International Journal on Science and Technology (IJSAT)
E-ISSN: 2229-7677 ● Website: www.ijsat.org ● Email: editor@ijsat.org

Design and Synthesis of Thiazole Derivatives as Novel Anti-Oxidant Agents

J.Tharun Kumar[1], P.Ashwitha[2], R.Vaishnavi[3], B.Sindhuja[4], M.Anusha[5], B.Sadwika[6], K.Nandini[7], A.Srinivas[8]

Department of Pharmaceutical Chemistry, Unity College of Pharmacy, Raigir, Bhongir, Yadadhri Bhuvanagiri, Telangana, India, 508 116

Abstract:

A straightforward and effective methodology was established for the synthesis of 2-(2-arylidenehydrazinyl)-4,5-diphenylthiazoles (Va-Vg) through the reaction of 1,3-diphenyl-propane-1,3-dione with suitable aromatic aldehydes to produce 2-methoxy-4,5-dimethylthiazole, which is subsequently reacted with hydrazine hydrate and further treated with diverse aromatic aldehydes. The synthesized compounds were structurally verified employing IR, NMR, and mass spectrometry. Furthermore, investigations into antioxidant activity were performed, demonstrating the promising bioactivity of the synthesized thiazole derivatives. Compound Ve exhibited the highest antioxidant activity in comparison to the standard, with an IC50 value of 23.71, followed by Vd with an IC_{50} value of 32.11. Compounds Vc and Vf demonstrated moderate antioxidant activity, with IC_{50} values of 47.3 and 51.6, respectively.

Keywords: Thiazole derivatives, IR, NMR, Mass, Anti-Oxidant, IC_{50}.

1. Introduction:

The synthesis of heterocycles has transformed into a sophisticated methodology for the creation of innovative molecules pertinent to pharmaceuticals development. Heterocyclic compounds function as scaffolds upon which pharmacophores can be arranged to yield effective and selective therapeutics. Thiazoles symbolize a well-established class of heterocyclic compounds demonstrating a range of biological activities, with their medicinal uses being well-documented. Thiazole is a yellow liquid utilized in the synthesis of numerous pharmaceuticals and dyes. The increasing nucleophilicity of alkyl groups, combined with the basicity of thiazole, is, however, mitigated by the presence of hetero atoms such as nitrogen, which reduces nucleophilicity and basicity [1]. Varied reaction conditions, catalysts, and solvents significantly influence the synthesis of thiazole derivatives, while environmentally-friendly techniques and microwave irradiation are frequently employed methods in their preparation [2]. Thiazoles are five-membered heterocyclic compounds characterized by the presence of nitrogen and sulfur atoms, notably including the isothiazole isomer. Thiazoles serve as fundamental scaffolds in numerous natural compounds such as vitamin B1-thiamine, alkaloids, anabolic steroids, and flavones. [3].

The academic interest in the synthesis of compounds incorporating the thiazole moiety has been progressively escalating, attributed to their applications in photosensitizers, rubber vulcanization [4], liquid crystals [5], sensors [6], sunscreens [7], catalysts [8], dyes [9], pigments [10], and chromophores[11].Thiazoles have attracted persistent attention owing to their varied biological properties which have recently been applied in the formulation of pharmaceuticals utilized in the treatment of allergic conditions [12], hypertension [13], inflammatory diseases [14], schizophrenia [15], infections caused by microbes [16] HIV [17], and more recently for analgesic purposes [18].

Thiazole derivatives demonstrate a wide range of biological activities, encompassing cardiotonic, fungicidal, sedative, anesthetic, bactericidal, and anti-inflammatory properties [19]. Consequently, the current endeavor was undertaken to synthesize thiazole derivatives and assess their therapeutic potential in our ongoing pursuit of novel antioxidant pharmaceuticals.

