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RESEARCH ARTICLE

Microwave Assisted Synthesis & QSAR Study of Some Novel Pyrazole Thioamide Derivatives

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ABSTRACT

This work involves synthesis of Pyrazole thioamide derivatives from different chalcones 1[a-b] synthesized from substituted acetophenones and different aromatic aldehydes in basic medium by Claisen Schemidt reaction. These chalcones [1(a-b)] on condensation with different hydrazides [2(a-b)] and isothiocynates [3(a-b)] when irradiated with microwaves (20% 140watts) in scientific microwave oven, give different 2-phenyl-2,5-dihydro-pyrazole-1-carbothioic acid phenyl amide derivatives [4(a-g)]; Library of such pyrazolyl thiazine derivatives has been generated and the structures were subjected to PASS for their probabilities of being active biologically. QSAR study of the library was done to find out most active molecules.

KEYWORDS

Aromatic hydrazides, Pyrazole, QSAR Study, Green chemistry, Thiazines, Hydrazides, Microwave Irradiation

INTRODUCTION

Pyrazoles are important class of heterocyclic compounds, which find a widespread use in various application.[1-2] The pyrazole ring is a constituent of a variety of natural and synthetic products. Examples of a variety of pyrazole ring containing natural products are (s)-3-pyrazolylalanine[3], pyrazomycine[4], and 4, 5-dihydro-3-phenyl-6H-pyrrol (1-2-b) pyrazole[5], while lonazolac[6], fezolamine[7], difenamizole[8] and mepirizole[9] are examples of biologically active synthetic pyrazole derivatives. Lonazolac is a new nonsteroidal anti-inflammatory drug.[10] Nitropyrazole derivatives such as 4-nitro-pyrazole, 1-methyl-4-nitropyrazole and 4, 4-dinitro-1,1-methylene dipyrazole are known as antiparasitic agents.[11] It has been shown that 3, 4-bis(2,4-dinitrobenzoyl-hydoxymethyl) pyrazole has remarkable antimicrobial activity. It is more efficient than penicillin, levomycetin, and polymyxin.[12] Lesopitron is a new nonbenzodiazepine anxiolytic, without side effects which is currently in phase II trials.[13] Pyrazole derivatives are widely used in agrochemistry as insecticides, herbicides, or fungicides. For instance, a powerful fungicidal composition for the protection of plants from phytopathogenic fungi, containing 4-chloro-3-(3, 5-dichlorophenyl)-1H-pyrazole has been patented.[15]

Pyrazole moiety containing compounds are associated with antimicrobial, anti-pyretic, bactericidal, anti-inflammatory and hepato protective activities.[16-20]

Pyrazole derivatives are principally used in medicine and have enormous potential as pharmaceutical agents due to their biological activities such as endocrinological anti-inflamatory and anti-hyperglycic activities.[21-24]

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Various pyrazoline derivatives were found to possess important biological and pharmaceutical activities, which stimulated research activity in the field of these nitrogen containing heterocyclic compounds. Some examples of their most important effects include antimicrobial[25], central nervous system[26] and immunosuppressive[27] activities, their syntheses have been reviewed in only a few accounts. [28-30]

Pyrazoles are usually prepared by condensation between a hydrazine derivative and 1, 3 dicarbonyl compound or by 1, 3-dipolar cycloaddition of diazoalkenes or nitrile imines to olefins or acetylenes. Although these two basic synthetic methods are simple and efficient, the use of unsymmetrically substituted precursors often leads to a mixture of regioisomeric pyrazole derivatives. 3-(Dimethylamino) propenoates are actually masked 1,3 dicarbonyl compounds they can be transformed into substituted pyrazole upon treatment with hydrazine derivatives.[31]

Various Pyrazoles have been prepared from hydrazine derivatives. Whereas successful synthetic attempts have been reported for 1-[(2-acetoxyethoxy) methyl]-3,5-dimethyl-1H-pyrazole[32], 5-Amino-1-[(1,3-benzothiazol-2-ylthio)acetyl]-3-(methylthio)-1H-pyrazole-4-carbonitrile[33],3-methyl-(2′,4′-dibromophenyl)-2-pyrazoline-4-thiosemicarbo-hydrazone-5-one[34], 5-hydroxyl-3-(3-nitrophenyl)-4-phenylazopyrazole[35], 1-(5-Hydroxypentyl)-3,5-dimethyl-1H-pyrazole[36], 4-Fluoro-3,5-dimethyl-1H-pyrazole[37]etc in the recent literature.

