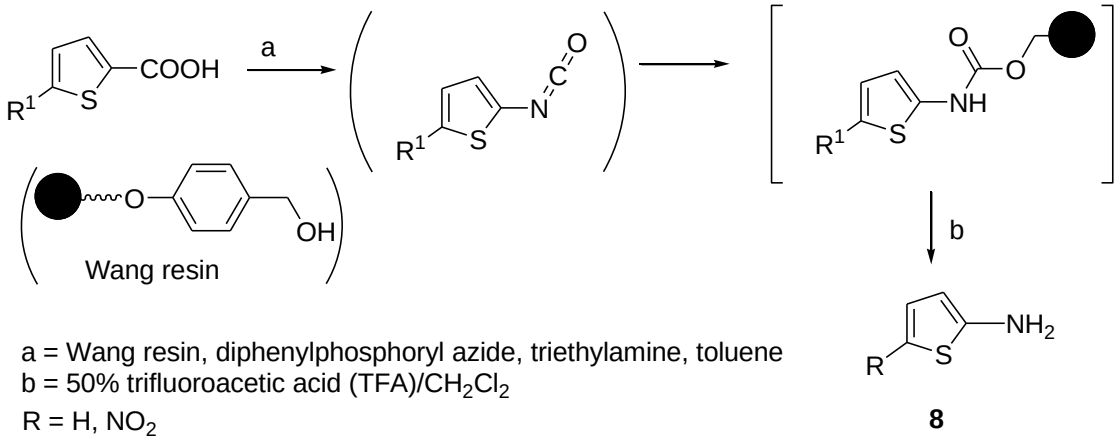
Scheme 4: Synthesis of 2-aminothiophenes *via* the fourth version of Gewald reaction

High catalyst loading, use of unstable and difficult to prepare starting substrates, numerous environmental impacts, long reaction times, high temperature and low yield of products are a few contributing factors for the reduced importance of this versatile protocol. Further, the substrate scope in Gewald reactions was only limited to activated nitriles. Therefore, in order to overcome these limitations, many modifications to the original Gewald reactions have been developed based on the novel catalyst loading (glacial acetic acid morpholine, ZnO nanoparticles, bovine serum albumin etc.), electrochemical and thermochemical activation of elemental sulfur, non thermal processes (microwave and ultrasound) and environmentally benign green approach (ionic liquids and ionic liquid based solvents) and by extending the limited substrate scope by replacing aldehyde, ketone or 1,3 dicarbonyl compound with functionally substituted enamine or cyclopropane and replacing the nitrile component with doubly activated nitlile equivalent to yield symmetrical and unsymmetrical 2-aminothiophenes and their derivatives.[15]

(ii) Solid-support synthesis

Groups of Sunami[16] and Morishima[17] reported an efficient and facile solid-phase approach by using carboxylic acids *via* Curtius rearrangement followed by alkylation for the preparation of

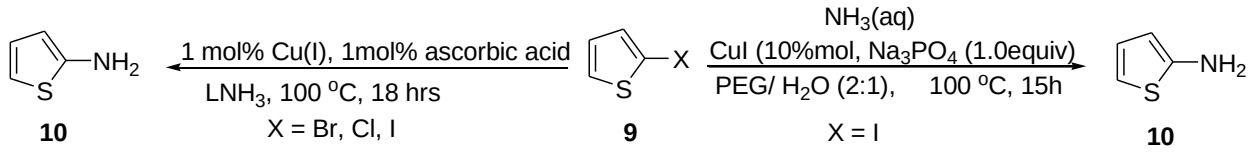
compounds **8** containing 2-aminothiophene structure as a pharmacophore in good yield (Scheme 5).



Scheme 5: Solid-support synthesis using Wang resin

(iii) Cross-coupling reaction

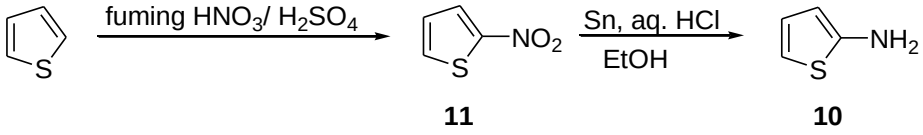
Groups of Junmin Chem[16] and Page[17] have discovered a simple, economical and environmentally benign one step procedure for the synthesis primary aryl amines **10** by cross-coupling of aryl halides **9** with aqueous ammonia using Cu (I) system as a catalyst with good functional group compatibility (Scheme 6).



Scheme 6: Cross-coupling reaction using Cu(I) system

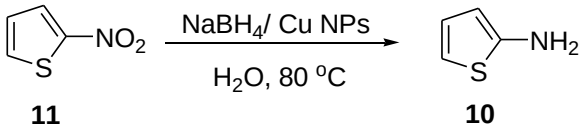
(iv) Nitration and reduction reactions

M. M. Stylianakis *et al.*[18] reported a two-step synthetic procedure involving nitration of thiophene using fuming nitric acid followed by hydrogenation of 2-nitrothiophene **11** using Sn metal and hydrochloric acid in ethanol to afford 2-aminothiophene **10** (Scheme 7).



Scheme 7: Nitration and reduction reaction

Zahra Shokri *et al.*[19] explored the green reduction of 2-nitrothiophene **11** using $NaBH_4$ in water as reaction medium and inexpensive non noble Cu nanoparticles to afford 2-aminothiophene **10** (Scheme 8).



11 **10**

Scheme 8: Reduction of 2-nitrothiophene 11 using Cu nanoparticles

B. Biological evaluation of 2-aminothiphene

2-Aminothiophene and their derivatives have been a topic of constant investigation due to their resourceful synthetic applicability and broad spectrum of biological activities reported by scientists all over the world. In the current review, all the activities shown by 2-aminothiophene and their derivatives have been discussed briefly.