2. Materials and Methods

Preliminary materials were procured from authorized vendors and utilized without additional purification. Thin layer chromatography was conducted on glass plates coated with silica gel G, employing a mobile phase of ethyl acetate and chloroform in a 1:1 ratio. The observations (spots) were conducted utilizing iodine vapors. Employing an open capillary apparatus, the melting points were determined and are presented as uncorrected values. Infrared spectra (in KBr) were obtained and expressed in cm^{-1} utilizing the DRS-8000A accessory on a Shimadzu IR Affinity-1 FTIR spectrophotometer. Utilizing a suitable deuterated solvent (CDCl3) and tetramethylsilane (TMS) as an internal reference; NMR (1H) spectroscopy was performed on a Bruker Avance 500MHz spectrometer.

Synthesis of 2-methoxy-4,5-diphenylthiazole (III)

A combination of 25 mmol (5.25 g) of benzil, 25 mmol of anisalaldehyde, and 10 g of ammonium thiocyanate was placed in a 250 mL round-bottom flask equipped with a reflux condenser and subjected to reflux with 5 mL of glacial acetic acid for a duration of 4 hours. The resulting mixture was allowed to stand overnight and subsequently filtered to eliminate any precipitate. Following this, 250 mL of distilled water was introduced to the filtrate, and the resulting precipitate was gathered. The filtrate was neutralized with ammonium hydroxide, and the secondary crop of solid was collected. Both solid crops were then combined and re-crystallized from ethanol.

The compound was confirmed by its IR Spectrum (KBr) of the compound exhibited characteristic absorption bands (cm^{-1}) at: 3122 (C-H,Ar-H),1575 (C=C), 1520(C=N), 1383 (C-N), 1195 (-OCH_3), 951 (C-S).

^{1}H NMR Spectrum (DMSO-d_6) has been found to exhibit characteristic proton signals (δ, ppm) at: 7.9 (d, 1H, ArH), 7.8 (d,1H,ArH), 7.5 (t, 1H, ArH) , 7.4 (t, 2H,ArH), 7.3 (t,1H, ArH), 7.0 (d, 1H, ArH), 6.7 (t, 1H, ArH), 6.5 (d, 1H, ArH), 3.8 (s, 3H, OCH_3).

By the above spectral data the compound was conformed as 2-Methoxy-4,5-Diphenylthiazole (III)

Synthesis of 2-hydrazinyl-4,5-diphenylthiazole (IV)

A combination of 2-methoxy-4,5-diphenylthiazole (III, 0.01 mol) and hydrazine hydrate (99%) (0.01 mol) was prepared in 50 ml of alcohol, subjected to reflux on a water bath for 5 hours. The alcohol volume was reduced by half and subsequently cooled. The resultant product was filtered, purified through washing with small portions of cold alcohol followed by repeated rinses with cold water, and then dried. Further purification of the product was achieved through recrystallization using appropriate solvents. The compound was characterized utilizing spectral data. The yield of the compound was determined to be 77%, with a melting point of 258 °C.

The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands (cm^{-1}) at: 3133 (C-H,Ar-H),1633 (C=C), 1549(C=N), 1393 (C-N), 1134 (C-S)., 882 (N-N) .

^{1}H NMR Spectrum (DMSO-d_6) has been found to exhibit characteristic proton signals (δ, ppm) at: 7.7 (d, 1H, ArH), 7.6 (d,1H,ArH), 7.3 (t, 1H, ArH) , 7.2 (t, 2H,ArH), 7.1 (t,1H, ArH), 6.9 (d, 1H, ArH), 6.6 (t, 1H, ArH), 6.5 (d, 1H, ArH), 4.2 (s, 1H, NH), 2.2 (s, 2H, NH_2).

