WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 2, 1368-1377. Research Article ISSN 2277– 7105

DESIGN, SYNTHESIS, CHARACTERIZATION & IN-SILICO PREDICTION OF SUBSTITUTED 2-AMINOTHIOPHENE, 1,3,4-THIADIAZOLE AND THIENO[2,3- d] PYRIMIDINE DERIVATIVES

P. L. N. Ranganath[1]*, N. D. Nizamuddin[2], S. K. Rubina[3] and A. Hemanth[4]

[1]Assistant Professor, Dept. of Pharmaceutical Chemistry, St. Johns College of Pharmaceutical Sciences, Yerrakota, Yemmignur, Andhra Pradesh, India.

[2]Associate Professor, Dept. of Pharmaceutical Chemistry, St. Johns College of Pharmaceutical Sciences, Yerrakota, Yemmignur, Andhra Pradesh, India.

[3]Asst. Professor, Department of Pharmaceutics, St. Johns college of Pharmaceutical Sciences.

[4]Assoc. Professor, Department of Pharmaceutics, St. Johns college of Pharmaceutical Sciences.

Article Received on
13 Dec. 2018,
Revised on 03 Jan. 2019,
Accepted on 24 Jan. 2019
DOI: 10.20959/wjpr20192-14205

***Corresponding Author**
P. L. N. Ranganath
Assistant Professor, Dept. of Pharmaceutical Chemistry, St. Johns College of Pharmaceutical Sciences, Yerrakota, Yemmignur, Andhra Pradesh, India.

ABSTRACT

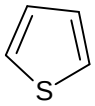
Thiophene has a promising role in the chemical pool heterocyclic compounds fused with an other heteroaromatic systems have numerous pharmacological activities like antimicrobial, antiviral, anti-inflammatory, antidiabetic, antioxidant, anticancer, antidepressant, antiplatelet, antituberculosis, anticonvulsants, anti hypertensive, antioxidant and antifungal properties. Keeping this in view, the present work deals the retrosynthesis of some novel Substituted 2- Amino thiophene, 1,3,4-Thiadiazole And Thieno[2,3-d]Pyrimidine derivatives.

KEYWORDS: 2- Amino thiophene derivatives, 1,3,4-Thiadiazole derivatives, Thieno[2,3-d]pyrimidine derivatives.

INTRODUCTION

Thiophene belongs to a class of heterocyclic compounds containing a five membered ring made up of one sulphur as heteroatom with the formula C_4H_4S. Thiophene and its derivatives exist in petroleum or coal. Thiophene is taken from the word *theion*, the Greek word for sulfur, and another Greek word *phaino* which means shinning. Thiophene can be fused with

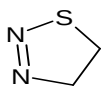
various heterocyclic systems giving rise to various new heterocyclic system with enhanced biological activity.[1-5]



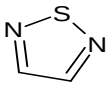
Thiophene

1

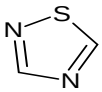
1, 3, 4- Thiadiazole moiety have been widely used by the medicinal chemist in the past to explore its biological activities. The Development of 1, 3, 4-Thiadiazole Chemistry is linked to the discovery of Phenylhydrazines and hydrazine in the late nineteenth century. The first 1, 3, 4-Thiadiazole was described by Fischer in 1882 but the true nature of the ring system was demonstrated first in 1890 by Freund and Kuh. There are several isomers of thiadiazole, that is 1,2,3 Thiadiazole **(2)**, 1,2,5 Thiadiazole **(3)**, 1,2,4 Thiadiazole **(4)** and 1,3,4 Thiadiazole **(5)**.



2



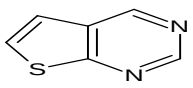
3



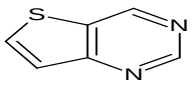
4

5

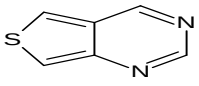
Thienopyrimidine is a bicyclic heterocyclic compound wherein a five membered thiophene ring is fused to a six membered heterocylic ring with two nitrogen atoms. Three possible types of annelation of thiophene to the pyrimidine ring and correspondingly, three isomeric thienopyrimidines are known thieno[2,3-d]pyrimidine**(6)**, thieno[3,2-d]pyrimidine**(7)** and thieno[3,4-d]pyrimidine**(8)**. The structures and the conventional numbering of these heterocyclic systems are shown below.



