



Received on 22 April, 2014; received in revised form, 15 June, 2014; accepted, 19 July, 2014; published 01 December, 2014

MICROWAVE ASSISTED SYNTHESIS & QSAR STUDY OF SOME NOVEL PYRAZOLYL THIAZINE DERIVATIVES

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Keywords:

Pyrazolyl thiazine, Substituted acetophenone, Substituted aromatic aldehydes, Hydrazides, Substituted isothiocyanates, MW assisted condensation

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ABSTRACT: This work involves synthesis of pyrazolyl thiazine derivatives from different chalcones [1(a-b)] synthesized from substituted acetophenones and different aromatic aldehydes in basic medium by Claisen-Schmidt reaction. These chalcones [1(a-b)] on condensation with different hydrazides [2(a-b)] and isothiocyanates [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)] which on further MW assisted condensation with substituted acetophenones and different aromatic aldehydes, furnish pyrazolyl thiazine derivatives [7(a-j)]. 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.

INTRODUCTION: Thiazine is a six membered heterocyclic ring which contains two hetero atoms (N and S) placed at the 1, 3 or 1, 4 positions. 1, 3 Thiazines are very useful units in the field of medicinal and pharmaceutical chemistry and have been reported to exhibit variety of biological activities¹. A large group of dyes has phenothiazine structure including methylene blue. Thiazines are used in dyes, tranquilizers and insecticides. Thiazine is fairly basic diuretic supplement which reduces water and increases vascularity, so it is also used as anabolic agent in medicine². The 1, 3-thiazine nucleus is active core of cephalosporin which is among the widely used β -lactam antibiotics.

The ability of thiazine to exhibit antitubercular, antibacterial, anti-HIV and cannabinoid receptor agonist has been reported³. Sawant et al synthesized 1, 3-thiazines and carried out antimicrobial screening which revealed that the compounds with methoxy substituent were found better antimicrobial agents⁴. The potential use of chlorpromazine derivatives of this phenothiazine as an antimicrobial, increasing activity of antibiotics to which bacteria are susceptible and reverse resistance of *Staphylococcus aureus* and *Corynebacteria topenicillin* strongly supports that phenothiazine can be exploited for the management of bacterial infections⁵.

Whereas, chalcones undergo a variety of chemical reactions and are found useful in synthesis of variety of hetero cyclic compounds like pyrimidine and thiazole derivatives which are synthesized through the reaction of chalcones with urea and thiourea in the presence of alkaline media in refluxing ethanol⁶. F. K. Mohammed et al

QUICK RESPONSE CODE 	DOI: 10.13040/IJPSR.0975-8232.5(12).5556-63
	Article can be accessed online on: www.ijpsr.com
DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(12).5556-63	

synthesized new chromene base heterocyclic thiazine from 2-amino-5-hydroxy-4-phenyl-7-methyl-4H[1-chromeno-3-carbonitrile; which showed a good biological activity⁷. The derivatives of 1,3 thiazines having N-C-S linkage have been used as antitubercular, antibacterial, antimicrobial, antitumor, insecticidal, fungicidal, herbicidal agents, in tranquilizers and various dyes etc.⁸⁻¹⁶. Further, 1, 3-thiazine core moieties have remarkable potential as anti radiation agents. 1,3-Thiazines are used in various organic synthesis and transformations as reaction intermediates⁸⁻¹⁶. In light of these biological activities it appeared of interest to synthesize 1, 3 thiazine derivatives.