By the above spectral data the compound was conformed as 2-hydrazinyl-4,5-diphenylthiazole (IV)

Synthesis of 2-(2-arylidenehydrazinyl)-4,5-diphenylthiazoles (V) [20]

2-hydrazinyl-4,5-diphenylthiazole (IV, 0.01 mol) underwent treatment with diverse aromatic aldehydes (0.015 mol) via refluxing in 20 mL of absolute alcohol, accompanied by the addition of minimal acetic acid for a period of 8 hours. The resultant product was subsequently filtered, dried, and purified through recrystallization employing suitable solvents. The characterization of these compounds was performed in accordance with their spectral data, and the physical properties are detailed in Table 1.

For example, 2-hydrazinyl-4,5-diphenylthiazole (IV, 0.01 mol) underwent treatment with 4-chlorobenzaldehydes (0.015 mol) through reflux in 20 mL of absolute alcohol, augmented by a few drops of acetic acid, over a period of 8 hours. The resultant product was subsequently subjected to filtration, drying, and purification via re crystallization employing ethanol. The obtained compound was characterized by its spectral data and identified as 2-(2-(4-chlorobenzylidene) hydrazinyl)-4,5-diphenylthiazole.

The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands (cm^{-1}) at: 3010 (C-H,Ar-H),1616 (C=N), 1597(C-C), 1580 (C=C, Ar), 1313 (C-N), 1179 (N-N), 1102(C-Cl), 864 (C-S).

^{1}H NMR Spectrum (DMSO-d_6) has been found to exhibit characteristic proton signals (δ, ppm) at: 8.7 (s, 1H, CH), 7.8 (d, 1H, ArH), 7.7 (d,1H,ArH), 7.6 (d, 2H, ArH), 7.5 (d, 2H, ArH), 7.3 (t, 1H, ArH) , 7.1 (t, 2H,ArH), 7.0 (t,1H, ArH), 6.8 (d, 1H, ArH), 6.7 (t, 1H, ArH), 6.4 (d, 1H, ArH), 4.2 (s,1H, NH).

Evaluation of Antioxidant Activity using DPPH scavenging

The 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical was prepared as a freshly made 0.004% (w/v) methanol solution and stored at 10°C in darkness. A 0.01 mg/mL (0.001% (w/v)) solution of DPPH in methanol was prepared, with 1 mL of this solution being added to 4 mL of the synthesized samples in methanol to achieve four distinct concentrations (10, 25, 75, and 100 µg/mL). Employing a UV-visible spectrophotometer, absorbance measurements were immediately recorded. Following stabilization of the absorbance (after 16 minutes), the decrease in absorbance at 517 nm was continuously monitored, with data collected at one-minute intervals. Ascorbic acid served as a reference compound, and the absorbance of both the DPPH radical and the control (without antioxidant) were concurrently evaluated. Each determination was performed in triplicate, and the average was subsequently calculated [21].

The DPPH radical's percentage inhibition (PI) was then computed according to the formula**:**

$$\mathbf{PI = [\{(AC- AT)/ AC\} x 100]}$$

Where AC = Absorbance of the control and AT = absorbance of the sample+DPPH .

The 50% inhibitory concentration (IC50), the concentration required to inhibit DPPH radical by 50%, was estimated from graphic plots of the dose response curve.

RESULTS & DISCUSSIONS

The free radical scavenging capacities of synthesized compounds and ascorbic acid (Vitamin C) at various concentrations were assessed using the DPPH assay. Antioxidants engage with DPPH, a nitrogen-centered radical exhibiting a distinctive absorption at 517 nm, resulting in the formation of 1,1-diphenyl-2-picryl hydrazine. The extent of discoloration (color change) reflects the scavenging capacities of the antioxidant compounds, wherein all tested representative pyrazole derivative compounds, alongside ascorbic acid (Vitamin C) as the positive control, demonstrated a dose-dependent reduction of the DPPH radical. Radical scavenging activity was quantified as the concentration (µg/mL) necessary to diminish DPPH (40 µg/mL) by 50% (IC_{50}).

All newly synthesized derivatives were subjected to in-vitro screening using DPPH at varying concentrations of 10 µg/ml, 25 µg/ml, 50 µg/ml, 75 µg/ml, and 100 µg/ml.