6

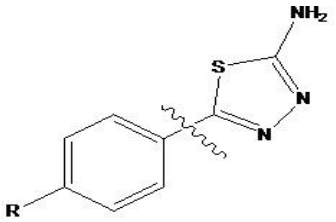


7

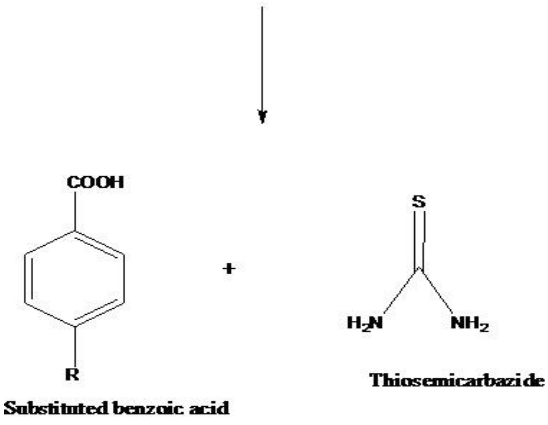


8

Retrosynthetic analysis of substituted 1,3,4-thiadiazole derivatives



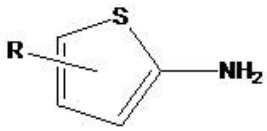
2 Substituted 2,5 thiadiazole



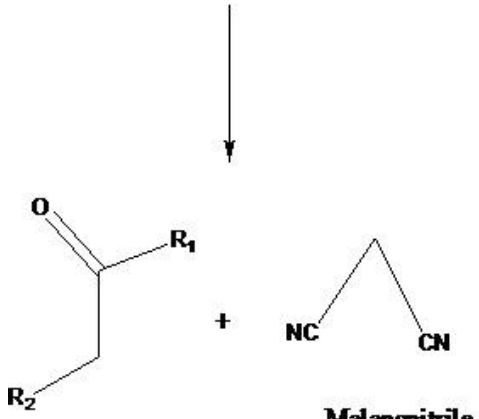
Substituted benzoic acid

Thiosemicarbazide

Retrosynthetic analysis of substituted 2- amino thiophene derivatives



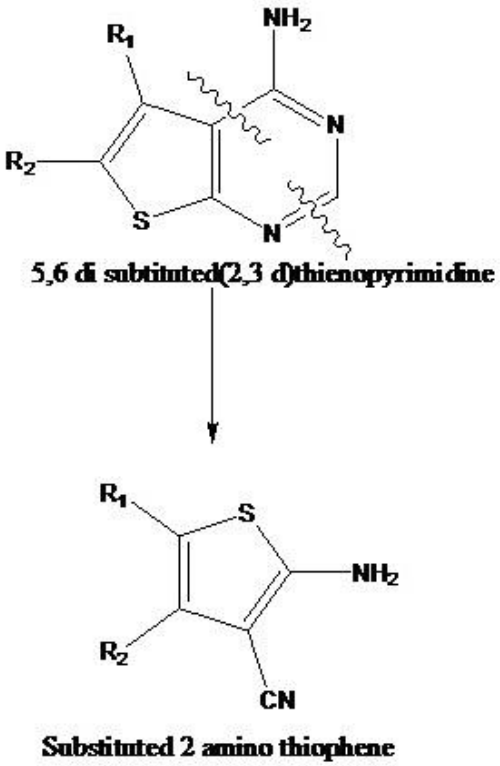
Substituted 2 amino thiophene



Di substituted ketone

Malanonitrile

Retrosynthetic analysis of 5,6 di substituted (2,3 d) thienopyrimidine

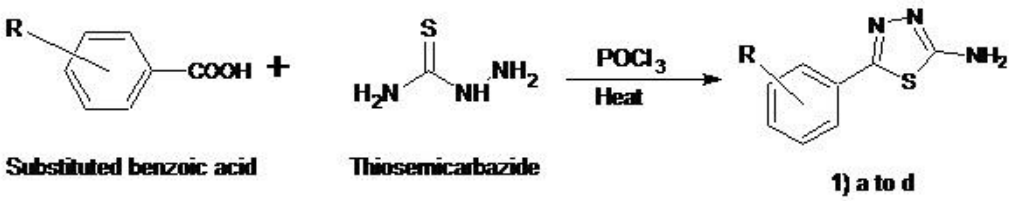


MATERIALS AND METHODS

Melting points of the compounds were determined using open Capillary Melting point apparatus and were reported -uncorrected. IR spectra were detected in BRUKER FT-IR 4000: using KBr disk. All the chemicals and solvents used in this study were of analytical grade. Reaction progress was checked by TLC in a solvent-vapoursaturated chamber on glass plates coated with silica gel GF 254 followed by visualization under UV light (254 nm). The solvent system used for thin layer chromatography was Hexane: Ethyl Acetate (7:3).

Synthesis of substituted thiadiazole derivatives[6]

Substitued Amino Benzoic Acid (0.1mol) and thiosemicarbazide (0.1mol) in phosphorous oxychloride(30ml) were refluxed gently for 30mins and cooled followed by careful addition water (90ml) the separated solid was filtered and suspended in water and basified with aqueous potassium hydroxide followed by filtration, drying and crystallization from mixture of DMF and ethanol.

