MICROWAVE ASSISTED SYNTHESIS OF 2-(SUBSTITUTEDBENZILIDENE)-4-AMINO DIHYDRO THIOPHEN-3(2H)-ONE (IA-IH) AND THEIR BIOLOGICAL ACTIVITIES ON PASS

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***Abstract*:-**A facile and convenient synthesis of 2-(substituted benzilidene)-4-amino-dihydro thiophen-3(2H)-one (Ia-Ih) under microwave irradiation have been reported in this work. All compound shows good yield. The structure of all these synthesised compounds has been conform on the basis of IR and NMR. The biological activities of these synthesised compounds were predicted successfully on the PASS online software.

Key words: Microwave assisted synthesis, Thiophene, PASS.

INTRODUCTION

Heterocycles form by far the largest classical organic divisions of organic chemistry and are of immense importance biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals are heterocycles while countless additives and modifiers used in industrial applications ranging from cosmetics reprography, information storage and plastics are heterocycles in nature.

Sulfur containing heterocycles paved way for the active research in the pharmaceutical Chemistry. Nowadays benzothiophene derivatives in combination with other ring systems have been used extensively in pharmaceutical applications. A large number of compounds containing thiophene system have been investigated because of their broad spectrum of biological activities. Cytotoxic and Anti-proliferative Activity of Novel Thiophene, Thieno[[2,3-b]]pyridine and Pyran Derivatives Derived from 4,5,6,7-tetrahydrobenzo[b]thiophene Derivative was reported by Mohareb *et al.*[1]. A Pd(II)-catalyzed Sonogashira type cross-coupling reaction between 2-iodothiophenol and phenylacetylene has been developed by Chen *et al.*[2] . The application of this method was demonstrated by the synthesis of 2-(4-(tert-butyl)phenyl)benzo[b]thiophene 1,1-dioxide and (4-methoxyphenyl)(2-(4-methoxyphenyl benzo[b]thiophen-3-yl)methanone, which exhibit a uorescence quantum yield of up to 1 and can be used as a cannabinoid receptor ligand, respectively.

A new series of 3-aryl thiophene-2-aryl and hetero aryl chalcones were synthesised by Venkataramireddy *et al.*[3] 2-Acetyl-5-bromothiophene and 4-(5-bromothiophen-2-yl)-2-methyl-1,3-thiazole, as deactivated bromide candidates, were prepared by Dawood *et al.*[4] Mahmoodi and Kiyani[5] presented two new thiophenyl derivatives of 1,3diazabicyclo[3,1,0]hex-3-enes. One-Pot Two-Component [3+2] Cycloaddition/Annulation Protocol for the Synthesis of Highly Functionalized Thiophene Derivatives was reported by Nandi *et al.*[6]

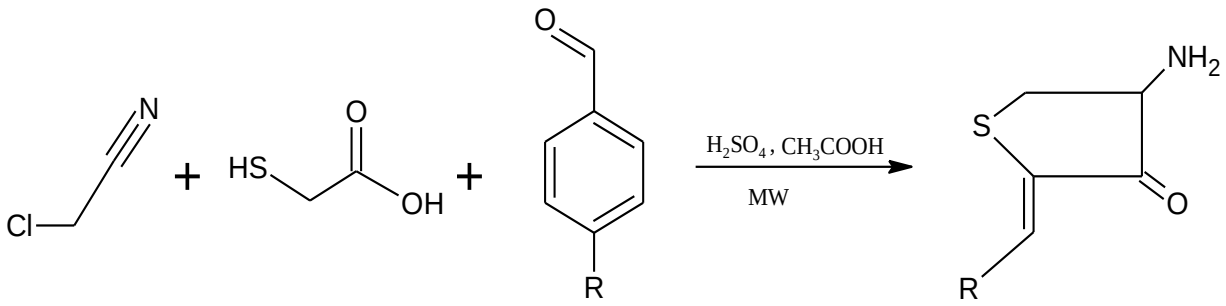
We would like to report simple and fast microwave promoted procedure for efficient additive-free conversion of thiophene and biological activities of synthesised compounds on PASS software.