IC_{50} values of all the newly synthesized compounds were compared with the IC_{50} value of the standard Ascorbic acid (45.21). The results were produced in the Table 2.

All the newly synthesized compounds showed the Anti-Oxidant activity in the range of 23.71-68.56.

Among all the synthesized compounds Compound **Ve** (Ar= 4-methoxypheny) showed highest Anti-oxidant activity when compared with the standard with the **IC_{50} 23.71**, which was followed by the Compound **Vd** (Ar=4-aminophenyl) with IC_{50} value of 32.11.

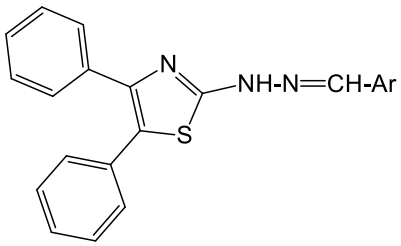
Compounds Vc (Ar= 4-chlorophenyl) and **Compound Vf** (Ar= 4-hydroxyphenyl) showed moderate anti-oxidant activity with IC_{50} values of 47.3 and 51.6 respectively.

Compound Va (Ar= pheny;) and **compound Vb (**Ar=α-propylene phenyl) showed very less anti-oxidant activity with with IC_{50} values of 65 and 68.56 respectively.

Conclusion:

The notable free radical scavenging activity observed via the DPPH method may be ascribed to the presence of electron-donating groups.

Table1. Physicochemical properties of 2-(2-arylidenehydrazinyl)-4,5-diphenylthiazoles (Va-Vg)

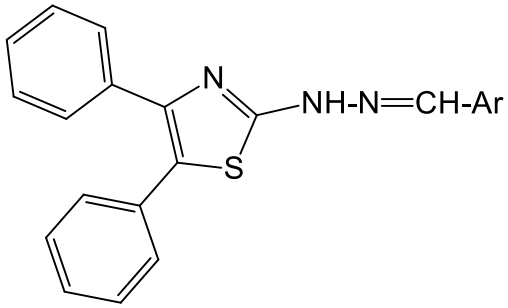


Compound	Ar	Mol. Formula	Mol. Weight	M.P (in ^{O}C)	% of Yield
Va	Phenyl	$C_{22}H_{17}N_3S$	355	220-222	59
Vb	Cinnamalyl	$C_{24}H_{19}N_3S$	381	245-247	68
Vc	4-Chlorophenyl	$C_{22}H_{16}ClN_3S$	390	214-216	71
Vd	4-aminophenyl	$C_{22}H_{18}N_4S$	370	216-218	75
Ve	4-methoxyphenyl	$C2_3H_{19}N_3OS$	385	202-204	74
Vf	4-hydroxyphenyl	$C_{22}H_{17}N_3OS$	371	221-223	61
Vg	4-dimethylaminophenyl	$C_{24}H_{22}N_4S$	398	263-265	72

Table 2: Percentage of Inhibition of 2-(2-arylidenehydrazinyl)-4,5-diphenylthiazoles (Va-Vg)

Percentage of Inhibitions							
Con	Va	Vb	Vc	Vd	Ve	Vf	Vg
10ug/ml	23.36	36.09	45.7	50	66.46	23.36	36.09
25ug/ml	22.33	26.55	43.5	46.77	69.42	22.33	26.55
50ug/ml	26.17	39.67	51.32	69.01	77.3	26.17	39.67
75ug/ml	35.53	46.57	62.52	75.1	84.86	35.53	46.57
100ug/ml	40.94	54.03	64.97	67.22	87.42	40.94	54.03

Table 3: IC_{50} Values of Anti-Oxidant activity of 2-(2-arylidenehydrazinyl)-4,5-diphenylthiazoles (Va-Vg)