(i) Anticonvulsant

K. Pavan Kumar *et al.*[22] synthesized and assessed anticonvulsant activity of some 2-aminothiophenes derivatives 2-amino-*N*-(4-chlorophenyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide **12**, (*E*)-2-((1*H*-indol-2-yl)methyleneamino)-*N*-(4-chlorophenyl)-4,5,6,7-tetrahydrobenzo[*b*]thiop -hene-3-carboxamide **13**, (*E*)-2-((1-(morpholinomethyl)-1*H*-indol-2-yl)methyleneamino)-*N*-(4-chlorophenyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide **14**, (*E*)-2-((1-((piperazin-1-yl)methyl)-1*H*-indol-2-yl)methyleneamino)-*N*-(4-chlorophenyl)-4,5,6,7-tetrahydrobenzo[*b*] thiophene-3-carboxamide **15** and (*E*)-2-((1-((4-methylpiperazin-1-yl)methyl)-1*H*-indol-2-yl)methyleneamino)-*N*-(4-chlorophenyl)-4,5,6,7-tetrahydrobenzo[*b*]thiop -hene-3-carboxamide **16** in mice against strychnine, picrotoxin, lithium-pilocarpine-induced seizures (Figure 2). The authors found that all these screened compounds have shown moderate activity against standard drug diazepam while the compound **13** ((P< 0.0001) has shown exceptionally good anticonvulsant activity due to the presence of free indole moiety. Further, in the studies related to picrotoxin and lithium-pilocarpine-induced convulsions the compounds **12**, **14**, **15** and **16** have shown moderate activity against standard drugs.

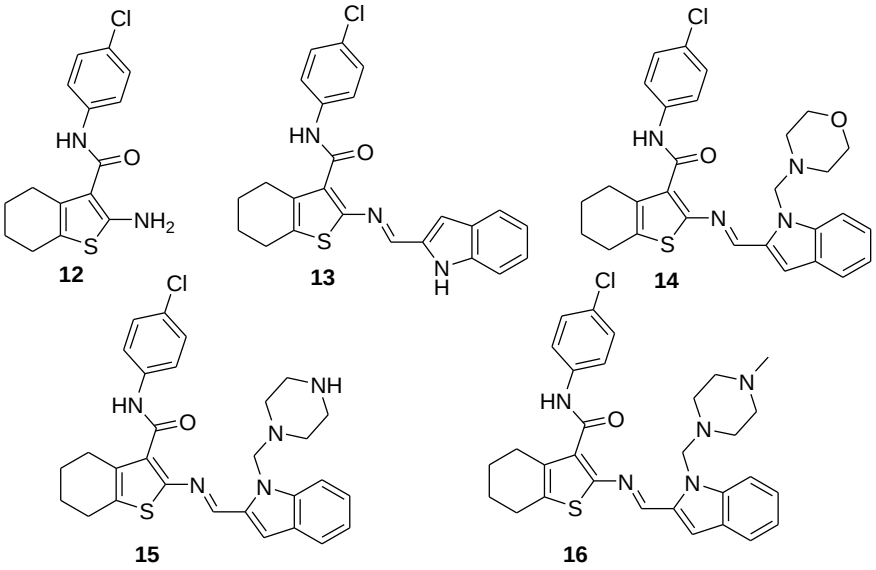


Figure 2: Anticonvulsant activity of 2-amiothiophene derivatives 12-16

(ii) Anti-inflammatory

Khan and coworkers[23] reported the screening of 2-aminothiophene analogs for anti-inflammatory activity with IC_{50} 121.47 µM as highest level of potential achieved. Yiding Hu *et al.*[24] studied the metabolic activation of anti-inflammatory agent 1-(5-(2,3,5-trichlorobenzamido)-3-carbamoylthiophen-2-yl)urea **17**, 1-(5-(3-chlorophenylcarbamoyl)-3-carbamoylthiophen-2-yl)urea **18** and 1-(2-carbamoyl-5-(quinoline-4-carboxamido)thiophen-3-yl)urea **19** in liver microsomes in the presence of glutathione or *N*-acetylcysteine as trapping agents (Figure 3). To conduct the metabolic phenotyping experiments, authors first attached the glutathione molecule to the thiophene ring and found that, 2,5-diaminothiophene moiety undergo oxidation to reactive intermediate i.e. 2,5-diimine thiophene. Further, they concluded that the disruption of reactive intermediate (2,5-diimine thiophene) resulted in the elimination of glutathione conjugate both *in vitro* and *in vivo*. These findings provide a rational approach in drug design to migrate potential safety risks in drug research and development.

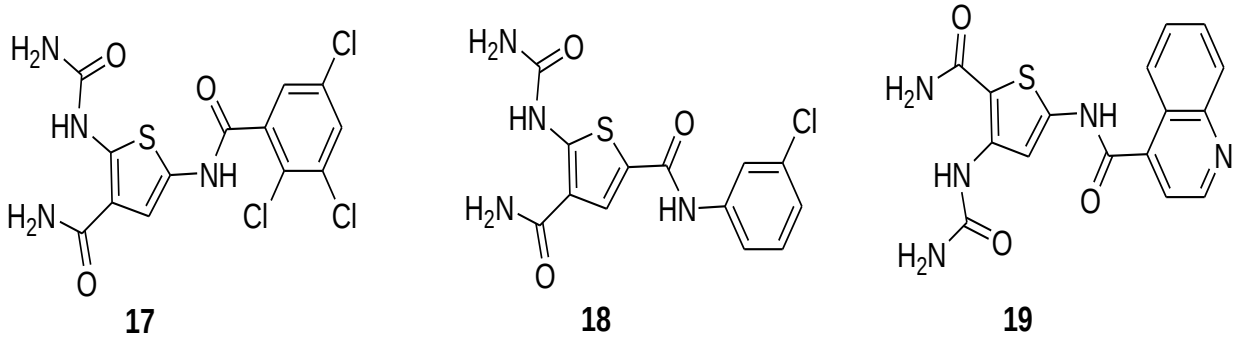


Figure 3: Anti-inflammatory activity of 2-amiothiophene derivatives 17-19

(iii) Antifungal and antiproliferative

Francisco J. B. Mendonca and group[25] reported the synthesis and *in vitro* antifungal activity of 2-(substituted-amino)-4,5-dialkyl-thiophene-3carbonitrile derivatives **20** and **21** against 42 isolates of *Candida* and 2 isolates of *Criptococcus* with MFC values ranging between 100-800 □g/mL (Figure 4).