MATERIALS AND METHOD

All the reactions are carried out in microwave irradiation in an LG microwave oven MG604AA at 900w, 2450MHz. IR spectra were recorded on Perkin Elmer R-32 and Varian XL-100A high NMR spectrometer using TMS as refrence in $CDCl_3$ and D_2O, the elemental analysis carried out on “Carbo Erba 1106 analyzer”. The purity of sample was checked by TLC on silica gel-G plates. Melting points were determined in open capillaries.

Synthesis of 2-(substituted benzylidene)-4-amino-dihydro thiophen-3(2H)-one (Ia-Ih)

A mixture of chloroacetonitrile a (0.01M), thioglycolic acid b (0.01M) and aromatic aldehyde c (0.01M) in presence of Acetic acid (10ml) and H_2SO_4 (5-6 drops) was refluxed under microwave irradiation 420W for 4 min with intermittent heating. Then the reaction mixture was cooled and poured over ice cold water; the product thus separated out was filtered and crystallized from ethanol to get the series of eight compounds of thiophene (Ia-Ih).



a b c (Ia-Ih)

Synthesis of 2-(4-nitrobenzylidene)-4-amino-dihydro thiophen-3(2H)-one (Ia)

Method of preparation is as given in general procedure to get the product 2-(4-nitrobenzylidene)-4-amino-dihydro thiophen-3(2H)-one (Ia) with 92% yield.

IR (nujol): 3105, 3128(-NH_2), 3044,2989(Ar-CH), 2854,2828(-CH(aliphatic)), 1949 (Parasubstituted), 1707 (C=O cyclic ketone), 1603(N-H bending), 1521(Ar-C=C), 1489 (NO_2), 1412 (CH_2bending), 1374 (C-N), 1348(>C=O), 1198(C=O stretch), 1070,1009(C=C bending), 738,724(OOP-NH).

PMR (CDCl3): δ 3.3 (dd,-CH_2(J^2=15.5Hz)), 3.4(dd, -CH_2(J^2=15.5Hz)), 5.4(br, -NH_2), 7.6(d, Ar-Ha(J^3=8.7Hz)), 8.1(d, Ar-Ha'(J^3=8.7Hz)), 8.2(d, Ar-Hb(J^3=8.6Hz)), 8.4(d, Ar-Hb'(J^3=8.6Hz)), 10.1(s, =CH(diamagnetic).

^{13}CNMR: C2(150.5), C3(192.32(keto)), C3(170.4(enol)), C4(51.7), C5(34.0), C6(146.8), C7(140.03), C8=C12(124.2), C9=C11(128.8), C10(130.0).

Synthesis of 2-(2,4-dichlorobenzylidene)-4-amino-dihydro thiophen-3(2H)-one (Ic)

Method of preparation is as given in general procedure to get the product 2-(2,4-dichlorobenzylidene)-4-amino-dihydro thiophen-3(2H)-one (Ic) having 90% yield.