Compound	Ar	IC_{50} Value
Va	Phenyl	85.3
Vb	Cinnamalyl	55.71
Vc	4-Chlorophenyl	82.86
Vd	4-aminophenyl	45.85
Ve	4-methoxyphenyl	39.93
Vf	4-hydroxyphenyl	65.19
VIg	4-dimethylaminophenyl	39.29
Ascorbic Acid	-	45.21

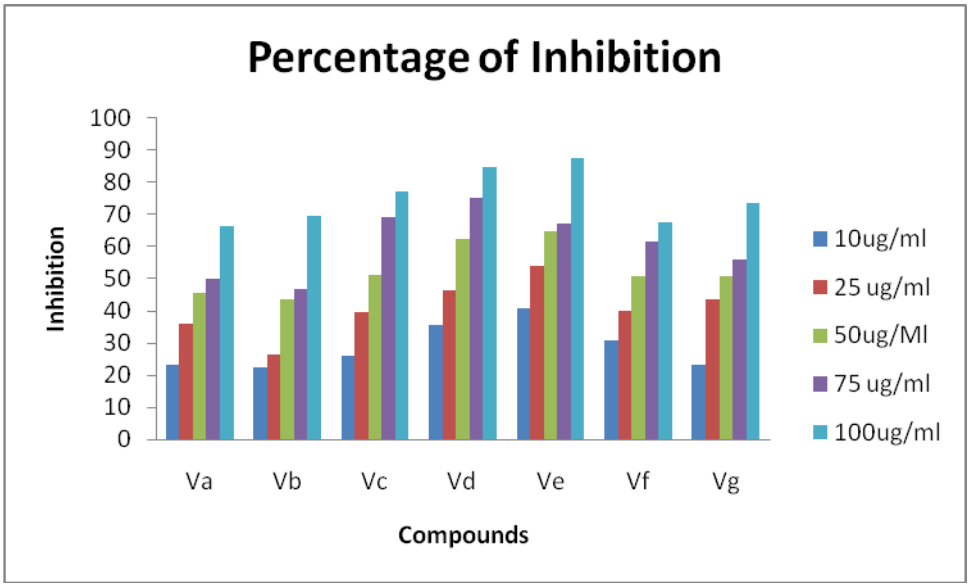


Fig.1. Bar diagram comparing anti-oxidant activity of test Thiazoles

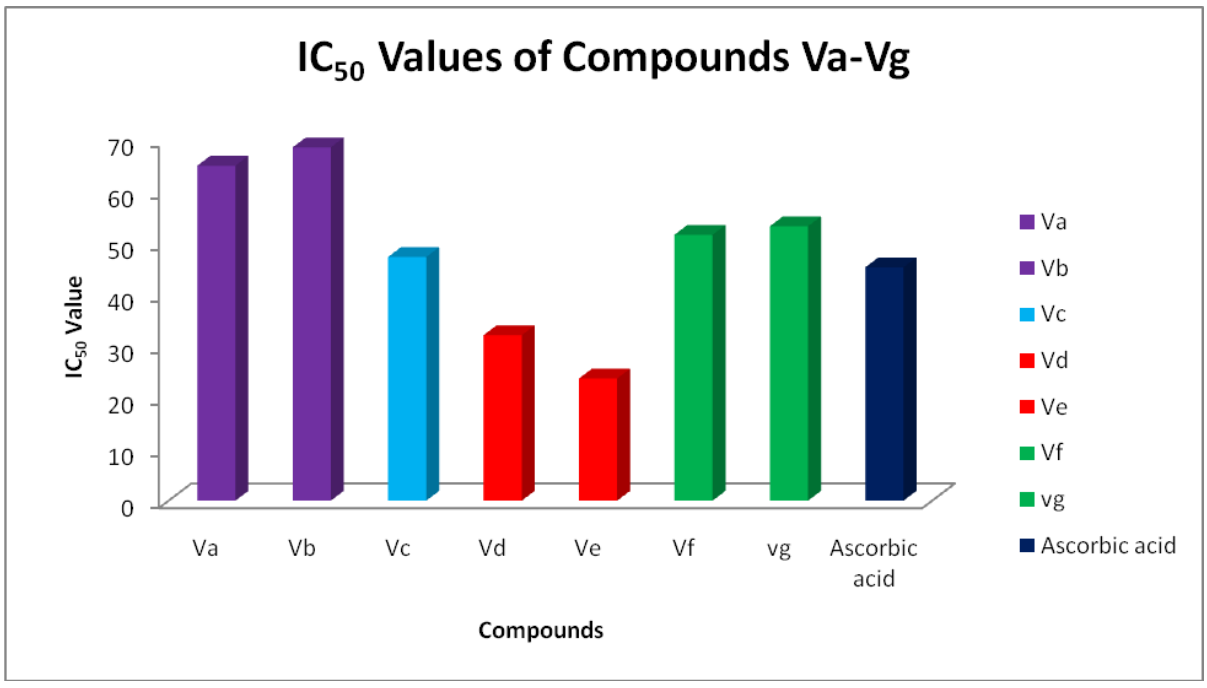
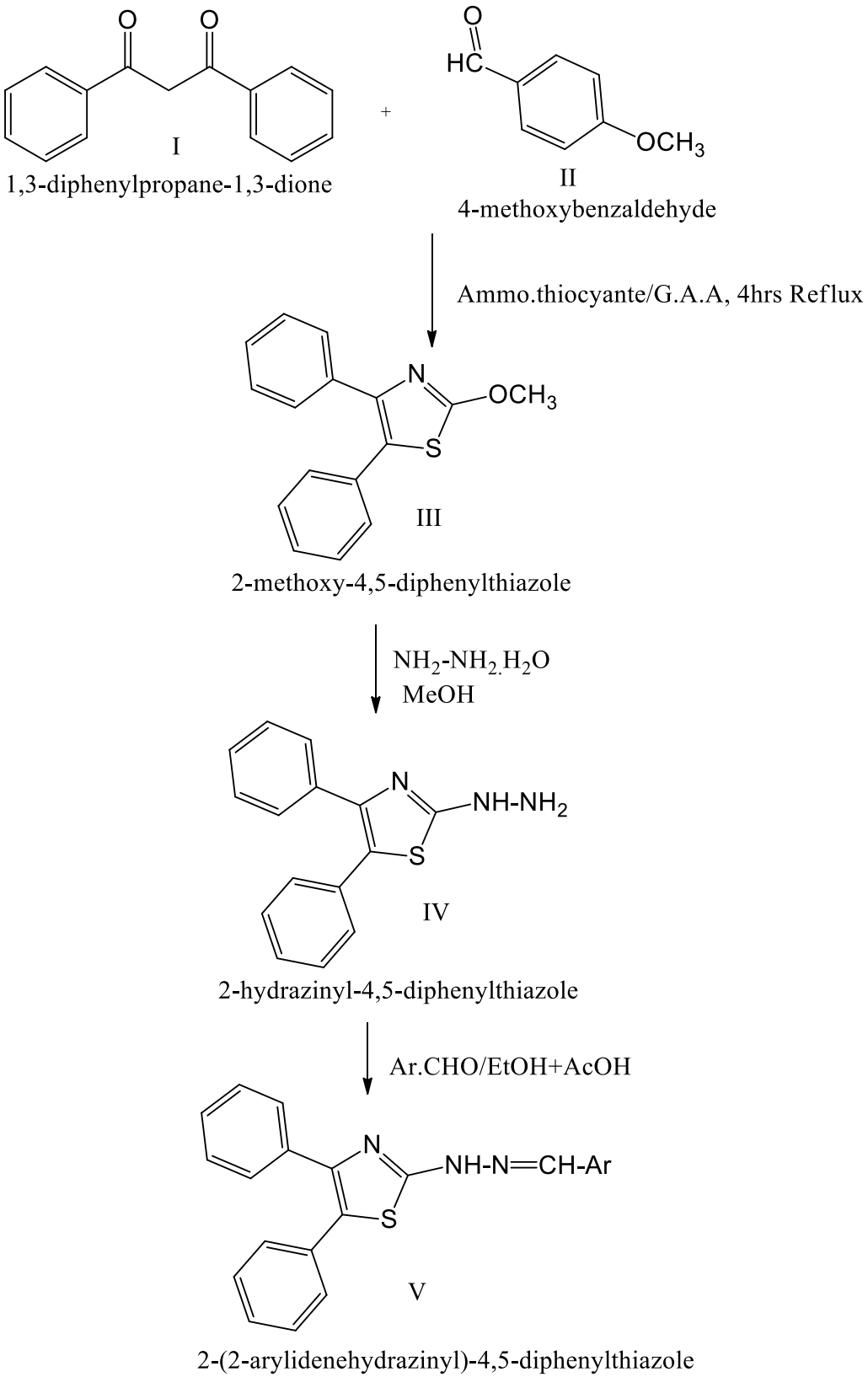