PASS

PASS is a software application that predicts 565 possible biological activities of a user selected (set of) compound(s). These activities include 5-hydroxytryptamine antagonists. neuromuscular blocking agents, Antibiotics, antidepressants, antiviral agents(AIDS), contraceptives, tumor necrosis factor antagonists and many others. Using PASS predictions, novel pharmaceutical agents have been discovered with anxiolytic. anti-inflammatory, antihypertensive, anticancer and other actions. PASS is applicable to chemical libraries containing millions of compounds.

The biological activities of chemical compounds are related to their physicochemical properties by some functions as shown in equation (1).

Biological activity = f (physicochemical properties)…….. (1)

Thus, "the biological activity spectrum" is defined as the "intrinsic" property of a compound depending only on its structure and physico-chemical characteristics. Prediction of this spectrum by PASS is based on SAR analysis of the training set containing thousands of compounds which have many kinds of biological activities. .In PASS *biological activities* are described qualitatively (“active” or “inactive”).

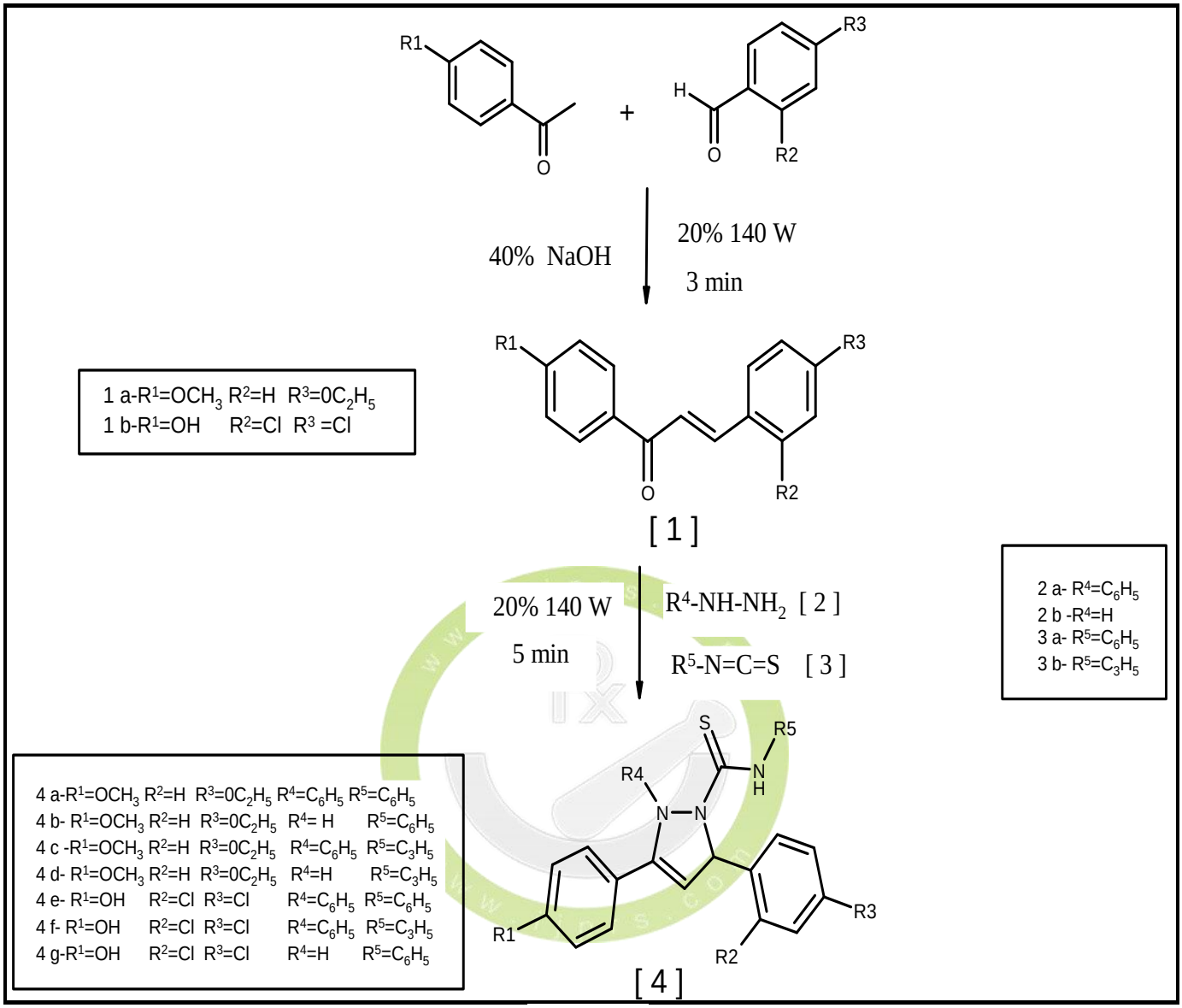
Importance of PASS

1. Experimental determination of biological activity of a drug is time and cost consuming procedure, so making the use of PASS is generally important.
2. PASS can be effectively used for finding of compounds with required properties and without undesirable side effects.
3. It used for selecting the most prospective compounds from the set of available samples for specific screening.
4. For determining of more relevant screens for particular compound.

Due to this significance of PASS, it is used in the present study as a tool to design the drug with highest probable activity.

EXPERIMENTAL