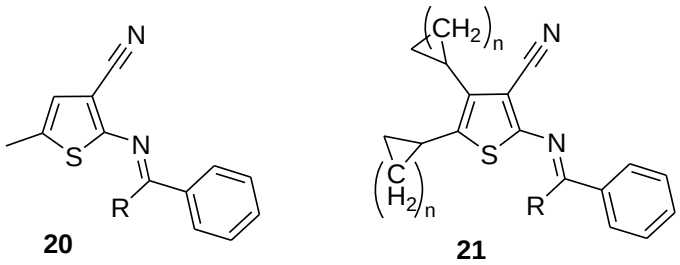


Figure 4: Anticonvulsant activity of 2-amiothiophene derivatives 20 and 21

Francisco J. B. Mendonca *et al.*[26] screened a series of 2-[(arylidene)amino]-cycloalkyl[*b*]thiophene-3carbonitrile **22** (Figure 5) for antifungal activity against *Candida krusei* and *Criptococcus neoformans* and antiproliferative activity against 3 human cancer cell lines (HT29, NCI H-292 and HEP) and obtained the best promising results of antifungal activity for the **22d, 22g**, **22i-k** and **22t** compounds whereas antiproliferative activity for the **22r** compound.

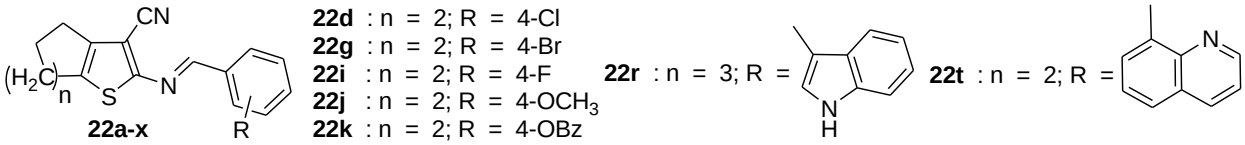
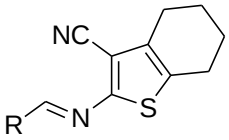


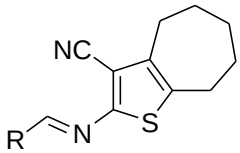
Figure 5: Antifungal and antiproliferative activity of 2-aminothiophene derivatives 22

A. C. Veras of Aguiar *et al.*[27] evaluated the antiproliferative activity of MIT assay submitted 2-aminothiophene derivatives **23** and **24** (Figure 6) in concentrations 5, 10, 25 and 50 mM during 24 and 48 h against human cancer cell lines of adenocarcinoma (HeLa), human pancreatic adenocarcinoma (PANC-1) and mice fibrolasts (3T3). Among the screened thiophene derivatives **23d** and **24a** have great antiproliferative potential in the Hela and PANC-1 cell linens when compared to the standard drug doxorubicin (Dox) and can be considered as potent molecular candidates for anticancer drugs.



23a-d

23a R = 5-Bromo-2-methoxi-benzylidene
23b R = 4-Nitro benzylidene
23c R = 4-Methoxi-benzylidene
23d R = 4-Fluoro benzylidene



24a-b

24a R = 5-Bromo-2-methoxi-benzylidene
24b R = 4-Chloro benzylidene

Figure 6: Antiproliferative activity of 2-aminothiophene compounds 23 and 24

(iv) Antifungal and antihelminthic

Pavan Kumar K. *et al.*[28] synthesized and screened novel Mannich baess and Schiff bases of 2-amino thiophenes viz. (*E*)-ethyl 2-(4-hydroxy-3-methoxybenzylideneamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate **25**, (*Z*)-ethyl 2-(2-oxoindolin-3-ylideneamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate **26**, (*Z*)-ethyl 2-(1-((piperazin-1-yl)methyl)indolin-3-ylideneamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate **27**, (*Z*)-ethyl 2-(1-(morpholinomethyl)indolin-3-ylideneamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate **28**, (*E*)-ethyl 2-(4-nitrobenzylideneamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate **29**, (*Z*)-2-(2-oxoindolin-3-ylideneamino)-4,5,6,7-tetrahydro-N-p-tolylbenzo[*b*] thiophene-3-carboxamide **30** (Figure 7) for the antifungal antihelminithic activity against the fungus *Aspergillus niger*, *Cladosporium* and antihelminthic activity against *Pheretima posthuma*. They found that the compounds (**26** and **30**) having indole ring with free NH group have shown the moderate activity against standard drugs when compared to other derivatives. Further, the presence of piperazine and morpholine substitution on indole ring have made the compounds **27** and **28** to exhibit moderate antihelminitic activity and low antifungal activity.

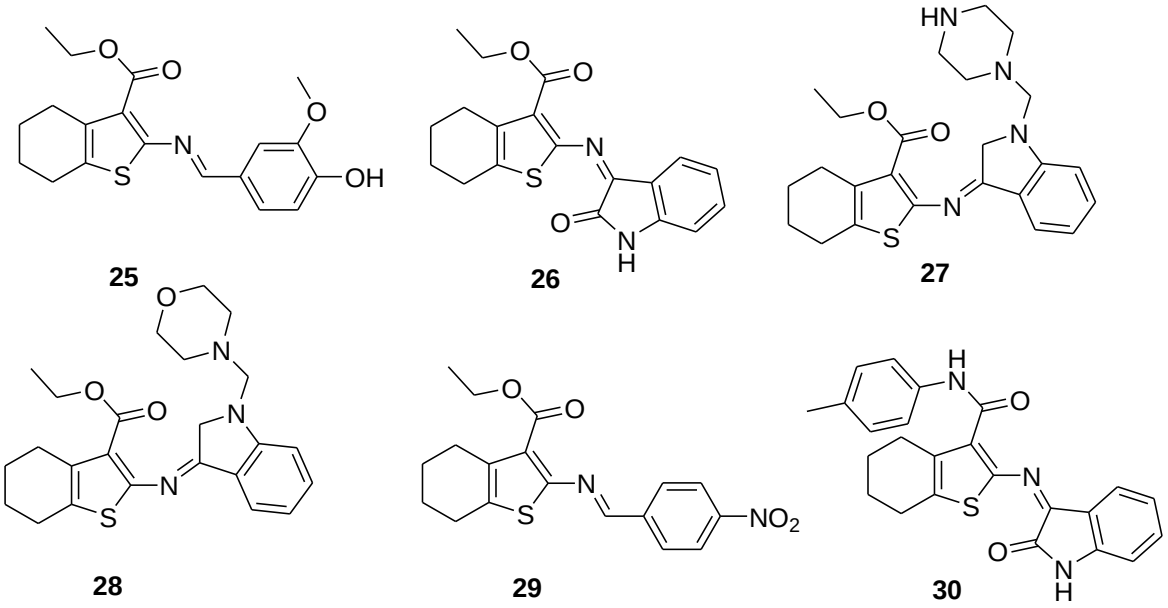


Figure 7: Antifungal and antihelminthic activity of 2-amiothiophene derivatives 25-30

(v) Anxiolytic

R. M. Freitas *et al.*[29] reported the 2-aminothiophene derivative viz. 2-[(2,6-dichlorobenzylidene)amino]-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carbonitrile **31** as potential compound bearing anxiolytic properties in animal models with comparable results against standard tranquillizing drug Diazepam (Figure 8).