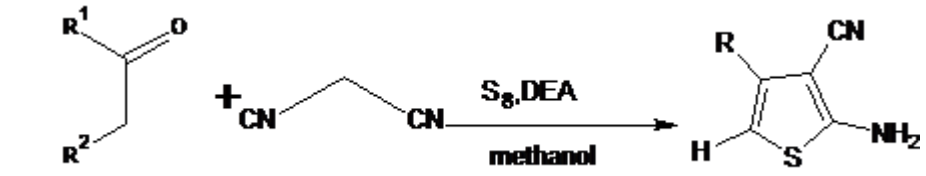


R= a) 4 amino
b) 3 amino
c) 2 hydroxy
d) benzoic acid

Scheme: 1

Synthesis of substituted 2- amino thiophene[7]

Equimolar amount (0.05mol) of sulphur (1.6g) malononitrile and (3.15g) di subtituted ketone was taken in a RBF containing 10ml of methanol (The reaction is exothermic and explosive, so the reagents should be added dropwise by keeping in an icebath) the mixture was stirred for 5min then diethylamine (0.06mol, 6.23ml) was slowly added to the reaction mixture at 50^0C with constant stirring for 10-15mins later the reaction mixture was allowed to stirr for 5hours at RT and left in refrigerator overnight the crystals thus formed were collected by filtration under reduced pressure and washed with cold methanol completion of reaction was determined by TLC. TLC was also done to determine the completion of reaction using (hexane and ethyl acetate).



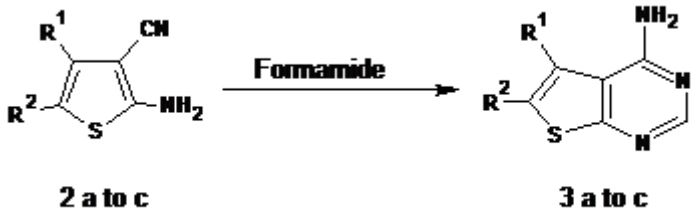
a)Acetone
b)Acetophenone
c)Ethyl acetoacetate

Scheme: 2

Synthesis of substituted (2,3 d)- thienopyrimidine derivatives[8]

Equimolar amount (0.05mol) of sulphur (1.6g) malononitrile and (3.15g) disubstituted ketone was taken in a RBF containing 10ml of methanol (The reaction is exothermic and explosive,