However, synthesis of very few pyrazolyl thiazine derivatives like 2- [2- [3 -(2-amino - 4 - chloro-phenyl)- 4 - formyl - pyrazol - 1 - yl] - 6 - (4-chloro-phenyl)-6H-[1, 3] thiazin - 4 - yl] -N-phenyl-acetamide, 2 -{6-(4-chloro-phenyl) - 2 - [4-formyl-3- (4-nitro-phenyl)-pyrazol-1-yl] - 6H -[1,3] thiazin-4-yl]- N- phenyl- acetamide, 2 -[2-[3-(4-amino-phenyl) - 4 - formyl-pyrazol -1 -yl]-6-(4-chloro-phenyl)-6 H-[1, 3]thiazin-4-yl] - N - phenyl-acetamide, 2 - {6-(4-chloro-phenyl)-2-[4-formyl-3-(2-hydroxy-phenyl)-pyrazol-1-yl]- 6H-[1,3]thiazin-4-yl]-N-phenyl-acetamide have been reported.¹⁷

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 activities. 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).

$$\text{Biological activity} = f(\text{physicochemical properties}) \dots \dots (1)$$

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").¹⁸⁻²¹

Importance of PASS:

Experimental determination of biological activity of a drug is time and cost consuming procedure, so making the use of PASS is generally important.

PASS can be effectively used for finding of compounds with required properties and without undesirable side effects.

It used for selecting the most prospective compounds from the set of available samples for specific screening. 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.

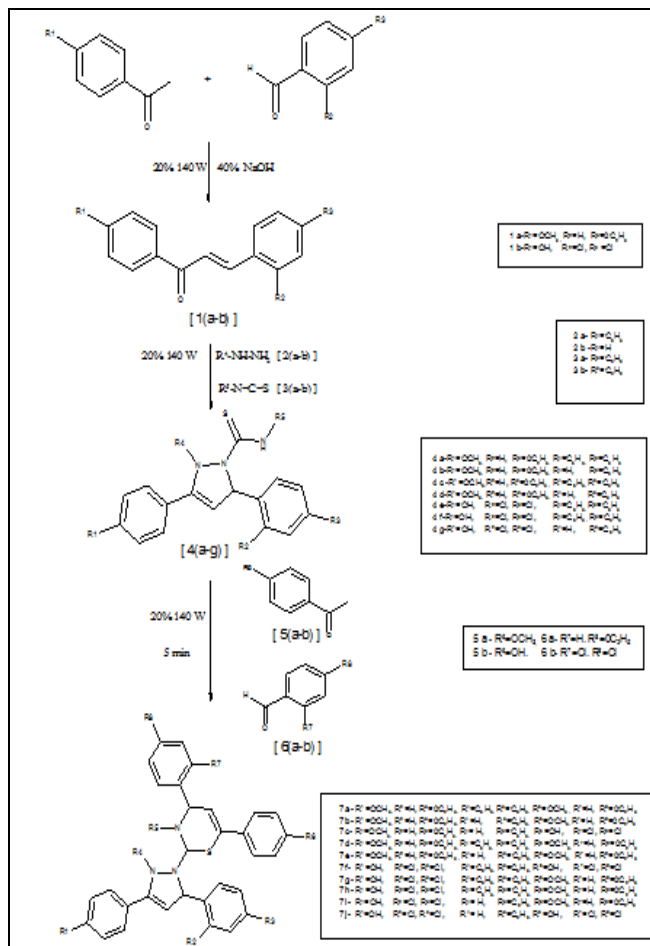


FIG.1:

MATERIALS AND METHOD:

Melting points were determined with Melting point apparatus using open capillary tubes and are uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^1H NMR spectra were recorded in CDCl_3 with TMS as internal standard on a Bruker spectrometer at 400 MHz. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Purity of the compounds was checked by TLC on silica- G plates of 2 mm thickness using n-hexane and ethyl acetate as solvent system. The visualization of spot was carried out in an iodine chamber. Biological activities are predicted by using computer programme PASS.