Fig 2. Bar diagram comparing anti-oxidant activity of test novel thiazoles


O
O
I
1,3-diphenylpropane-1,3-dione
+
O
HC
OCH3
II
4-methoxybenzaldehyde
Ammo.thiocyante/G.A.A, 4hrs Reflux
N
OCH3
S
III
2-methoxy-4,5-diphenylthiazole
NH2-NH2.H2O
MeOH
N
NH-NH2
S
IV
2-hydrazinyl-4,5-diphenylthiazole
Ar.CHO/EtOH+AcOH
N
NH-N=CH-Ar
S
V
2-(2-arylidenehydrazinyl)-4,5-diphenylthiazole

Scheme-1

References:

1. Trautwein A.W., Submuth R.D., and Jung G.: Hantzsch pyrrole synthesis on solid support. Bioorg. Med. Chem. Lett. 1998, 17(8) 2381-2.
2. Kamila S., Mendoza K., and Biehl E. R.: Microwaveassisted Hantzsch thiazole synthesis of N-phenyl-4-(6-phenylimidazo [2, 1-b] thiazol-5-yl) thiazol-2-amines from the reaction of 2-chloro-1-(6-phenylimidazo [2, 1-b] thiazol-5-yl) ethanones and thioureas. Tetrahedron Lett. 2012, 37(53) 4921-4.
3. Hama J. R., Omer R. A., Rashid R. S. M., Mohammad N.-E.-A., and Thoss V.: The Diversity of Phenolic Compounds along Defatted Kernel, Green Husk and Leaves Walnut (Juglansregia L.). Anal. Chem. Lett. 2016, 1(6) 35.
4. Milne GWA. Handbook of Antineoplastic Agents. London, UK: Gower/Ashgate; 2000
5. Mori A, Sekiguchi A, Masui K, Shimada T, Horie M, Osakada K, et al. Facile synthesis of 2,5-diarylthiazoles via palladium-catalyzed tandem C−H substitutions. Design of tunable light emission and liquid crystalline characteristics. Journal of the American Chemical Society. 2003;125:1700
6. Kim BY, Kim HS, Helal A. A fluorescent chemosensor for sequential recognition of gallium and hydrogen sulfate ions based on a new phenylthiazole derivative. Sens. Actuators B-Chem. 2015;206:430.
7. Bach T, Heuser S. Synthesis of 2-(o-hydroxyaryl)-4-arylthiazoles by regioselective Pd(0)-catalyzed cross-coupling. Tetrahedron Letters. 2000;41:1707.
8. Dondoni A. Heterocycles in organic synthesis: Thiazoles and triazoles as exemplar cases of synthetic auxiliaries. Organic & Biomolecular Chemistry. 2010;8:3366
9. Metwally MA, Abdel-Latif E, Amer FA, Kaupp G. Synthesis of new 5-thiazolyl azo-disperse dyes for dyeing polyester fabrics. Dyes and Pigments. 2004;609(3):249-264.
10. Borisenko VE, Koll A, Kolmakov EE, Rjasnyi AG. Hydrogen bonds of 2-aminothiazoles in intermolecular complexes (1,1 and 1,2) with proton acceptors in solutions. Journal of Molecular Structure. 2006;783(1):101-115.
11. Maj J, Rog Z, Skuza G, Kolodziejezyk K. Antidepressant effects of pramipexole, a novel dopamine receptor agonist. Journal of Neural Transmission. 1997;104(4-5):525-533
12. Hargrave KD, Hess FK, Oliver JT (1983) N-(4-substituted thiazol-yl)oxamic acid derivatives, new series of potent orally active antiallergy agents. J Med Chem 26:1158–1163.
13. Patt WC, Hamilton HW, Taylor MD, Ryan MJ, Taylor DG Jr, Cornolly CJC, Doherty AM, Cluck SR, Sircar I, Steinbaugh BA, Batly BL, Painchaud CA, Rapundalo ST, Michniewicz BM, Olson SCJ (1992) Structure–activity relationship of a series of 2-amino-4-thiazole containing rennin inhibitors. J Med Chem 35:2562–2572.
14. Manjunatha K, Poojary B, Lobo PL, Fernandes J, Chikkanna C (2010) Synthesis of some fused triazole derivatives containing 4-isobu-tylphenylethyl and 4-methylthiophenyl moieties. Z Naturforsch 65:1353–1358.
15. Jean JC, Wise LD, Caprathe BW, Telex H, Bergmeier S, Humbles CC, Heffner TG, Meltzner LT, Parsleys TA (1990) 4-(1,2,5,6-Tetrahydro-1-alkyl-3-pyridinyl)-2-thiazolamines: a novel class of compounds with central dopamine agonist properties. J Med Chem 33:311–317