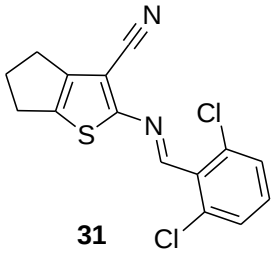


Figure 8: Anxiolytic activity of 2-[(2,6-dichlorobenzylidene)amino]-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carbonitrile 31

(vi) Antagonist

Joseph L. Duffy and group[30] discovered a novel class of aminothiophene-derivatives **32-42** as potent antagonists of human glucagon receptor where, the compound **13** reported to have exhibited conceivable potency with IC_{50} 34 nM (Figure 9).

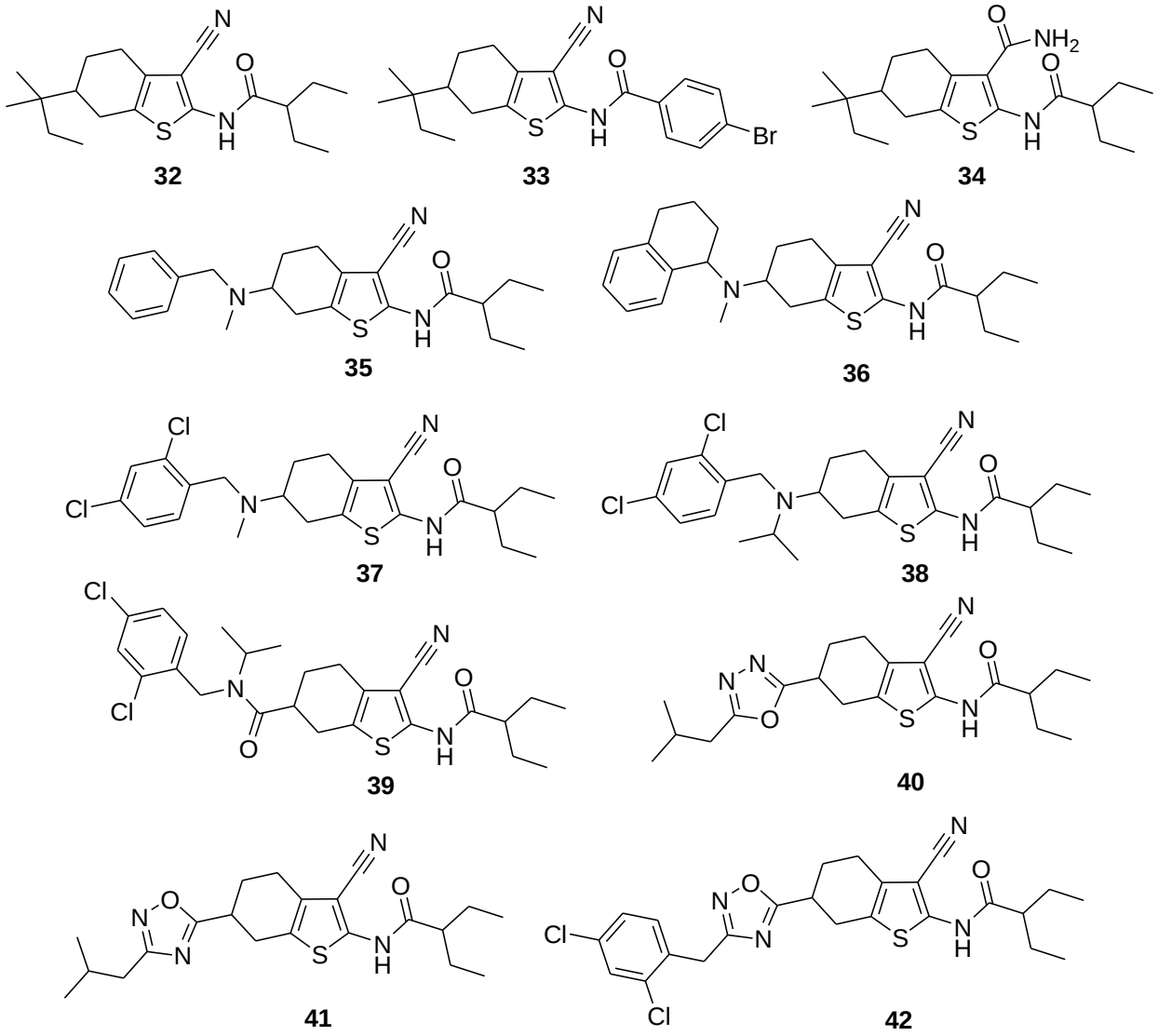


Figure 9: Antigonist activity of 2-aminothiphene derivatives 32-42

(vii) Antiarrhythmic, serotonin antaonist and antianxiety

A.E.-G.E. Amr *et al.*[31] screened aminothiophene derivatives **43-55** for antiarrhythmic, serotonin antaonist and antianexiety activities and reported that all these tested derivatives have shown enhanced activity when compared their calculated LD50 values against standard drugs viz. Procaine amide, Lidocaine, Diazepam and Buspirone (Figure 10).