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR spectra were recorded in $CDCl_3$ with TMS as internal standard on a Bruker spectrometer at 400 MHz. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046 Purity of the compounds were checked by TLC on silica- G plates. Anti-



Scheme -1

Table 1: Analytical Data and Elemental Analysis of Compounds (1a-b)

Compd	Molecular formula (Mol. Wt.)	LC-MS Data	Yield	M.P. (°C)	Elemental Analysis					
					%C		% H		%O	
					Found	Calcd.	Found	Calcd.	Found	Calcd.
1a	$C_{18}H_{18}O_3$ (282)	307	86	116	76.61	76.64	6.47	6.51	17.01	17.06
1b	$C_{16}H_{12}Cl_2O_2$ (307.18)	336	75	155	62.57	63.02	3.92	3.96	10.43	10.47

microbial activities are chek by using pass software.

Preparation of (E)-3-(4-Ethoxy-phenyl)-1-(4-methoxy-phenyl)-propenone [1(a-b)]

4-Methoxyacetophenone 1.50 g, (0.01 mol) and 4-ethoxybenzeldehyde 2.82 g (0.01 mol) were mixed in ethanol (25 mL) in 100 mL RBF, 40% NaOH solution (3mL) was added and the reaction mixture was irradiated with microwaves at 20% microwave power (140 W) for 3 mins. The reaction mixture was cooled and neutralized with 2N HCl (2-3 mL) to obtain the product. The separated product was filtered, washed with ethanol (5 mL) and recrystallized from ethanol. The yields, melting points and other characterization data of these compounds are given in Table-1.

Preparation of 5-(4-Ethoxy-phenyl)-3-(4-methoxy-phenyl)-2- phenyl-2,5-dihydro-pyrazole-1-carbothioic acid phenyl amide [4(a-g)]

(E)-3-(4-ethoxy-phenyl)-1-(4-methoxy-phenyl)-propenone [1-a] 2.82 g (0.01 mol) , phenyl hydrazine 1.08 g (0.01 mol), phenyl isothiocynate 1.35g (0.01 mol) was taken in 100 mL RBF with 30 ml ethanol and subjected to microwave irradiations at 20% microwave power (140 W) for 5 mins. The reaction mixture was cooled and poured in ice to obtain solid which was filtered, washed with little methanol and recrystallized from 50% ethanol. The yields, melting points and other characterization data of these compounds are given in Table -2.

Table 2: Analytical Data and Elemental Analysis of Compounds (4a-g)