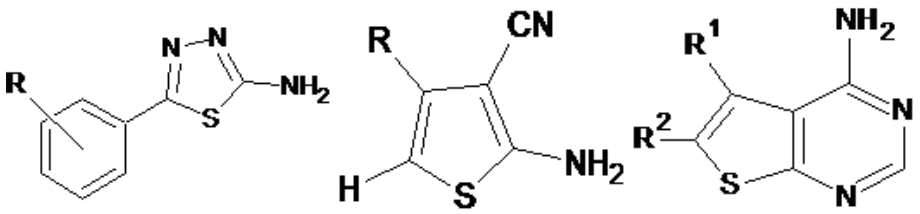
so the reagents should be added drop wise by keeping in an icebath) the mixture was stirred for 5 mins then diethylamine (0.06mol, 6.23ml) was slowly added to the reaction mixture at 50^0C with constant stirring for 10-15 mins later the reaction mixture was allowed to stirr for 5hours at RT and left in refrigerator overnight the crystals thus formed were collected by filtration under reduced pressure and washed with cold methanol completion of reaction was determined by TLC. TLC was also done to determine the completion of reaction using benzene: methanol system (benzene 4.5ml:methanol 1-2 drops). to an RBF substituted thiophene (0.01mol) and formamide (8ml) were taken. It was refluxed for one and half hours above 100^0C. The reaction mixture was allowed to cool to room temperature and stirred overnight. To the suspension water was added, filtered and washed with water. The product obtained was recrystalized using ethanol. TLC was also done to determine the purity of the compound using hexane and ethyl acetate.



2 a to c 3 a to c

Scheme: 3.

List of synthesized compounds are follows



1A-1D **2A-2C** **3A-3C**

1A. 5-phenyl-1,3,4-thiadiazol-2-amine

1B. 2-(5-amino-1,3,4-thiadiazol-2-yl)phenol

1C. 5-(3-aminophenyl)-1,3,4-thiadiazol-2-amine

1D. 5-(4-aminophenyl)-1,3,4-thiadiazol-2-amine

2A. 2-amino-4-methylthiophene-3-carbonitrile

2B. 2-amino-4-phenylthiophene-3-carbonitrile

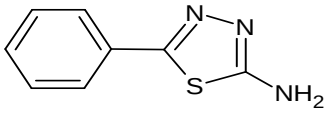
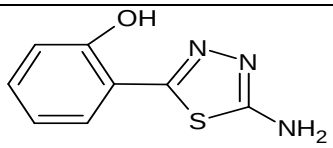
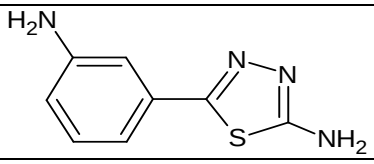
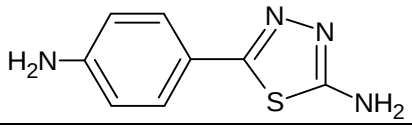
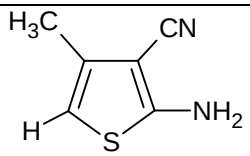
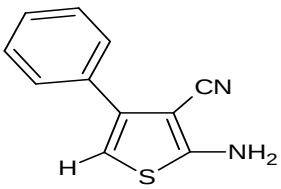
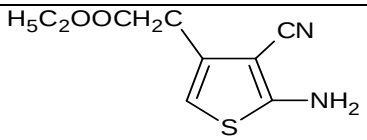
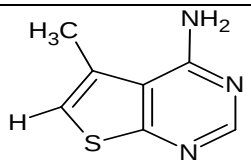
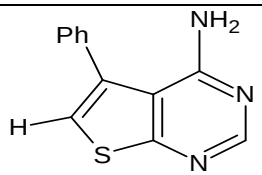
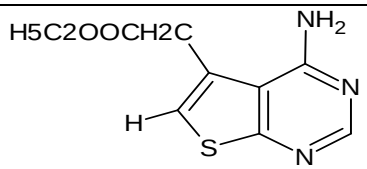
2C. ethyl (5-amino-4-cyanothiophen-3-yl)acetate

3A. 5-methylthieno[2,3-*d*]pyrimidin-4-amine

3B. 5-phenylthieno[2,3-*d*]pyrimidin-4-amine

3C. ethyl (4-aminothieno[2,3-*d*]pyrimidin-5-yl)acetate

Table 1: Physical analysis data of Synthesized compounds (1a-1d, 2a-2c & 3a-3c).