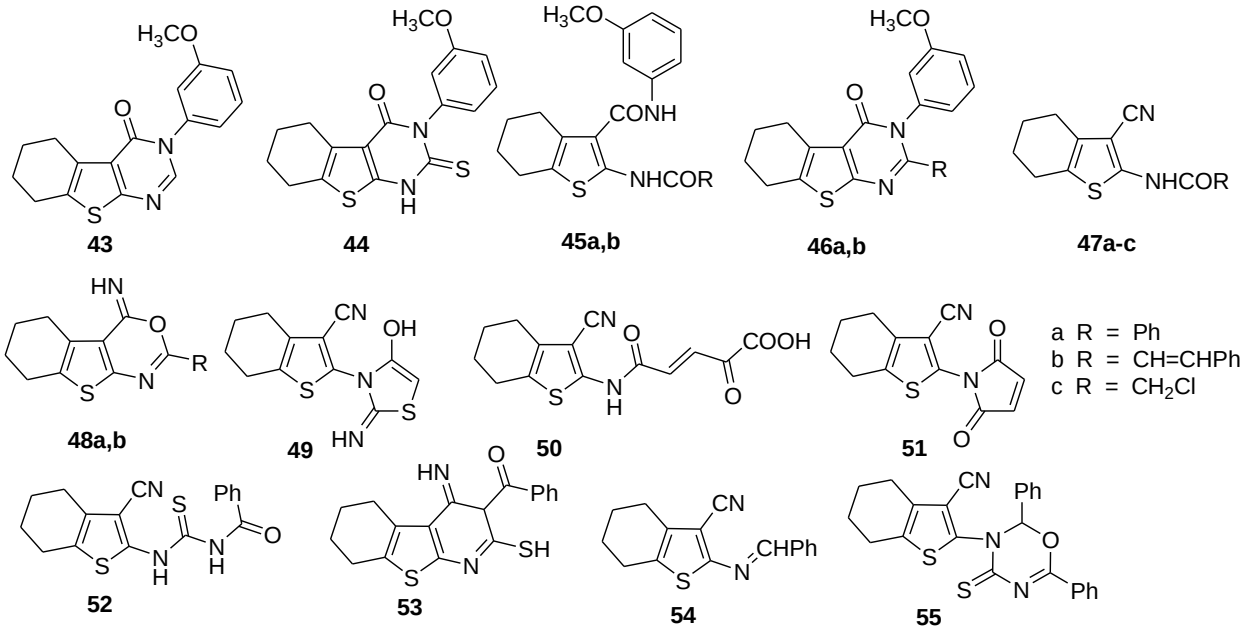
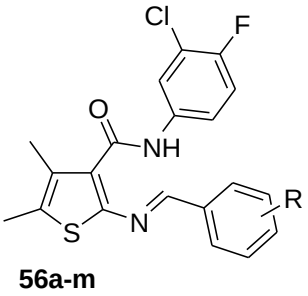


Figure 10: Antiarrhythmic, serotonin antaonist and antianexiety activity of 2-aminothiphene derivatives 43-55

(viii) Anti-platelet aggregation

Jagadish ER *et al.*[32] evaluated *in-vitro* anti-platelet aggregation activity of new substituted aminothiophenes **56** by GVR Born method using *Heparin* as the standard and further suggested that among the tested derivatives **56a**, **56b**, **56d** and **56i** compounds have shown significant activities (Figure 11).



56a R = 2-chloro
56b R = 4-chloro
56c R = 2-nitro
56d R = 3-nitro
56e R = 4-methyl
56e R = 4-methoxy
56g R = 4-hydroxy-3-methoxy
56h R = 4-dimethyl amino
56i R = 2-hydroxy
56k R = 3,4-dimethoxy
56l R = 3,4,5-trimethoxy
56m R = H

Figure 11: Anti-platelet aggregation activity of 2-aminothiphene derivatives 56

(ix) Antimitotic

Romeo Romagnoli *et al.*[33] studied biological evaluation of 2-aminobenzo[*b*]thiophene derivatives **57** for antimitotic activity and further, reported the compound 2-amino-6-methyl-3-(3,4.5-trimethoxybenzoyl)benzo[*b*]thiophene **57d** as cancer cell growth inhibitor at significantly low (subnanomolar) concentrations (Figure 12).

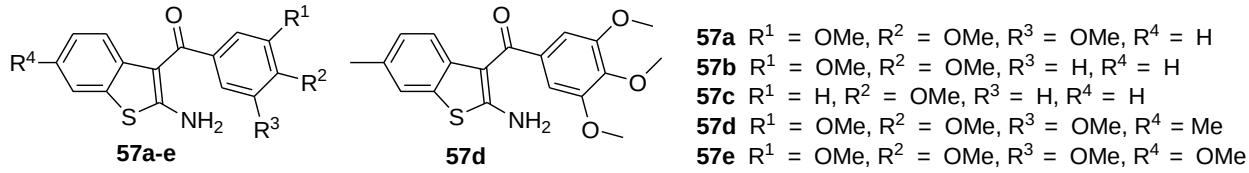


Figure 12: Antimitotic activity of 2-aminothiphene derivatives 57

(x) Glycogen synthase kinase-3*β* inhibitior

Baki *et al.*[34] demonstrated a high throughput luminescent assay based on the Kinase-Glo™ system (Promega, Madison, WI) and analyzed five different chemical classes viz. 3-substituted-2-aminothiophenes **58**, 3,5-disubstituted-isothiazole-4-carbonitriles **59**, substituted thiazolidinones **60**, benzo[*c*]isothiazole-3-ones **61**, 2-substituted thienopyridines and benzothiophenes **62** to yield several highly active glycogen synthase kinase-3β (GSK-3 β)GSK-3 β inhibitors with IC_{50} values between 0.34 and 1 μM (Figure 13).

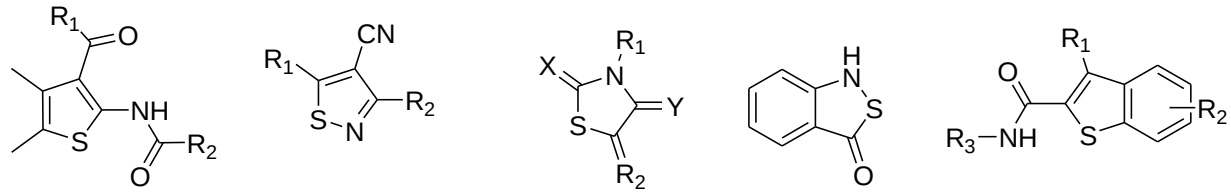


Figure 13: Glycogen synthase kinase-3β inhibition activity of 3-substituted-2-aminothiophenes 58-62

(xi) Antileishmanial

An antileishmanial study carried by M. R. Oliveira *et al.*[35] on 2-aminothiophene derivatives **63** and **64** against the promastigote and amastigote forms of *Leishmania amazonensis* revealed the lower levels of cytotoxicity to host cells (murine macrophages and human red cells) and further, the best values were obtained for the compounds containing lethal indole ring. Out of all the studied compounds the three compounds **64e**, **64f** and **64g** have been found to be effective against macrophage infection whereas anti-amastigote activity of compounds **64g** and **64f** has been associated with the modulation of the host immune response (Figure 14).