Synthesis of (E)-3-(4-ethoxy-phenyl)-1-(4-methoxy-phenyl)-propenone [1-a]:

4-Methoxyacetophenone 1.50 g, (0.01 M) and 4-ethoxybenzaldehyde 2.82 g (0.01 M) 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 to get Yield 2.56 g (86%) of [1-a] (see Figure 1)

M. Formula: $\text{C}_{18}\text{H}_{18}\text{O}_3$, M. Wt: 282, M.P.116 $^\circ\text{C}$, Elemental analysis: C, 76.61(76.67%); H, 6.47(6.49%); O, 17.01(17.05%). IR (KBr) ν_{max} , 1040(C-O), 1209(O-CH $_3$), 1410(CH=CH), 1515(C-C), 1670(C=O), 3019(Ar-CH). ^1H NMR(CDCl_3): δ , 1.42-1.45 (3H,t,CH $_3$), 3.82 (3H,s,OCH $_3$), 4.09-4.12(2H,q,OCH $_2$), 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), 7.557.57 (2H,d,=CH), 6.81-6.83 (2H,d,=CH) ppm. ^{13}C NMR(chemical shifts): 14.74(O-CH $_2$ -CH $_3$), 55.28(O-CH $_3$), 64.46(O-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=).

Synthesis of (E)-3-(2, 4-dichloro-phenyl)-1-(4-hydroxy -phenyl)-propenone[1-b]:

Similarly condensation of 4-methoxyacetophenone with 2, 4 di-chlorobenzaldehyde produced (E)- 3 (2, 4 - dichloro-phenyl) – 1 - (4-hydroxy - phenyl)-

propenone [1-b]. M.W irradiation time: 3 mins; Yield 2.19 g (75%) of [1-b] (Table 1)

Mol. Formula: $\text{C}_{16}\text{H}_{12}\text{Cl}_2\text{O}_2$ Mol. Wt. 307.18, M.P. 155 $^\circ\text{C}$, Elemental analysis: C, 62.57(62.59%); H, 3.92(3.94%); O, 10.43(10.46%). IR (KBr): ν_{max} , 3019(Ar-CH), 1670(C=O), 1515(C-C), 1410 (CH=CH), 1040(-OCH $_3$). ^1H NMR (CDCl_3): δ , 3.82(3H,s,OCH $_3$), 6.97-6.99(2H,d,=CH), 8.02-8.04(2H,d,=CH), 7.45-7.47(1H,d,=CH), 7.79-7.81 (1H,d,=CH),7.48-7.50(1H,d,=CH), 7.20-7.22 (1H, d,=CH), 7.37(1H,s,=CH) ppm. ^{13}C NMR (chemical shifts): 55.28 (OCH $_3$), 163.30 (CH), 113.71 (2x=CH), 130.67 (3x=CH), 189.74 (C=O), 124.63 (=CH), 145.05(=CH), 133.65(>C=), 129.90(=CH), 127.34(=CH), 132.85 (=CH), 128.23 (=CH), 134.30(>C=).

Synthesis of 5-(4-ethoxy-phenyl)-3-(4-methoxy-phenyl)-2- phenyl-2, 5-dihydropyrazole-1-carbothioic acid phenyl amide [4 -a]:

(E) – 3 - (4-ethoxy-phenyl) – 1 - (4-methoxy-phenyl)-propenone [1-a] 2.82 g (0.01 M), phenyl hydrazine 1.08 g (0.01 M), phenyl isothiocyanate 1.35g (0.01 M) 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 to get yield 4.26 g (84%) of [4-a] (Table 1)

M. Formula: $\text{C}_{31}\text{H}_{29}\text{N}_3\text{O}_2\text{S}$, M. Wt: 507.66, M.P. 215 $^\circ\text{C}$, Element analysis: C, 73.35(73.39%); H, 5.76(5.78%); N, 8.28(8.34%). IR (KBr): ν_{max} 1020(C-N), 1040(C-O), 1160(OCH $_3$), 1200(C=S), 1230(N-N), 1609(C-C), 3018(Ar-CH), 3500(NH). ^1H NMR(CDCl_3): δ 1.30-1.32 (3H,t,CH $_3$), 3.86 (3H, s, OCH $_3$), 3.99-4.03 (2H,q,CH $_2$), 5.94-5.95 1H,d,=CH), 5.97-5.99 (1H,d,CH), 6.87-6.97 (8H, m,Ar-H), 7.44-7.72 (10H,m,Ar-H), 8.65 (1H,d,NH) ppm. ^{13}C NMR (chemical shifts): 13.81(O-CH $_2$ -CH $_3$), 55.12(O-CH $_3$), 61.10 (O-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) ppm. The same experimental procedure was utilized to prepare other analogs of this serial [4(b-g)]. Their physical constant data is given in Table 1.