Compound	Synthesized compounds	Mol. formula	Mol. Mass	M.P/B.P (^{0}C)	% yield
1A		$C_8H_7N_3S$	177.22	78-80	63.61
1B		$C_8H_7N_3OS$	193.2	42-45	32.2
1C		$C_8H_8N_4S$	192.24	72-75	66.14
1D		$C_8H_8N_4S$	192.24	45-50	63.8
2A		$C_6H_6N_2S$	138.19	120-125	14.26
2B		$C_{11}H_8N_2S$	200.25	128-130	27.63
2C		$C_9H_{10}N_2O_2S$	210.25	147-150	91.91
3A		$C_7H_7N_3S$	165.22	80	91.06
3B		$C_{12}H_9N_3S$	227.28	85	77.80
3C		$C_{10}H_{11}N_3O_2S$	237.27	70	92.19

RESULTS AND DISCUSSIONS

A facile method has been devised to synthesize the title compounds where the pharmacophores benzoic acid, salicylic acid, 3-aminobenzoicacid, 4-aminobenzoicacid were incorporated into the formation of substituted 1, 3, 4-thiadiazoles. acetone, acetophenone, ethyl acetoacetate were incorporated into the formation of substituted 2-amino thiophene, and the resulting three end products of substituted 2-amino thiophenes are incorporated in to the formation of substituted (2,3-d) thienopyrimidines. The methods included mild conditions and the yields were satisfactory. The proposed reaction leads to expected products and in all cases the products were obtained in pure form. However they purified by re-crystallization from ethanol.

All the title molecules **1A, 1B, 1C, 1D, 2A, 2B, 2C, 3A, 3B & 3C** were predicted for selected physicochemical, biological properties using software and computer program PASS. The results of these predictions are given in Table No. **2 & 3**.

Table 2: IR Spectral data of synthesized compounds(1a-1d, 2a-2c & 3a-3c).

Compound	IR (KBr disc) position of absorption band (cm^{-1})	Compound	IR (KBr disc) position of absorption band (cm^{-1})
1A	3198.08(Aromatic) 3300(Amine) 1662.28(Imine) 761.24(Thiol)	**2B**	3207.97(Aromatic) 3318.41(Amine) 2064.68(Nitrile) 699.40(Thiol)
1B	1304.05(Hydroxyl) 3375.05(Aromatic) 758.38(Thiol) 3375.05(Amine) 1630(Imine)	**2C**	2204.24(Nitrile) 3316.71(Amine) 757.14(Thiol) 1494.48(Methylene) 1674.97(Ester) 1494.46(Methyl)
1C	3254.40(Amine) 2927.43(Aromatic) 750.82(Thiol) 1683.75(Imine	**3A**	1686.76(Imine) 3427.13(Amine) 669.29(Thiol) 1392.86(Methyl)
1D	3484.12(Amine) 3284.80(Aromatic) 1684.30(Imine)	**3B**	1681.08(Imine) 3426.67(Amine) 667.08(Thiol) 2922.55(Aromatic)
2A	2202.92(Nitrile) 3319.82(Amine) 1497.53(Methyl)	**3C**	1674.97(Imine) 3316.71(Amine) 757.14(Thiol) 1494.46(Methylene) 1868.35(Ester) 1494.46(Methyl)

PASS computer program predicts all title compounds to be Anti-viral & Anti-protozoal in nature as mentioned below.

Table 3: Predicted biological activities of synthesized compounds(1a-1d, 2a-2c & 3a-3c).