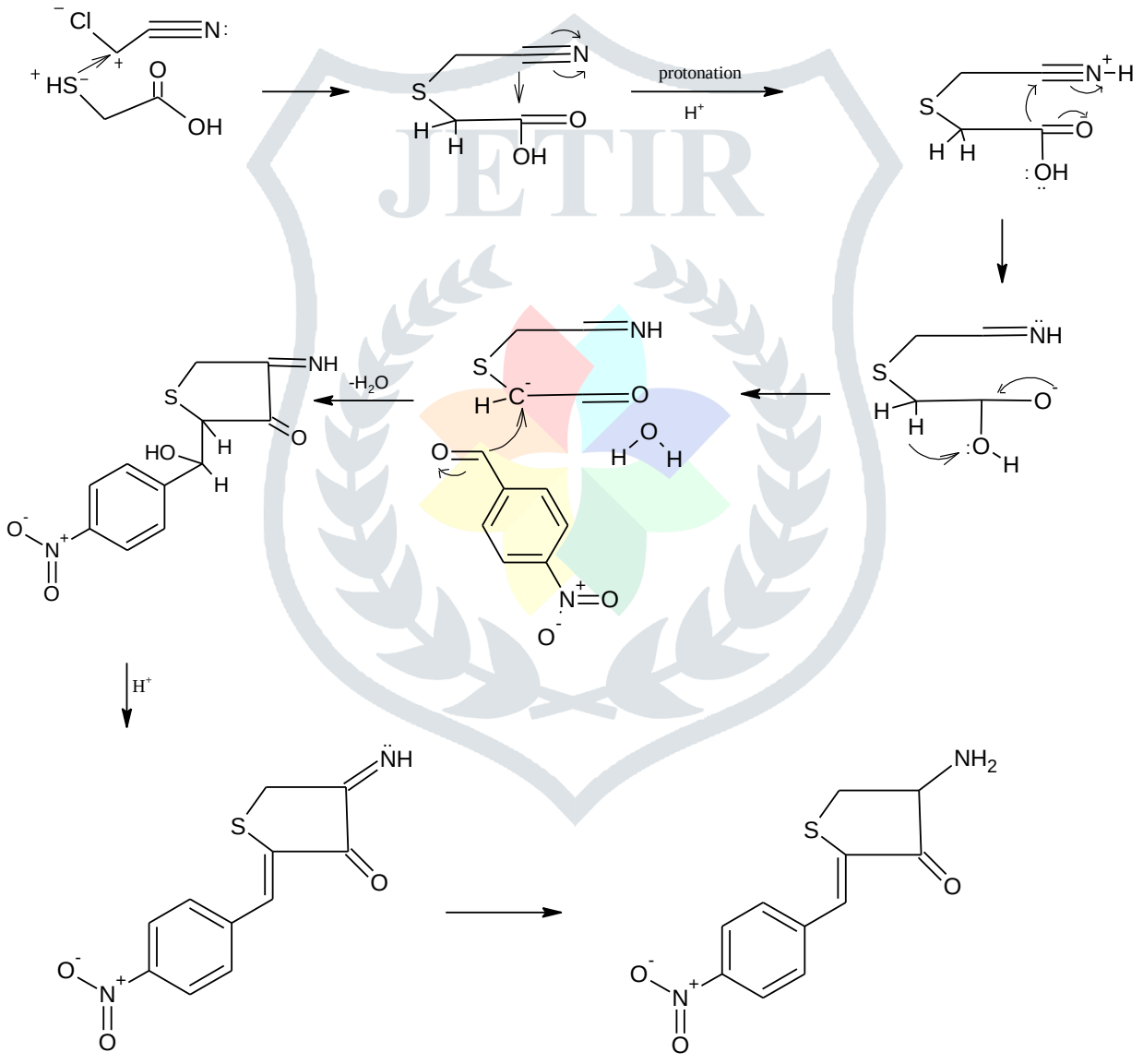
IR (nujol): 3079, 3022(-NH_2 stretch), 3007, 2913(Ar-CH), 2664, 2551(-CH(aliphatic)), 1922(Combination band (Parasubstituted)), 1707(C=O), 1584(-NH bending), 1463(-CH_2 asymmetric bending), 1425(C=C), 1388(C-N), 1197(C-O stretch), 1098,1046 (C=C bending), 895,871(C-Cl (aryl halide)), 793,770,712(C-S-C), 684(Ar-H OOP (monosubstituted)).

PMR (CDCl3): δ 3.2(dd, -CH_2(J^2=15.36)), 3.4(dd, -CH_2(J^2=15.36)), 5.6(s, =CH or NH_2), 7.4(dd, Ar-Hb (J^3_{ba}=8.44, J^4=2.1)), 7.5(d, Ar-Hc (J^4=2.16)), 7.6(d, Ar-Ha(J^3_{ab}=8.44)), 10.31(s, =C-OH or =CH), 7.5(d, J^3_{ba} =8.4 Hz, J^4=2.1(enol)), 7.7(d, J^4_c = 1.92 Hz (enol)), 7.8(d, J^3_{ab} = 8.4 Hz).
^{13}CNMR: C2(128.8), C3a(188.34 (keto)), C3b(170.3(enol)), C4(48.9), C5(33.8), C6(135.45), C7(133.7), C8(130.13), C9(127.63), C10(133.03), C11(130.37), C12(130.75).