TABLE 1: PHYSICAL CONSTANTS OF THE COMPOUND [4(b-g)]

Comp.	R ¹	R ²	R ³	R ⁴	R ⁵	Yield %	M.P. °C	M. Formula	Elemental Analysis Found(Calcd)%		
									C	H	N
4-b	OCH ₃	H	OC ₂ H ₅	H	C ₆ H ₅	75	201	C ₂₅ H ₂₅ N ₃ O ₂ S	69.58 (69.63)	5.84 (5.85)	9.74 (9.78)
4-c	OCH ₃	H	OC ₂ H ₅	C ₆ H ₅	C ₃ H ₅	78	210	C ₂₈ H ₂₉ N ₃ O ₂ S	71.31 (71.34)	6.20 (6.22)	8.91 (8.97)
4-d	OCH ₃	H	OC ₂ H ₅	H	C ₃ H ₅	84	205	C ₂₂ H ₂₅ N ₃ O ₂ S	66.81 (66.86)	6.37 (6.39)	10.62 (10.65)
4-e	OH	Cl	Cl	C ₆ H ₅	C ₆ H ₅	79	235	C ₂₈ H ₂₁ Cl ₂ N ₃ OS	64.87 (64.90)	4.08 (4.10)	8.10 (8.14)
4-f	OH	Cl	Cl	C ₆ H ₅	C ₃ H ₅	74	225	C ₂₅ H ₂₁ Cl ₂ N ₃ OS	62.24 (62.28)	4.39 (4.41)	8.71 (8.75)
4-g	OH	Cl	Cl	H	C ₆ H ₅	85	213	C ₂₂ H ₁₇ Cl ₂ N ₃ OS	59.73 (59.77)	3.87 (3.89)	9.50 (9.56)

TABLE 2: PHYSICAL DATA OF THE COMPOUND [7 (b-j)]:

Comp.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	Yield %	M.P. °C	M. Formula	Elemental Analysis Found (Calcd)%		
												C	H	N
7-b	OCH ₃	H	OC ₂ H ₅	H	C ₆ H ₅	OCH ₃	H	OC ₂ H ₅	75	238	C ₄₃ H ₄₃ N ₃ O ₄ S	74.00 (74.05)	6.21 (6.23)	6.02 (6.07)
7-c	OCH ₃	H	OC ₂ H ₅	H	C ₆ H ₅	OH	Cl	Cl	78	230	C ₄₆ H ₃₉ Cl ₂ N ₃ O ₃ S	70.40 (70.47)	5.01 (5.03)	5.35 (5.38)
7-d	OCH ₃	H	OC ₂ H ₅	C ₆ H ₅	C ₃ H ₅	OCH ₃	H	OC ₂ H ₅	84	242	C ₄₆ H ₄₇ N ₃ O ₄ S	74.87 (74.89)	6.42 (6.44)	5.69 (5.74)
7-e	OCH ₃	H	OC ₂ H ₅	H	C ₃ H ₅	OCH ₃	H	OC ₂ H ₅	79	233	C ₄₀ H ₄₃ N ₃ O ₄ S	72.59 (72.65)	6.55 (6.58)	6.35 (6.39)
7-f	OH	Cl	Cl	C ₆ H ₅	C ₆ H ₅	OH	Cl	Cl	85	255	C ₄₃ H ₃₁ Cl ₄ N ₃ O ₂ S	64.92 (64.97)	3.93 (3.96)	5.28 (5.33)
7-g	OH	Cl	Cl	C ₆ H ₅	C ₆ H ₅	OCH ₃	H	OC ₂ H ₅	77	245	C ₄₆ H ₃₉ Cl ₂ N ₃ O ₃ S	70.40 (70.47)	5.01 (5.04)	5.35 (5.39)
7-h	OH	Cl	Cl	C ₆ H ₅	C ₃ H ₅	OCH ₃	H	OC ₂ H ₅	79	249	C ₄₃ H ₃₉ Cl ₂ N ₃ O ₃ S	68.98 (69.03)	5.25 (5.29)	5.61 (5.67)
7-i	OH	Cl	Cl	H	C ₆ H ₅	OCH ₃	H	OC ₂ H ₅	81	267	C ₄₀ H ₃₅ Cl ₂ N ₃ O ₃ S	67.79 (67.83)	4.98 (5.05)	5.93 (5.98)
7-j	OH	Cl	Cl	H	C ₆ H ₅	OH	Cl	Cl	69	252	C ₃₇ H ₂₇ Cl ₄ N ₃ O ₂ S	61.76 (61.79)	3.78 (3.83)	5.84 (5.87)

