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SYNERGETIC AND ONE-POT SYNTHESIS OF 2-HYDAZINYL 1,3-THIAZINYL *2H*-CHROMEN-2-ONE DERIVATIVES

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ABSTRACT
Considering the significance of thiazine as an excellent biologically active compound, we reported the synthesis of Hydrazinylthiazine derivatives from corresponding Chalcone and Thiosemicarbazide on heating with sodium hydroxide. Recently, we synthesized limited number of chalcones from pyrazolo aldehydes (1Ar,2Ar, and 3Ar) and ketones. Eleven derivatives of 2-hydrazinyl 1,3-thiazinyl 2*H*-chromen-2-ones were prepared, incorporating other substituents to enhance their activity. The synthesis process yielded all the Hydazinylthiazine derivatives in good yields and we further characterized them using IR, ^{1}H NMR and Mass spectroscopic methods.

KEYWORDS: Chalcones, Chromenones, Hydazinylthiazines, Thiazines, Thiosemicarbazide.

INTRODUCTION
Heterocyclic molecules containing nitrogen and sulphur, especially, thiazines hold a significant position in the field of medical and pharmaceutical chemistry. Thiazines are six-membered heterocycles with four carbon, one nitrogen and one sulphur atoms in their structure. Due to their adaptability, accessibility, and chemical simplicity, thiazine derivatives are currently being developed. Phenothiazines are one of the important thiazine compounds. They are antipsychotic drugs used to treat psychotic disorders such as schizoprenia and also as vermifuge for liver stock.[i]
1,2-Thiazine, 1,3-thiazine, and 1,4-thiazines[ii] are the three isomers of thiazine. Among them 1,3-thaiazine and its derivatives with N-C-S linkage have been used extensively as sedatives, antitubercular, antibacterial, antimicrobial, anticancer, insecticidal, fungicidal, and herbicidal agents.[iii-v]1,3-thiazines are even utilized in numerous chemical syntheses and transformations

as reaction intermediates. Moreover, the 1,3-thiazine core moiety shows excellent anti-radiation capability.

1, 3-Thiazine moiety is the core structure of cephalosporins (3,6-dihydro-2*H*,1,3-thiazine) and other medicinally significant substances like Xylazin (an agonist at the 2 class of adrenergic receptor used for sedation, anaesthesia, muscle relaxation, and analgesia in animals), Chlormezanone (used as a muscle relaxant and anxiolytic)[vi,] which reveals the importance of building highly interesting 1,3-thiazine and 1,3-thiazolidine complexes.[vii, viii]

In addition to their antifungal activity, 1,3-thiazines have also demonstrated potential CNS activity[ix] analgesic and anti-inflammatory activity[x] and activity as chemotherapeutic drugs (i.e., leishmanicides)[xi]. Our synthetic programme has focused on producing efficient new heterocycles[xii-xiv] showing biological activity including antibacterial[xv],antifungal[xiv], antitubercular[xvii], and anti-inflammatory[xviii] activities that have been found for 1,3-thiazine derivatives. Several techniques have been used to successfully synthesize 1,3-thiazines. For example, from S-alkylthiocarbamates and unsaturated ketones[xix] or by chlorovinyl ketones and thioamides in the presence of perchloric acid[xx]. Recently, substituted hydrazinyl 1,3-thiazine derivatives were synthesized, found to be shown antihelminthic, anti-inflammatory and larvicidal activity against salt water shrimp eggs.[xxi,xxii]

2H-Chromenone is an excellent core in the preparation of drug molecules used for the treatment of cancer, diabetes, tuberculosis and other microbial infections.

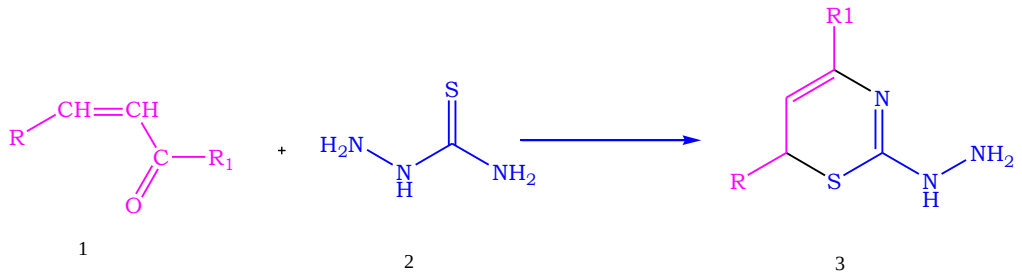
Pyrazole moiety is the core structure of drugs like antipyrine (analgesic), celecoxib (ani inflammatory), phenylbutazone (antipyretic) pyrazofurin (anticancer), fezolamide (antidepressant),crizotinib (cytoprotective), rimonabant(anti-obesity), and sildenafil (vasodilator).