Result and discussion

Owing to environmental concern the development of ecofriendly and ecoremical processes, where in even slightly hazardous by products are not desirable, taken this in account we report here an active thiophene derivatives as potent pharmacophor using green chemistry protocol. In this synthesis chloroacetonitrile is a simple organic compound with a linear structure both ends of the molecule have reactive groups, a cyno group on one side which can be connected into an amine where as a chloro substituted on the other side plays an important role in different alkylation reaction.

Plausible reaction pathway for the synthesis of thiophene derivatives in which thiol group of thioglycolic acid is readily alkylated with chloroacetonitrile. Halogen of $ClCH_2$ moiety allows the alkylation at the sulphur atom with the elimination of HCl. Then in presence of acidic medium H^+ protonation of nitrogen of cyno group takes place which ultimately initiate the intermolecular cyclisation due to electrophilic attack of carbonyl carbon atom. Simultaneously it enhances the acidity of reactive methylene group adjacent to carbonyl group and facilitates the attack of aldehyde carbon with the loss of water molecule. The mechanism is shown in scheme bellow.



By using the above method of synthesis remaining six compounds were synthesised with good yield and characterised by spectral and elemental analysis. The compounds are given in table - 1, and the observed and calculated CHNS percentage on all these compounds is given in table – 2.

In IR, doublet in range of 3079-3128 shows the presence of $–NH_2$ group, peak at 1707 cm^{-1} conforms the presence of C=O group in the structure. In H^1NMR peak at δ value 3.2, 3.3 shows double doublet for $–CH_2$, peak at 5.4, 5.6 shows singlet for $–NH_2$ and peaks in the range of 7-10 shows all hydrogen's of aromatic region. In C^{13}NMR values for carbon number 3 shows the presence of keto enol tutomerisum in which keto form is more stable than enol form. By using all this spectral study the structure of synthesised compound were conformed.

Table – 1

EXPT NO	COMPOUND (Ia-Ih)	R	M. F.	M. P. (^{0}C)	YIELD (%)
1	2-(4-nitrobenzylidene)-4-amino-dihydro thiophen-3(2H)-one(Ia)	-$C_6H_4NO_2$	$C_{11}H_{10}N_2SO_3$	98	98
2	2-(4-bromobenzylidene)-4-amino-dihydro thiophen-3(2H)-one (Ib)	-C_6H_4Br	$C_{11}H_{10}NSOBr$	100	78
3	2-(2,4-dichlorobenzylidene)-4-amino-dihydro thiophen-3(2H)-one (Ic)	-$C_6H_3Cl_2$	$C_{11}H_9NSOCl_2$	105	95
4	4-amino-2-benzylidene dihydro thiophen-3(2H)-one (Id)	-C_6H_5	$C_{11}H_{11}NSO$	99	91
5	2-(3-hydroxybenzylidene)-4-amino-dihydro thiophen-3(2H)-one (Ie)	-C_6H_5O	$C_{11}H_{11}NSO_2$	115	84
6	2-(3-methoxybenzylidene)-4-amino-dihydro thiophen-3(2H)-one (If)	-C_7H_7O	$C_{12}H_{13}NSO_2$	103	79
7	2-(2-chlorobenzylidene)-4-amino-dihydro thiophen-3(2H)-one (Ig)	-C_6H_4Cl	$C_{11}H_{10}NSOCl$	104	90
8	4-amino-2-ethylidenedihydro thiophen-3(2H)-one (Ih)	-C_2H_5	C_6H_9NSO	138	82

Table - 2

Elemental analyses of some similar compounds (Ia-Ih)