Compd	Molecular formula (Mol. Wt.)	LC-MS Data	Yield	M.P. (°C)	Elemental Analysis					
					%C		% H		%O	
					Found	Calcd.	Found	Calcd.	Found	Calcd.
4a	$C_{31}H_{29}N_3O_2S$ (507.66)	531	84	215	73.35	73.38	5.76	5.79	8.28	8.33
4b	$C_{25}H_{25}N_3O_2S$ (431.56)	456	75	201	69.58	69.63	5.84	5.88	9.74	9.78
4c	$C_{28}H_{29}N_3O_2S$ (471.63)	494	78	210	71.31	71.34	6.20	6.24	8.91	8.96
4d	$C_{22}H_{25}N_3O_2S$ (395.53)	410	84	205	66.81	66.85	6.37	6.40	10.62	10.67
4e	$C_{28}H_{21}Cl_2N_3OS$ (518.47)	540	79	235	64.87	64.90	4.08	4.13	8.10	8.15
4f	$C_{25}H_{21}Cl_2N_3OS$ (482.44)	507	74	225	62.24	62.27	4.39	4.42	8.71	8.76
4g	$C_{22}H_{17}Cl_2N_3OS$ (442.37)	462	85	213	59.73	59.78	3.87	3.91	9.50	9.56

RESULTS AND DISCUSSION

It was observed that 4-Methoxyacetophenone on condensation with 4-ethoxybenzeldehyde, yields (E)-3-(4-Ethoxy-phenyl)-1-(4-methoxy-phenyl)-propenone (1a-b). The structures of (1a-b) were confirmed by elemental analysis and IR spectra showing an absorption band at 1060 (-O), 1240(O-CH_3), 1595 (C=C), 3030-3080 cm^{-1} (C-H, of Ar). ^{1}HNMR: 1.42-1.45(3H,t,O-CH_2-$\underline{CH_3}$), 3.82(3H,s,O-$\underline{CH_3}$), 4.09-4.12 (2H,q,O-$\underline{CH_2}$-CH_3), 8.02-8.04 (2H,d,=CH), 7.45-7.47 (1H, d,=CH), 6.97-6.99 (2H,d,=CH), 7.79-7.81 (1H,d,=CH), 7.55-7.57 (2H,d,=CH), 6.81-6.83 (2H,d,=CH). ^{13}C N-MR: 14.74 (O-CH_2-$\underline{CH_3}$), 55.28 (O-$\underline{CH_3}$), 64.46 (O-$\underline{CH_2}$-CH_3), 163.30 (CH), 113.71 (2x=CH), 130.67 (3x=CH), 188.14 (C=O), 121.57 (=CH), 144.55 (=CH), 127.51 (>C=), 129.73 (2x=CH), 144.72 (2x=CH), 158.30 (>C=). The C, H, N analysis data of all compounds are presented in Table-1.

The structures assigned to 5-(4-Ethoxy-phenyl)-3-(4-methoxy-phenyl)-2- phenyl-2, 5-dihydro-pyrazole-1-carbothioic acid phenyl amide (4a-g) were supported by the elemental analysis and IR spectra showing an absorption bands at 1060 (-O-), 1107 (C=S), 3230(NH), 1240 (O-CH_3), 1340 (C-N), 3050 (Ar-CH), 1595 (C=C) ^{1}H NMR: 1.30-1.32 (3H,t,O-CH_2-$\underline{CH_3}$), 3.86 (3H,s,O-$\underline{CH_3}$), 3.99-4.03 (2H,q,O-$\underline{CH_2}$-CH_3), 5.94-5.95 (1H,d,pyrazole=CH), 5.97-5.99 (1H,d,pyrazole CH), 6.87-6.97 (8H,m,Ar-H), 7.44-7.72 (10H,m,Ar-H), 8.65 (1H,s,NH). ^{13}C N-MR: 13.81 (O-CH_2-$\underline{CH_3}$), 55.12 (O-$\underline{CH_3}$), 61.10 (O-$\underline{CH_2}$-CH_3), 62.20 (CH), 112.05, 128.05, 136.46, 160.00 (6 Aromatic C), 132.51 (=CH), 149.20 (=CH), 133.56, 127.04, 113.91, 160.43 (6 Aromatic C), 138.94, 125.15, 128.62, 126.04 (6 Aromatic C), 125.90, 128.60, 121.28, 137.83 (6 Aromatic C), 179.95 (C=S). The C, H, N, S analysis data of all compounds are presented in Table-2.

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in Scheme-1.

The IR data also direct for assignment of the predicted structure. The final structure of all compounds is confirmed by LC-MS. LC-MS data of Samples 4a and 4c gives the molecular ion peak (m/z) at 531 and 494 respectively. These values are corresponds to their molecular weight.