Synthesis of 4-(4-ethoxy-phenyl)-2-[5-(4-ethoxy-phenyl) - 3 - (4-methoxy-phenyl)-2-phenyl- 2, 5-dihydro-pyrazol-1-yl] - 6-(4-methoxy-phenyl) - 3 - phenyl - 3, 4-dihydro-2H-[1,3] thiazine [7-a]:

A mixture of 5-(4-ethoxy-phenyl) -3- (4-methoxy-phenyl) -2- phenyl-2, 5- dihydro-pyrazole-1-carbothioic acid phenyl amide[4-a] 0.507 g (0.001M),4-methoxy acetophenone [5-a] 0.150g (0.001 M) and 4-ethoxy benzaldehyde [6-a] 0.150 g (0.001 M) taken in RBF with 30 ml ethanol and the reaction mixture was subjected to microwave irradiations at 20% microwave power (140 W) for 5 mins. The reaction mixture was cooled and poured in ice. The solid separated was filtered, conveniently dried and recrystallized from ethanol to get 6.65 g 86% of [7-a] (**Figure 1**.)

M. Formula: C₄₉H₄₇N₃O₄S, M.Wt.774.00, M.P. 245°C, Element analysis: C, 76.01(76.04%); H, 6.10(6.12%); N, 5.45(5.48%). IR (KBr): ν_{max} , 1025(C-N), 1060(C-O), 1165(O-CH₃), 1235(N-N),

1595 (C=C), 3018(Ar-CH). ¹H NMR(CDCl₃-200.13Mz) δ ppm: 1.37-1.40(6H,t,CH₃), 3.86 (6H,s,OCH₃), 3.99-4.03 (4H,q,CH₂), 4.80-4.81(1H,d,CH), 4.85-4.86 (1H,d,CH), 5.50 (1H,s,CH), 5.94-5.95 (1H,d,CH), 5.97-5.99 (1H,d,CH), 6.87-6.97 (8H,m,C₆H₄), 7.15-7.30 (8H,m,C₆H₄), 7.44-7.72 (10H,m,C₆H₅). ¹³CNMR (chemical shifts): 4.68 (2x $\underline{\text{C}}\text{H}_3$),55.42 (2x $\underline{\text{O}}\text{C}\text{H}_3$), 58.52($\underline{\text{C}}\text{H}$),63.58(2x $\underline{\text{C}}\text{H}_2$),69.87($\underline{\text{C}}\text{H}$),70.90($\underline{\text{C}}\text{H}$),113.73(4x $\underline{\text{C}}\text{H}$),114.81(4x $\underline{\text{C}}\text{H}$),119.36(2x $\underline{\text{C}}\text{H}_3$),126.64($\underline{\text{C}}\text{H}$),127.00(4x $\underline{\text{C}}\text{H}$),127.58(4x $\underline{\text{C}}\text{H}_3$),130.07 (4x $\underline{\text{C}}\text{H}$),130.64(4x $\underline{\text{C}}\text{H}$),131.34(2x $\underline{\text{C}}\text{H}$), 133.89 ($\underline{\text{C}}\text{<$), 138.64 ($\underline{\text{C}}\text{H}$), 139.14(2x $\underline{\text{C}}\text{H}$), 143.85 ($\underline{\text{C}}\text{H}$), 149.36(2x $\underline{\text{C}}\text{H}$), 160.89(2x $\underline{\text{C}}\text{H}$), 163.21 (2x $\underline{\text{C}}\text{H}$).MS m/z (%): 774 [M⁺, 1%], 282 (100), 225 (30), 165 (22), 135(51), 92(25), 77(28);

Similarly, the other derivatives [7(b-j)] were synthesized. Their physical data is given in **Table 2**.