16. Lobo PL, Poojary B, Manjunatha K, Suchetha N (2010) Synthesis and antimicrobial evaluation of some new 2-(6-oxo-5,6-dihydro[1,3] thiazolo[3,2-b]-2-aryloxymethyl-1,2,4 triazol-5-yl)-N-arylaceta-mides. Z Natureforsch 65:617–624
17. Bell FW, Cantrell AS, Hogberg M, Jaskunas SR, Johansson NG, Jordon CL, Knick MD, Lind P, Morin JM Jr, Noreen R, Oberg B, Palkowitz JA, Parrish CA, Sahlberg C, Ternansky RJ, Vesicle RT, Vrang L, West SJ, Zhang H, Zhou XX (1995) Phen-ethythiazolethiourea (PETT) compounds; a new class of HIV-1 reverse transcriptase inhibitors. Synthesis and basic structure activity relationship studies of PETT analogs. J Med Chem 38: 4929–4936
18. Carter JS, Kramer S, Talley JJ, Penning T, Collins P, Graneto MG, Seibert K, Koboldt C, Masferrer J, Zweifel B (1999) Synthesis and activity of sulfonamide-substituted 4,5 diaryl thiazoles as selective cyclo oxygenase-2 inhibitors. Bioorg Med Chem Lett 9:1171–1174.
19. V. Deepti, M. Aruna Kumari, N. Harikrishna, G. Ramesh and C. Venkata Rao. Synthesis of novel 2-amino thiazole derivatives, Der Pharma Chemica. 2013; 5(2):181-184.
20. Srinivas Ampati, Srinivas Naik. A, Rama Ganta, Vidyasagar Jenugu, Raju Jukanti, Sarangapani Manda, *Journal of Pharmacy Research* 2010, 3(10),2444-2446.
21. Shivani Choudhary, Suvarna G. Kini, Muhammad Mubeen, Der PharmaChemica, 2013, 5(4), 213-222.