Compound	P_a	P_i	Activity
1A	0,613 0,368	0,004 0,050	Anti-protozoal Anti-viral
1B	0,640 0,400	0,004 0,035	Anti-protozoal Anti-viral
1C	0,593 0,452	0,009 0,074	Anti-protozoal Anti-viral
1D	0,138 0,235	0,008 0,100	Anti-protozoal Anti-viral
2A	0,286 0,232	0,076 0,132	Anti-protozoal Anti-viral
2B	0,170 0,455	0,169 0,073	Anti-protozoal Anti-viral
2C	0,208 0,456	0,112 0,072	Anti-protozoal Anti-viral
3A	0,180 0,380	0,153 0,045	Anti-protozoal Anti-viral
3B	0,418 0,446	0,034 0,078	Anti-protozoal Anti-viral
3C	0,385 0,446	0,044 0,078	Anti-protozoal Anti-viral
Standard (Metronidazole)	0,974 0,359	0,001 0,149	Anti-protozoal Anti-viral

CONCLUSION

All the title molecules **1A, 1B, 1C, 1D, 2A, 2B, 2C, 3A, 3B & 3C** were synthesized, characterized and screened for their antiviral & anti protozoal activities.

The results of antiviral & anti protozoal activities revealed that title compounds **1A-1D, 2A-2C & 3A-3C** exhibited significant activity. These compounds have benzoic acid, salicylic acid, 3-aminobenzoicacid, 4-aminobenzoicacid were incorporated into the formation of substituted 1, 3, 4-thiadiazoles. acetone, acetophenone, ethyl acetoacetate were incorporated into the formation of substituted 2-amino thiophene, and the resulting three end products of substituted 2-amino thiophenes are incorporated in to the formation of substituted (2,3-d) thienopyrimidines. The study revealed the necessity of synthesizing many more compounds having these moieties. Such compounds may emerge as much more potent antiviral & anti protozoal activities.

All the title molecules **1A-1D, 2A-2C & 3A-3C** were predicted for selected physicochemical, biological Properties. The activity suggests a novel compound **1A, 2A & 3A** have been shown highest activity. Rest of the compound exhibited mild to moderate activity when

compare to that of standard. From the above studies it is finally concluded that the 4-substituted-2-amino-1, 3-thiazole nucleus shows antiviral & anti protozoal activities.

REFERENCES

1. R. M. Mohareb et.al., Heterocyclic synthesis with ethyl α-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylhydrazono)acetates: An expeditious synthetic approach to polyfunctionally substituted pyran, pyridine, and pyridazine *derivatives, Hetero Atom Chem., 2004; 15: 300- 306.*
2. F. H. Havaldar et.al., J. Serb. Chem. Soc., 2004; 69: 527-532.
3. A. G. Waterson et.al., Synthesis and evaluation of aniline headgroups for alkynyl thienopyrimidine dual EGFR/ErbB-2 kinase inhibitors, Bioorg. & Med. Chem. Lett., 2009; 19: 1332-1336.
4. S. Pedeboscq et.al., Synthesis and study of antiproliferative activity of novel thienopyrimidines on glioblastoma cells, Euro. J. Med. Chem., 2010; 45: 2473-2479.
5. N. H. Ouf et.al., Synthesis and antiinflammatory activity of some pyrimidines and thienopyrimidines using 1-(2-Benzo[d][1,3]dioxol-5-yl)vinyl)-4-mercapto-6-methylpyrimidine-5-yl)ethan-2-one as a starting material, Monatsh Chem., 2008; 139: 579-585.
6. Kadi AA et.al., Synthesis, antimicrobial and antiinflammatory activities of novel 5-(1-adamantyl)-1,3,4-thiadiazole derivatives. Eur J Med. Chem., 2010; 45(11): 5006-5011.
7. K. Gewald, E. Schinke, H. Bottcher, Chem. Ber., 1966; 26: 94-96.
8. Abhay Kumar Vermaet al. / Journal of Pharmacy Research, 2014; 8(11): 1677-1681.