RESULT AND DISCUSSION:

It was observed that 4-methoxyacetophenone on condensation with 4-ethoxybenzaldehyde, 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 1595 (C=C) and signals at 7.79-7.81(1H, d, =CH), 7.55-7.57(2H, d, =CH) in ¹H NMR representative of the completion of the reaction and formation of the desired product.

Similarly absorption bands at 1107(C=S), 3230(NH), 1340(C-N) in IR spectra and signal at 8.65(1H, s, NH) in ¹H NMR of (4a-g) confirmed 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).

The structures assigned to 4-(4-Ethoxy-phenyl)-2-[5-(4-ethoxy-phenyl)- 3 - (4-methoxy - phenyl) - 2-phenyl-2, 5-dihydro-pyrazol-1-yl] - 6 -(4-methoxy-phenyl)-3-phenyl-3, 4-dihydro - 2H- [1,3]thiazine [7(a-j)] were supported by the elemental analysis and IR spectra showing an absorption bands at 1025(C-N),1595 (C=C). The molecular weights of all derivatives were confirmed by observing the molecular peaks in their respective mass spectra.

QSAR Analysis of Activities With PASS:

The relationship between structure and different biological activities was studied using computer programme PASS. The structures of derivatives [7(a-j)] were subjected to software to find the predictions of their probabilities of being active [Pa] and inactive [Pi] for the set of biological activities.

The following three activities were predicted with top probability for the series of compounds [7(a-j)]

1. Aspulvinone dimethyl allyl transferase inhibitor
2. Gluconate 2-dehydrogenase (acceptor) inhibitor
3. CYP2D15 substrate

Aspulvinone dimethyl allyl transferase inhibitor:

The enzyme also named as dimethylallyl-diphosphate or aspulvinone-E

Dimethyl allyl transferase which catalyses the reaction occurring in organism *Aspergillus terreus*.

2dimethylallyl diphosphate + aspulvinone E \rightleftharpoons 2 diphosphate + aspulvinone H.

Aspergillus terreus is a threat to animal and human species because of its complete resistance to amphotericin B, a crucial treatment for fungal infections.

The catalytic activity of the said enzyme in the organism is probably inhibited by the compound under study.

Gluconate 2-dehydrogenase (acceptor) inhibitor:

In enzymology, a gluconate 2-dehydrogenase (acceptor) (EC 1.1.99.3) is an enzyme that catalyzes the chemical reaction occurring in organisms like *Gluconobacter frateurii* and *Campylobacter jejuni*.

D-gluconate + acceptor \rightleftharpoons 2-dehydro-D-gluconate + reduced acceptor

C. jejuni is commonly associated with poultry, and it naturally colonises the digestive tract of many bird species.

The catalytic activity of the said enzyme in the organism is probably inhibited by the compound under study.

CYP2D15 substrate:

CYP2D15 catalyses exclusively the O-demethylation of dextromethorphan in dog liver drug metabolism. The compounds may act as substrate to this protein in Dogs.

However, from the predictions one can conclude that the derivatives in the series are moderately active for all the three activities. Amongst them 7-a is having highest Pa for aspulvinone dimethyl allyl transferase inhibitor and CYP2D15 substrate activities. Whereas, 7-h is having highest Pa for Gluconate 2-dehydrogenase (acceptor) inhibitor activity as shown in **Table 3**. The comparison of the three activities has been given in **Figure 2**, **Figure 3** and **Figure 4** respectively.