Compound	Molecular formula	Analysis %		
		Element	Observed	Calculated
Ia	$C_{11}H_{10}N_2SO_3$	C	52.2	52.8
		H	4.04	4.00
		N	11.1	11.2
		S	12.4	12.8
		O	19.00	19.2
Ib	$C_{11}H_{10}NSOBr$	C	46.2	46.6
		H	3.21	3.53
		N	4.73	4.94
		S	11.0	11.3
		O	5.21	5.65
		Br	27.3	27.9
Ic	$C_{11}H_9NSOCl_2$	C	48.0	48.3
		H	3.03	3.29
		N	5.02	5.12

		S	11.2	11.7
		O	5.65	5.86
		Cl	25.3	25.6
Id	$C_{11}H_{11}NSO$	C	64.1	64.3
		H	5.02	5.36
		N	6.43	6.82
		S	15.0	15.6
		O	7.46	7.80
Ie	$C_{11}H_{11}NSO_2$	C	59.1	59.7
		H	4.63	4.97
		N	6.27	6.33
		S	14.0	14.4
		O	14.2	14.4
If	$C_{12}H_{13}NSO_2$	C	61.0	61.2
		H	5.21	5.53
		N	5.55	5.95
		S	13.5	13.6
		O	13.8	13.6
Ig	$C_{11}H_{10}NSOCl$	C	55.0	55.2
		H	4.02	4.18
		N	5.65	5.85
		S	13.5	13.3
		O	6.43	6.69
		Cl	14.1	14.6
Ih	C_6H_9NSO	C	50.0	50.3
		H	6.21	6.29
		N	9.66	9.79
		S	21.8	22.3
		O	11.0	11.1

PASS activity

We have used the "Biological Activity Spectrum of a substance" concept which seems to be a fundamental term for the description of biologically active substances. The "biological activity spectrum of a substance" is the list of biological activity names which reflects the result of chemical substance's interaction with different biological entities. The "biological activity spectrum" reflects the "intrinsic" property of a substance depending only on its structure and physical-chemical characteristics. Our goal is to provide maximum information on the biological activity for any substance including such types of biological activity whose molecular mechanism of action is still unknown. This aim determines the choice of chemical substance representation and the mathematical method on which the provided algorithm is based. The PASS approach is based on the suggestion, Activity Function (Structure). Thus, "comparing" structure of a new substance with that of well-known biologically active substances, it is possible to find out whether a new substance has a particular effect.

2D structural formula of a substance is chosen as the basis for structure description. Molecules were synthesized successfully by microwave assisted synthesis by using 8 types of different aldehydes and were obtained with good yield and purity. The structure of synthesis compounds was input in PASS software and predicted the biological activities of synthesis compounds Ia-h. The predictions were carried out on the basis of analysis of training set containing about 10000 of biological activities. In this Pa shows probability to be active and Pi shows probability to be inactive. The Pa and Pi values vary from 0.000 to 1.000. In this study we predict the compounds having biological activity Pa>0.5. If Pa>0.7, the substance is very likely to exhibit the activity in experiment. If Pa<0.5, the substance is unlikely to exhibit the activity in experiment. However, if the presence of this activity is confirmed in the experiment the substance might be a new chemical entity. Results of biological activities along with Pa and Pi predicted by PASS are described in tables bellow –

2-(4-nitrobenzylidene)-4-amino-dihydro thiophen-3(2H)-one (Ia)

Table – 3

Pa	Pi	Activity
0,865	0,005	Arylacetonitrilase inhibitor
0,765	0,005	Phosphatidylserine decarboxylase inhibitor
0,789	0,037	Ubiquinol-cytochrome-c reductase inhibitor
0,716	0,020	Fusarinine-C ornithinesterase inhibitor
0,705	0,043	Acrocylindropepsin inhibitor
0,705	0,043	Chymosin inhibitor
0,705	0,043	Saccharopepsin inhibitor
0,657	0,025	Glucan endo-1,6-beta-glucosidase inhibitor
0,626	0,005	Chitosanase inhibitor
0,601	0,019	Mucinaminylserine mucinaminidase inhibitor
0,615	0,036	GST A substrate
0,578	0,022	Bisphosphoglycerate phosphatase inhibitor
0,567	0,015	S-formylglutathione hydrolase inhibitor
0,572	0,026	Antiviral (Picornavirus)
0,609	0,065	Polyporopepsin inhibitor
0,543	0,008	Taurine-2-oxoglutarate transaminase inhibitor
0,555	0,028	Superoxide dismutase inhibitor
0,549	0,030	L-glutamate oxidase inhibitor
0,560	0,041	Phospholipid-translocating ATPase inhibitor
0,571	0,059	TP53 expression enhancer
0,601	0,100	Mucomembranous protector
0,504	0,019	Antiprotozoal (Trypanosoma)
0,506	0,024	Apyrase inhibitor