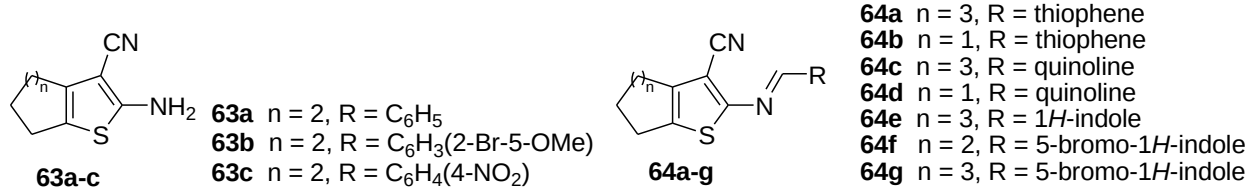
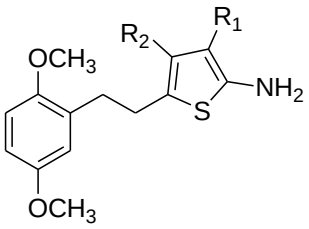


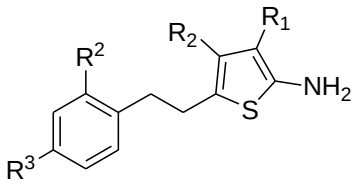
Figure 14: Antileishmanial activity of 2-aminothiophene derivatives 63 and 64

(xii) Antitumor

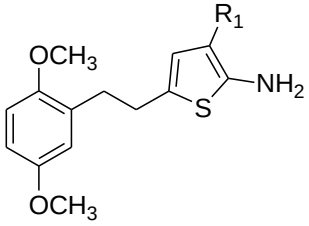
Romeo Romagnoli an coworkers[36] evaluated the 3,5-disubstituted 2-aminothiohene derivatives **65**, **66** and **67** as a novel class of antitumor agents. Among the synthesized compounds, the identified the 2-amino-3-cyano-[2-(2,5-dimethoxyphenylethyl]thiophene **65c** as the most promising derivative against a wide panel of cancer cell lines with IC_{50} valued 17-130 nM (Figure 15).



65a-e



66a-h



67a-b

35a $R^1 = CO_2Me$, $R^2 = H$
35b $R^1 = CO_2Et$, $R^2 = H$
35c $R^1 = CN$, $R^2 = H$
35d $R^1 = CO_2Me$, $R^2 = Me$
35e $R^1 = R^2 = CO_2Et$

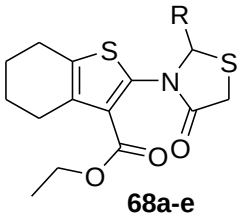
66a $R^1 = CO_2Me$, $R_2 = OMe$, $R_3 = H$
66b $R^1 = CO_2Me$, $R_2 = H$, $R_3 = OMe$
66c $R^1 = CO_2Me$, $R_2 = Me$, $R_3 = OMe$
66d $R^1 = CO_2Et$, $R_2 = OMe$, $R_3 = H$
66e $R^1 = CO_2Et$, $R_2 = H$, $R_3 = OMe$
66f $R^1 = CN$, $R_2 = OMe$, $R_3 = H$
66g $R^1 = CN$, $R_2 = H$, $R_3 =$ OMe
66h $R^1 = CN$, $R_2 = R_3 = H$

67a $R^1 = CO_2Me$
67b $R^1 = CN$

Figure 15: Antitumor activity 3,5-disubstituted 2-aminothiohene derivatives 65, 66 and 67

(xiii) Antimicrobial

Raghav Mishra and Isha Tomar[37] evaluated the low to moderate antimicrobial activity of some novel derivatives of 2-aminothiophene **68** (Figure 16) against two bacterial strains *Escherichia coli* and *Streptococcus pneumoniae* and two fungal stains *Pseudomonas aeruginosa* and *Candida albicans* at 100 µg/ml using Ampicillin as standard drug.



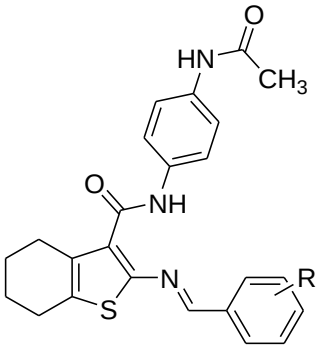
68a-e

68a R = C_6H_4(2-OH)
68b R = C_6H_4(4-OCH3)
68c R = C_6H_3(3,4-OCH_3)
68d R = C_6H_4(4-$N(CH_3)_2$)
68e R = C_6H_4(4-Cl), C_6H_5

Figure 16: Antimicrobial activity of 2-aminothiophene derivatives 68

Arora *et al.*[38] screened a series of novel 2-amino-*N*-(*p*-acetamidophenyl caboxamideo)-4,5,6,7-tetramethylene thiophenes **69** for antimicrobial activities where the antibacterial activity tested against Gram-positive bacteria (*Straphylococcus aureus* and *Bacillus subtilus*), Gram-positive bacteria (*Escherichia coli* and *Klebsiella pneumoniae*) and antifungal activities against fungi (*Candida albicans* and *Aspergillus niger*) at concentration 50 µg/0.1 mL using agar diffusion

method. Among all compounds **69b**, **69c**, **69g**, **69h** and **69i** have shown excellent activity comparable to standard drugs viz. Ampicillin, Norfloxacin and Miconazole nitrate (Figure 17).

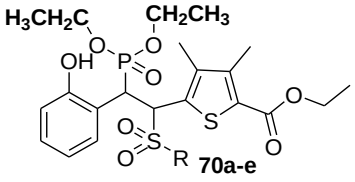


69a-l

69a R = 4-dimethyl amino
69b R = 4'-hydroxy
69c R = 2'-hydroxy
69d R = 2'-nitro
69e R = 3'-nitro
69f R = 3',4'-dimethoxy
69g R = 4'-hydroxy 3'-methoxy
69h R = 2'-chloro
69i R = 4'-chloro
69j R = 4'-methoxy
69k R = 4'-nitro
69l R = 4'-methyl

Figure 17: Antimicrobial activity of 2-amino-*N*-(*p*-acetamidophenyl caboxamideo)-4,5,6,7-tetramethylene thiophenes 69

Naga Raju. C *et al.*[39] carried out *in vitro* antimicrobial activity of phosphonated *N*-(substituted phenyl) sulfonamides of 2-aminothiophene **70** and reported the significant enhancement of these derivatives when compared with active α-aminophosphonate (Figure 18).