FIG. 3: PREDICTIONS OF BIOLOGICAL ACTIVITIES BY PASS

Activity Comp.	Aspulvinone dimethyl allyl transferase inhibitor	Gluconate 2-dehydrogenase (acceptor) inhibitor	CYP2D15 substrate
	Pa	Pa	Pa
7-a	0.573	0.533	0.528
7-b	0.442	0.480	0.406
7-c	0.425	0.615	0.372
7-d	0.437	0.617	0.403
7-e	0.361	0.536	0.280
7-f	0.323	0.454	0.317
7-g	0.314	0.562	0.310
7-h	0.0	0.623	0.0
7-i	0.0	0.522	0.0
7-j	0.0	0.401	0.0

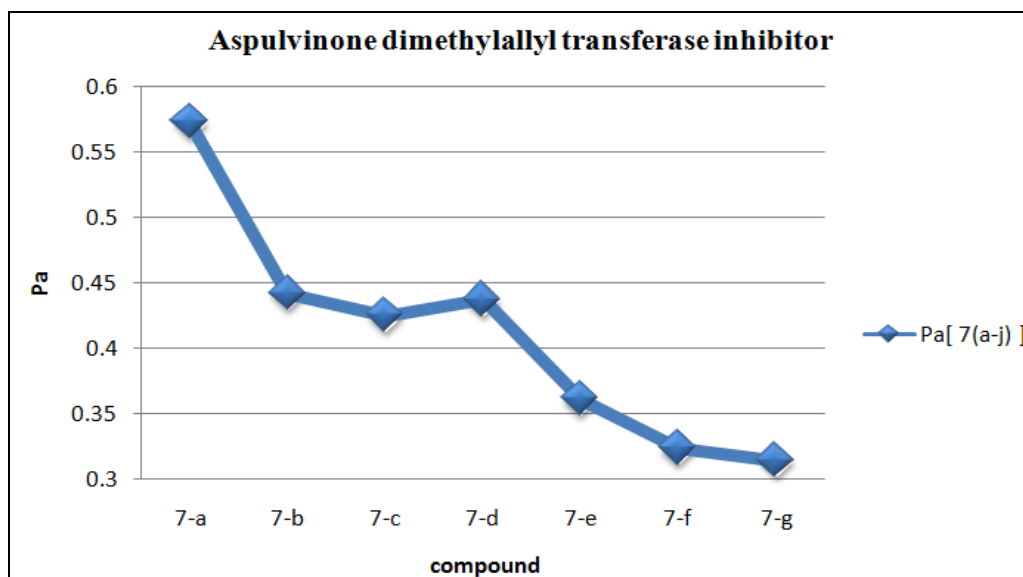


FIG.2: COMPARISON OF APULVINONE DIMETHYLALLYL TRANSFERASE INHIBITOR ACTIVITY OF COMPOUNDS 7-a TO 7-g

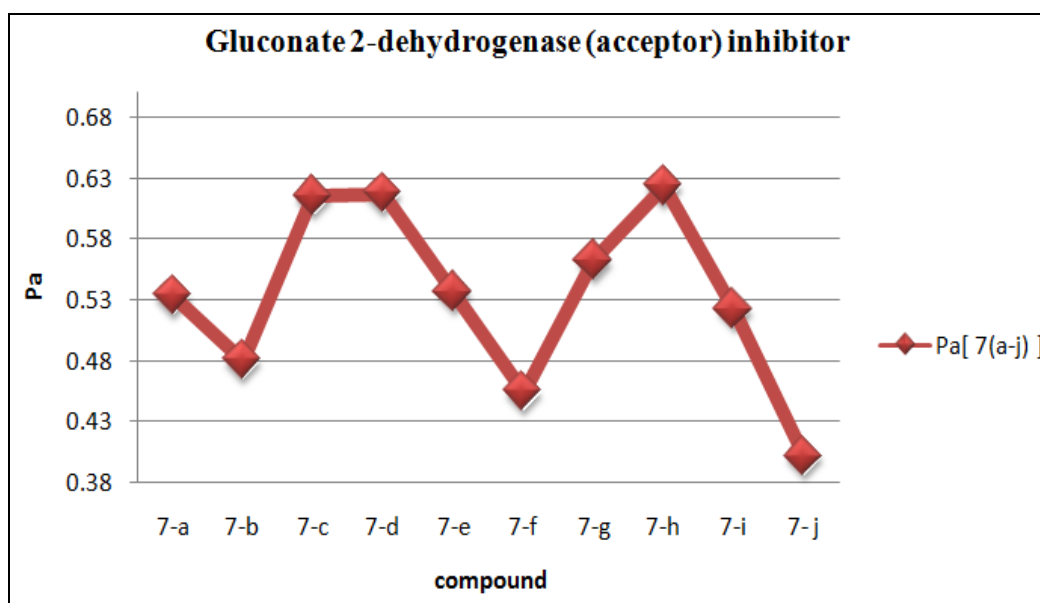


FIG. 3: COMPARISON OF GLUCONATE 2-DEHYDROGENASE (ACCEPTOR) INHIBITOR ACTIVITY OF COMPOUNDS 7-a TO 7-g

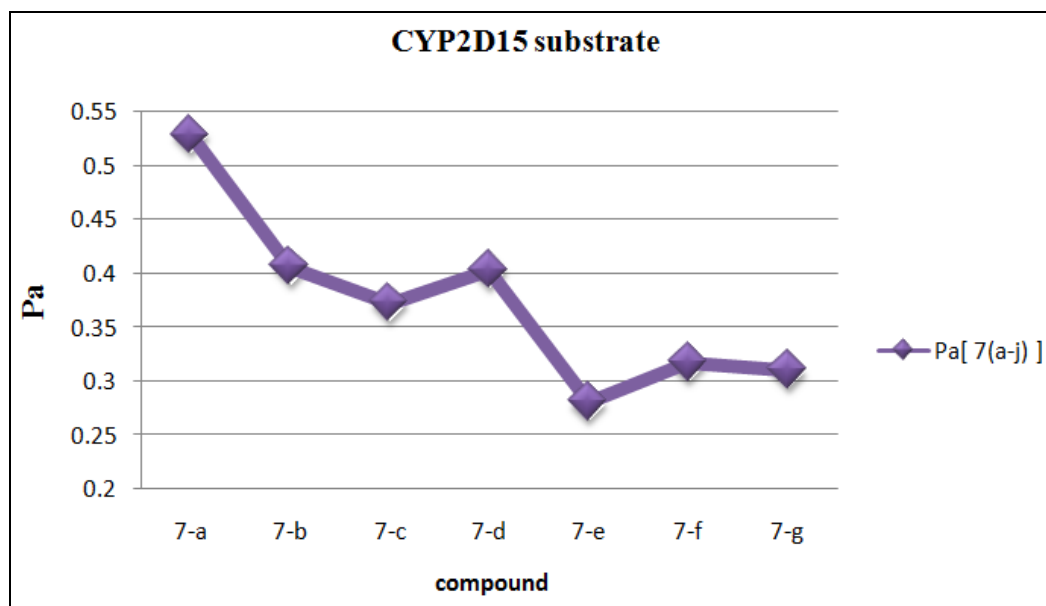


FIG. 4: COMPARISON OF CYP2D15 SUBSTRATE ACTIVITY OF COMPOUNDS 7-a TO 7-g

ACKNOWLEDGEMENT: The authors are thankful to the UGC for Faculty Improvement Programme for doing Ph.D. and for providing financial assistance to avail research facilities in Research Laboratory in Heterocyclic Chemistry at Devchand College, Arjunnagar through a major research project.

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How to cite this article:

Kapase VS, Khot SS, Kenawade SA and Dhongade SR: Microwave Assisted Synthesis & QSAR Study of Some Novel Pyrazolyl Thiazine Derivatives. Int J Pharm Sci Res 2014; 5(12): 5556-63. doi: 10.13040/IJPSR.0975-8232.5 (12).5556-63.

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