0,506	0,026	Cyclohexanone monooxygenase inhibitor
0,536	0,056	Lysase inhibitor
0,510	0,044	(R)-6-hydroxynicotine oxidase inhibitor
0,505	0,055	UDP-N-acetylglucosamine 4-epimerase inhibitor
0,546	0,118	Aspulvinone dimethylallyltransferase inhibitor

2-(4-bromobenzylidene)-4-amino-dihydro thiophen-3(2H)-one (Ib)

Table – 4

Pa	Pi	Activity
0,811	0,030	Aspulvinone dimethylallyltransferase inhibitor
0,717	0,010	Phosphatidylserine decarboxylase inhibitor
0,692	0,022	Feruloyl esterase inhibitor
0,668	0,072	Mucomembranous protector
0,581	0,036	UDP-N-acetylglucosamine 4-epimerase inhibitor
0,504	0,012	Taurine-2-oxoglutarate transaminase inhibitor
0,523	0,050	Thioredoxin inhibitor
0,505	0,091	Glutamyl endopeptidase II inhibitor

2-(2,4-dichlorobenzylidene)-4-amino-dihydro thiophen-3(2H)-one (Ic)

Table – 5

Pa	Pi	Activity
0,728	0,063	Phobic disorders treatment
0,670	0,043	Antiseborrheic
0,589	0,041	Complement factor D inhibitor
0,575	0,055	5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor
0,562	0,053	NADPH peroxidase inhibitor
0,563	0,068	Phosphatase inhibitor
0,505	0,055	UDP-N-acetylglucosamine 4-epimerase inhibitor
0,515	0,093	Glycosylphosphatidylinositol phospholipase D inhibitor
0,552	0,159	Gluconate 2-dehydrogenase (acceptor) inhibitor
0,529	0,138	Ubiquinol-cytochrome-c reductase inhibitor

4-amino-2-benzylidene dihydro thiophen-3(2H)-one (Id)

Table – 6

Pa	Pi	Activity
0,807	0,010	Arylacetonitrilase inhibitor
0,796	0,035	Aspulvinone dimethylallyltransferase inhibitor
0,723	0,013	UDP-N-acetylglucosamine 4-epimerase inhibitor
0,705	0,010	Thioredoxin inhibitor
0,680	0,004	Taurine-2-oxoglutarate transaminase inhibitor
0,660	0,005	Albendazole monooxygenase inhibitor