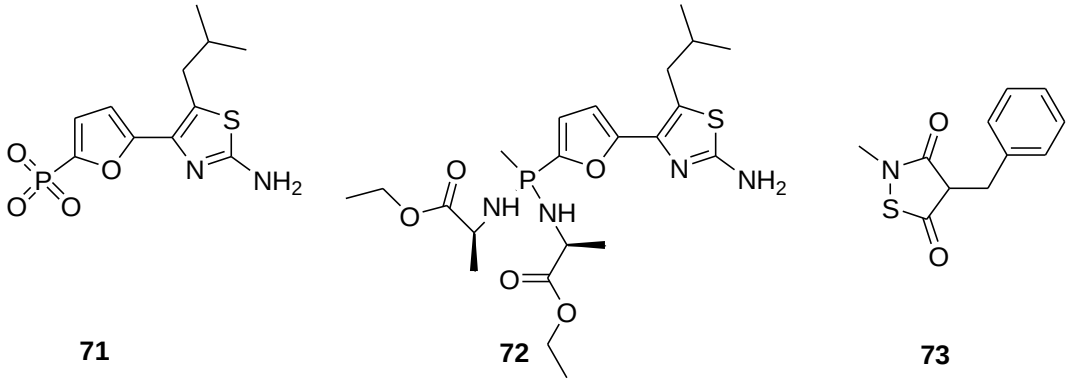
70a-e

70a R = F
70b R = Br
70c R = NO_2
70d R = Cl, NO_2
70e R = HO, NO_2

Figure 18: Antimicrobial activity of phosphonated *N*-(substituted phenyl) sulfonamides of 2-aminothiophene 70

(xiv) Toxicological and fluorescence studies

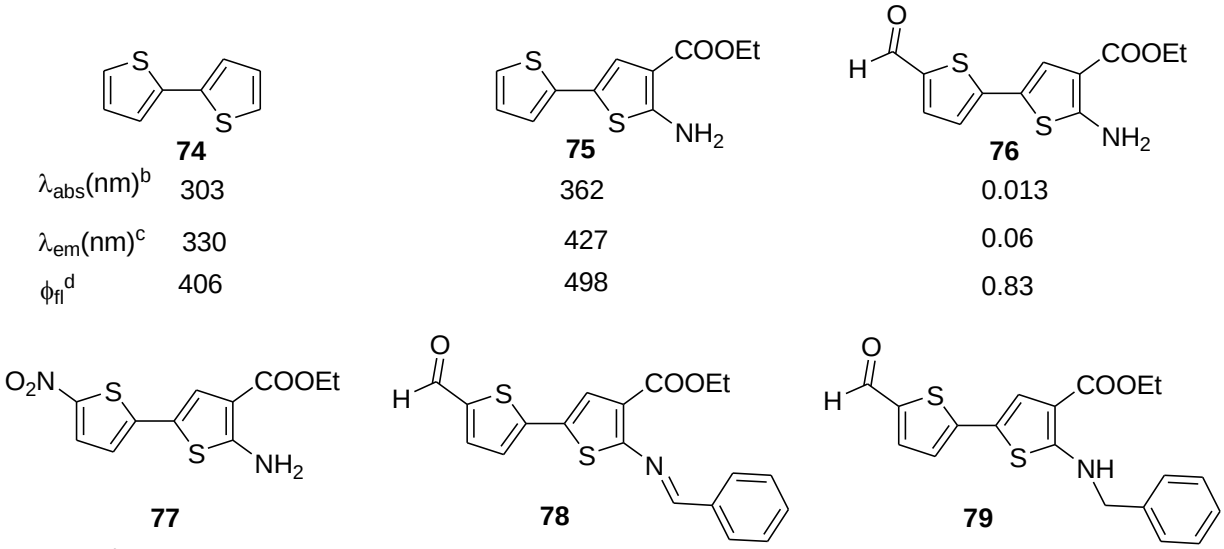
Philip J. Hajduk *et al.*[40] reported the toxicological evaluation of thiol-reactive 2-aminothiophene derivatives **71**, **72** and **73** (Figure 19) against a panel of additional proteins (aldehyde dehydrogenase, superoxide dismutase, and three cytochrome P450 enzymes to detect reactive false positive hits from high-throughput screening using a La Assay to analyse reactive molecules by nuclear magnetic resonance (ALARM NMR).



71 **72** **73**

Figure 19: Toxicological evaluation of thiol-reactive 2-amiothiophene derivatives 71-73

W. G. Skene *et al.*[41] demonstrated fluorescence on-off properties of 2-aminobithiophenes derivatives such that the resulting push-pull bithiophenes viz. 2-(thiophen-2-yl)thiophene **74**, ethyl 2-amino-5-(thiophen-2-yl)thiophene-3-carboxylate **75**, ethyl 2-amino-5-(5-formylthiophen-2-yl)thiophene-3-carboxylate **76**, ethyl 2-amino-5-(5-nitrothiophen-2-yl)thiophene-3-carboxylate **77**, (E)-ethyl 2-(benzylideneamino)-5-(5-formylthiophen-2-yl)thiophene-3-carboxylate **78** and ethyl 2-(benzylamino)-5-(5-formylthiophen-2-yl)thiophene-3-carboxylate **79** exhibited both unprecedented high fluorescence yields and stability (Figure 20).



	74	**75**	**76**
$\lambda_{abs}(nm)^b$	303	362	0.013
$\lambda_{em}(nm)^c$	330	427	0.06
ϕ_{fl}^d	406	498	0.83

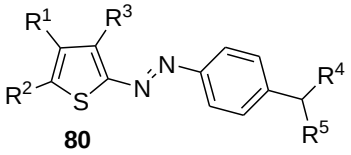
	77	**78**	**79**
$\lambda_{abs}(nm)^b$	494	600	0.76
$\lambda_{em}(nm)^c$	424	492	0
ϕ_{fl}^d	422	507	0.74

a Measured in anhydrous deaerated dichloromethane. b Absorbance maximum. c Fluorescence maximum. d Absolute quantum fluorescence yield measured with an integrating sphere.