QSAR Analysis of Activities with PASS

The relationship between structure and different biological activities was studied using computer programme PASS. The structures of derivatives [4(a-g)] were studied for the predictions of their probabilities of being active [Pa] and inactive [Pi] for the selected activities. The following three activities were predicted with top probability for the series of compounds [4(a-g)]

1. Antiallergic
2. Polarisation stimulant
3. Antiasthmatic

Antiallergic

Anti-Allergen Deodorizer is designed for safe use around individuals who suffer from allergies, asthma or chemical sensitivities. An allergen is a type of antigen that produces an abnormally vigorous immune response in which the immune system fights off a perceived threat that would otherwise be harmless to the body

Polarisation Stimulant

Something (such as a drug) that makes you more active or gives you more energy.

Antiasthmatic

These drugs are used for the treatment of asthma. They may be useful either in the treatment or prevention of asthma attacks. Asthma (from the Greek ἅσθμα. a*sthma*. "panting") is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms. Reversible airflow obstruction and bronchospasm. Common symptoms include wheezing, coughing, chest tightness and shortness of breath. Asthma is thought to be caused by a combination of genetic and environmental factors.

Table 3: Predictions of biological activities by PASS

Activity Comp.	Anti-allergic	Polarisation stimulant	Anti-asthmatic
	Pa	Pa	Pa
4-a	0.720	0.693	0.688
4-b	0.0	0.681	0.0
4-c	**0.727**	0.338	**0.772**
4-d	0.0	0.302	0.191
4-e	0.687	**0.723**	0.646
4-f	0.698	0.471	0.743
4-g	0.0	0.713	0.0

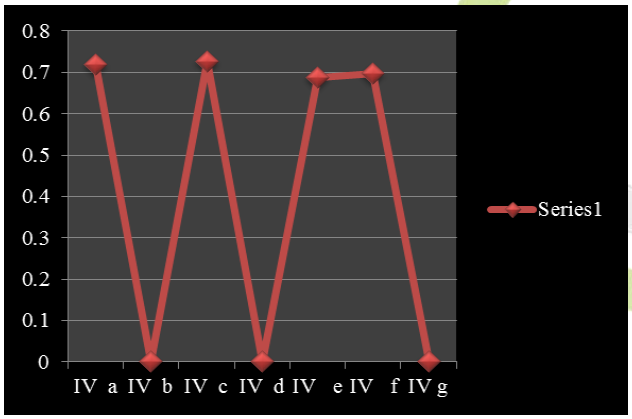


Figure 1: Antiallergic

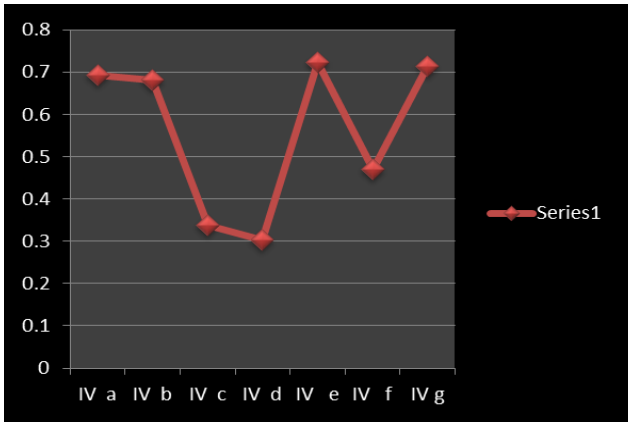


Figure 2: Polarisation Stimulant

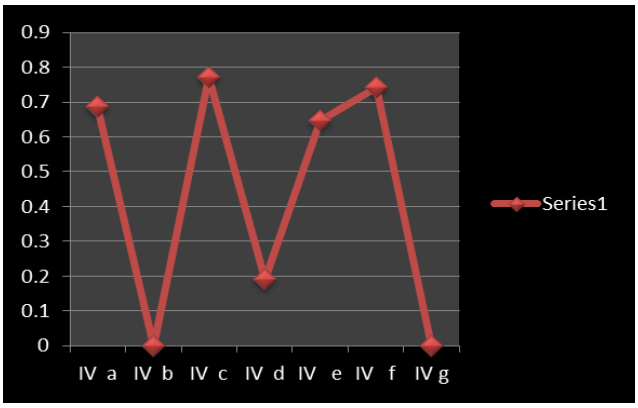


Figure 3: Antiasthmatic

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