0,665	0,025	Complement factor D inhibitor
0,650	0,019	Phosphatidylserine decarboxylase inhibitor
0,661	0,036	Glutamyl endopeptidase II inhibitor
0,647	0,036	NADPH peroxidase inhibitor
0,617	0,009	Isopenicillin-N epimerase inhibitor
0,633	0,026	Venombin AB inhibitor
0,613	0,013	S-alkylcysteine lyase inhibitor
0,670	0,071	Mucomembranous protector
0,623	0,038	Omptin inhibitor
0,673	0,089	Phobic disorders treatment
0,643	0,075	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
0,568	0,009	D-alanine 2-hydroxymethyltransferase inhibitor
0,643	0,090	Ubiquinol-cytochrome-c reductase inhibitor
0,578	0,025	Alopecia treatment
0,602	0,054	Antiseborrheic
0,551	0,012	FMO1 substrate
0,569	0,031	Insulysin inhibitor
0,577	0,044	Protein-disulfide reductase (glutathione) inhibitor
0,567	0,038	Neurotransmitter uptake inhibitor
0,530	0,009	Thiopurine S-methyltransferase inhibitor
0,548	0,037	Pterin deaminase inhibitor
0,548	0,040	Lysine 2,3-aminomutase inhibitor
0,509	0,006	Arylamine N-acetyltransferase inhibitor
0,535	0,033	Biotinidase inhibitor
0,578	0,080	Nicotinic alpha6beta3beta4alpha5 receptor antagonist
0,504	0,016	Chitosanase inhibitor
0,552	0,066	Fusarinine-C ornithinesterase inhibitor
0,556	0,071	Phosphatase inhibitor
0,531	0,046	Limulus clotting factor B inhibitor
0,517	0,038	Hydrogen dehydrogenase inhibitor
0,521	0,042	Antiviral (Picornavirus)
0,532	0,054	NADPH-cytochrome-c2 reductase inhibitor
0,512	0,041	Leukopoiesis stimulant
0,522	0,056	Macrophage colony stimulating factor agonist
0,511	0,059	Electron-transferring-flavoprotein dehydrogenase inhibitor
0,506	0,081	5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor
0,529	0,115	CYP2J substrate

2-(3-hydroxybenzylidene)-4-amino-dihydro thiophen-3(2H)-one (Ie)

Table – 7

Pa	Pi	Activity
0,805	0,010	Arylacetonitrilase inhibitor
0,817	0,029	Aspulvinone dimethylallyltransferase inhibitor
0,749	0,028	Antiseborrheic
0,703	0,012	Phosphatidylserine decarboxylase inhibitor

0,665	0,016	Thioredoxin inhibitor
0,703	0,055	Mucomembranous protector
0,651	0,013	Threonine aldolase inhibitor
0,640	0,025	UDP-N-acetylglucosamine 4-epimerase inhibitor
0,668	0,061	Membrane integrity agonist
0,625	0,035	Phosphatase inhibitor
0,610	0,023	Insulysin inhibitor
0,601	0,025	Peroxidase inhibitor
0,594	0,021	Alopecia treatment
0,607	0,037	Protein-disulfide reductase (glutathione) inhibitor
0,593	0,035	HIF1A expression inhibitor
0,600	0,045	NADPH peroxidase inhibitor
0,643	0,090	Ubiquinol-cytochrome-c reductase inhibitor
0,521	0,009	Thiopurine S-methyltransferase inhibitor
0,523	0,017	FMO1 substrate
0,562	0,063	TP53 expression enhancer
0,528	0,033	MAP kinase stimulant
0,515	0,028	Antifungal
0,521	0,041	Alkane 1-monooxygenase inhibitor
0,534	0,064	Nicotinic alpha4beta4 receptor agonist
0,512	0,044	Feruloyl esterase inhibitor
0,509	0,049	Aldehyde oxidase inhibitor
0,525	0,085	CYP2C12 substrate
0,510	0,070	Mucositis treatment
0,520	0,084	Glutamyl endopeptidase II inhibitor
0,516	0,080	Chlordecone reductase inhibitor
0,549	0,118	Membrane permeability inhibitor
0,538	0,116	Testosterone 17beta-dehydrogenase (NADP+) inhibitor

2-(3-methoxybenzylidene)-4-amino-dihydro thiophen-3(2H)-one (If)

Table – 8

Pa	Pi	Activity
0,840	0,023	Aspulvinone dimethylallyltransferase inhibitor
0,722	0,045	Gluconate 2-dehydrogenase (acceptor) inhibitor
0,553	0,035	Insulysin inhibitor
0,524	0,017	FMO1 substrate
0,534	0,058	Complement factor D inhibitor
0,585	0,114	Ubiquinol-cytochrome-c reductase inhibitor
0,541	0,121	Mucomembranous protector

2-(2-chlorobenzylidene)-4-amino-dihydro thiophen-3(2H)-one (Ig)