Figure 20: Absorbance and fluorescence data of 2-aminothiophene derivatives 74-79[a]

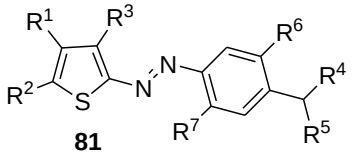
C. Synthon for biologically useful heterocyclic moieties

Dye is an organic compound which can absorb light in the visible region of the electromagnetic spectrum (400 nm to 750 nm). Dyes with heterocyclic diazo components have received much attention because of their high tinctorial power and excellent brightness. Towns *et al.*[15] summarized developments in azo disperse dyes derived from heterocyclic diazo components **80** and **81** (Figure 21).



80

R^1, R^2 = H, alkyl, alkoxy, aryl, CN, COOalkyl, $COONH_2$, NO_2
R_3 = CN, COOalkyl, $CONH_2$, COC_6H_5
R^4, R^5 = H, alkyl, hydroxyalkyl, cyanoalkyl, acetoxyalkyl, aryl, benzyl

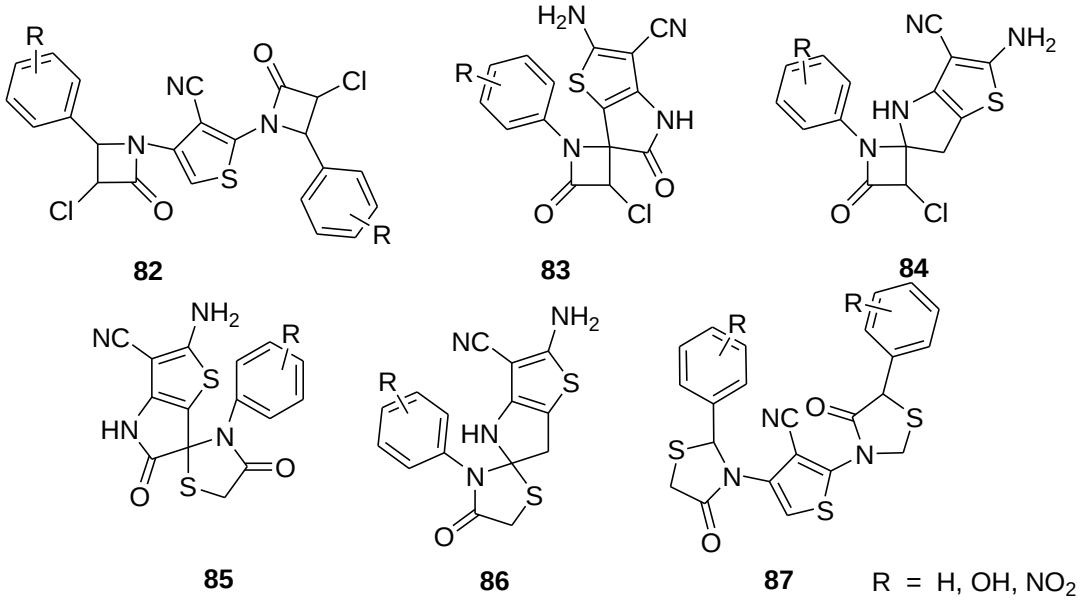


81

R^1, R^2 = H, alkyl, alkoxy, aryl, CN, COOalkyl, $COONH_2$, NO_2
R^3 = CN, COOalkyl, $CONH_2$, COC_6H_5
R^4, R^5 = H, alkyl, hydroxyalkyl, cyanoalkyl, acetoxyalkyl, aryl, benzyl
R^6 = H, CH_3, OCH_3
R^7 = H, CH_3, OCH_3, Cl, Br, CN, COOEt, CH_3CONH_2

Figure 21: Dyes containing 2-aminothiophene heterocycles 80 and 81

H. A. Soleiman and N. A. A. Elkanzi[42] carried out the heterocyclic synthesis of new spiro, isolated β-lactam **82-84** and thiazolidinone **85-87** containing 3-cyano-2,4-diamino thiophene moiety using 3-cyano-2,4-diamino thiophene as starting substrate (Figure 22).

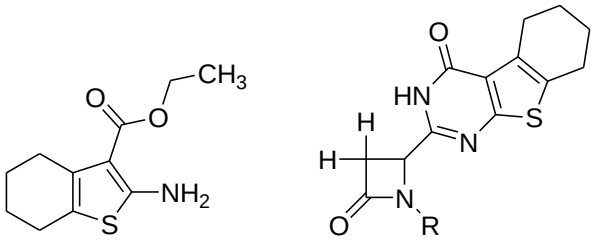


82 **83** **84**

85 **86** **87** R = H, OH, NO_2

Figure 22: New spiro, isolated β-lactam 82-84 and thiazolidinone 85-87 containing 3-cyano-2,4- diamino thiophene moiety

Seema Kanwar and S. D. Sharma[43] reported a facile and efficient method for the synthesis of β-lactams **89** containing thienopyrimidine as hetryl moiety using 2-amino-4,5,6,7-tetrahydrobenzo[*b*] thiophene-3-carboxamide **88** as starting substrate (Figure 23).



88 **89**

R = $C_6H_4(OCH_3\text{-}p)$, $C_6H_4(CH_3\text{-}p)$

Figure 23: β-Lactams 89 containing thienopyrimidine synthesized using 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide 88

CONCLUSION

In this review, an update on the synthetic procedures (Gewald, solid-support, cross-coupling, nitration and reduction reactions), toxicoological and biological evaluations (anticonvulsant, anti-inflammatory, antifungal, antihelminithic, antiproliferative, anxiolytic, antagonist, antiarrhythmic, antianxiety, anti-platelet, antimitotic, antiantileishmanial, antitumor and antimicrobial) of 2-aminothiophene and its analogues has been comprehended. Further, brief report on applications of 2-aminothiphene heterocycle as synthon in the field of fluorescence and luminescence, analytical, dye and □-lactam chemistry has been elaborated. This review will assist all those interested in 2-aminothiophene heterocyclic moiety to reach decisions in the choice of targets and tasks for further investigations. We sincerely apologize to those scientists whose work may not have included in this review either due to the limited description of the review or oversight.

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