Table – 9

Pa	Pi	Activity
0,734	0,061	Phobic disorders treatment
0,661	0,025	Complement factor D inhibitor
0,608	0,044	NADPH peroxidase inhibitor
0,599	0,055	Antiseborrheic
0,613	0,102	Ubiquinol-cytochrome-c reductase inhibitor
0,521	0,010	Taurine-2-oxoglutarate transaminase inhibitor
0,570	0,063	Phosphatase inhibitor
0,543	0,045	UDP-N-acetylglucosamine 4-epimerase inhibitor
0,550	0,064	5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor
0,531	0,047	Thioredoxin inhibitor
0,545	0,073	Glutamyl endopeptidase II inhibitor
0,575	0,109	Mucomembranous protector
0,578	0,138	Gluconate 2-dehydrogenase (acceptor) inhibitor
0,523	0,090	Glycosylphosphatidylinositol phospholipase D inhibitor
0,541	0,110	CYP2J substrate
0,523	0,094	CYP2J2 substrate
0,503	0,077	Omptin inhibitor
0,544	0,118	Aspulvinone dimethylallyltransferase inhibitor

4-amino-2-ethylidenedihydro thiophen-3(2H)-one (Ih)

Table – 10

Pa	Pi	Activity
0,727	0,022	Glutamyl endopeptidase II inhibitor
0,708	0,061	Aspulvinone dimethylallyltransferase inhibitor
0,665	0,021	UDP-N-acetylglucosamine 4-epimerase inhibitor
0,661	0,021	Venombin AB inhibitor
0,663	0,028	Omptin inhibitor
0,669	0,043	Antiseborrheic
0,685	0,063	Mucomembranous protector
0,632	0,021	Phosphatidylserine decarboxylase inhibitor
0,610	0,005	FMO1 substrate
0,615	0,022	Insulysin inhibitor
0,660	0,083	Ubiquinol-cytochrome-c reductase inhibitor
0,599	0,029	Thioredoxin inhibitor
0,603	0,046	Phosphatase inhibitor
0,627	0,080	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
0,553	0,010	Chitosanase inhibitor
0,554	0,024	Arylacetonitrilase inhibitor
0,538	0,009	Taurine-2-oxoglutarate transaminase inhibitor
0,569	0,047	Complement factor D inhibitor
0,521	0,018	Isopenicillin-N epimerase inhibitor
0,526	0,041	Fatty-acyl-CoA synthase inhibitor
0,515	0,044	Alopecia treatment

0,505	0,036	Erythropoiesis stimulant
0,500	0,048	Pterin deaminase inhibitor
0,511	0,066	NADPH eroxidise inhibitor
0,505	0,067	Protein-disulfide reductase (glutathione) inhibitor
0,539	0,111	CYP2J substrate
0,510	0,108	Polyporopepsin inhibitor
0,522	0,135	Membrane permeability inhibitor
0,528	0,159	Phobic disorders treatment

Conclusion

Green chemistry emerged from a variety of existing ideas and research efforts in the period leading up to the 1990s, in the context of increasing attention to problems of chemical pollution and resource depletion. By using the principles of green chemistry we developed the method of synthesis of eight different derivatives of thiophene (Ia-Ih), having good percentage of yield. The synthesised compounds are heterocyclic as heterocycles are an important class of compounds, making up more than half of all known organic compounds. Heterocycles are present in a wide variety of drugs, most vitamins, many natural products, biomolecules, and biologically active compounds, including antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and many more biological activities. Therefore, substantial attention has been paid to develop efficient new methods to synthesize heterocycles like thiophene.

The spectral study and elemental analysis of the synthesised compounds conforms the structure of these synthesised compounds. By knowing the importance of these types of heterocyclic compounds we find the PASS activities of these compounds on online PASS software. In this series of thiophine Ia-h compound 2-(4-nitrobenzylidene)-4-amino-dihydro thiophen-3(2H)-one (Ia) shows high Arylacetonitrilase inhibitor activity having Pa 0.865. PASS is a primary screening technique of compounds and in this present work, all compounds were tested by the software data of PASS online; so by using this screening study in future they need to be tested for more accurate activities and usefulness.

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