After thorough review on synthesis of hydazinyl thiazine,a new work-up approach has been developed to make it simple and inexpensive. The recollected solvents can be used further after distillation. After effective processing, we worked with derivatives of Pyrazolo aldehydes (1 Ar, 2 Ar, and 3 Ar), ketones, *2H*-Chromenones and reported the novel derivatives.

RESULTS AND DISCUSSION

A series of new substituted hydrazinyl 1,3-thiazine derivatives (3a-3k) were synthesized (Table-1).The synthesis involved the combination of a chalcone compound (1), which served as the starting material, with thiosemicarbazide compound (2). The reaction was carried out in the presence of 15 mL of 30% alcoholic sodium hydroxide. The progress of the reaction was monitored using thin layer chromatography (TLC). To obtain the chalcone (1) Claisen - Schimdt reaction was employed. This reaction involves the condensation between acetophenone and benzaldehyde in presence of either NaOH or KOH.

The structures of the synthesized compounds **3a-3k** were confirmed using various spectroscopic techniques, including IR, ^{1}H NMR and mass spectra. In the IR spectra of compounds **3a-3k,** absorption bands corresponding to the NH group appeared at 3434.62 cm^{-1}. The ^{1}HNMR spectra of the synthesized compounds **3a-3k** exhibited characteristic signals in the range of 6.0 for a triplet representing the NH proton (t, NH, 1H), 8.1 for a doublet representing two NH2 protons (d, 2H, N$\underline{H_2}$) and 7.6-8.9 for aromatic protons (ArH) present in the aromatic ring. Mass spectra of the synthesized compounds showed molecular ion peaks ranging from m/z 560- 650 (M+).

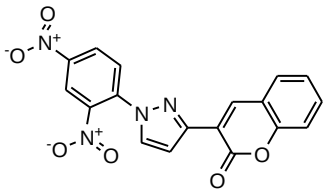
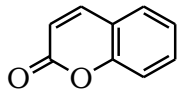
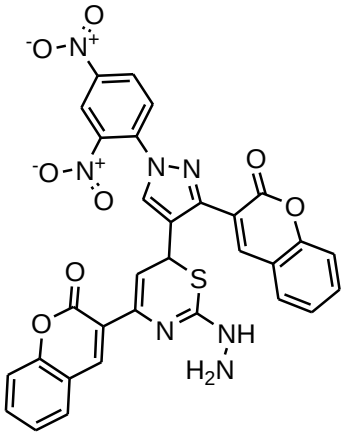
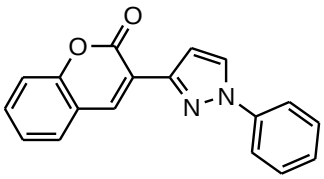
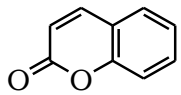
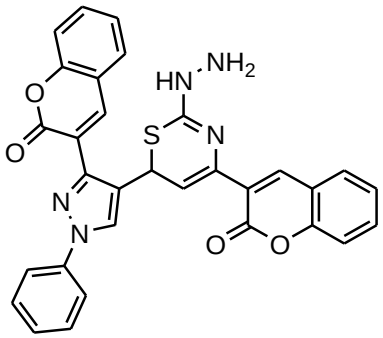


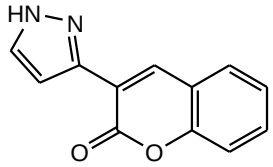
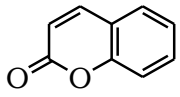
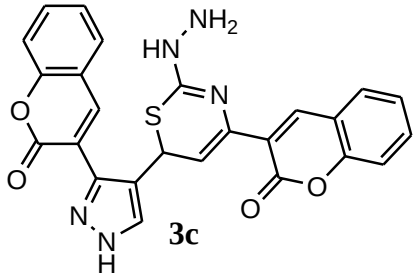
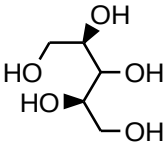
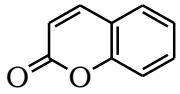
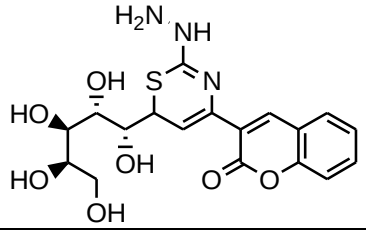
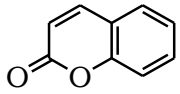
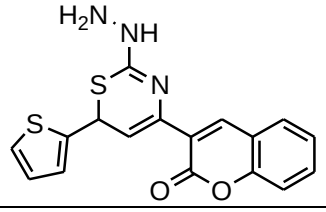
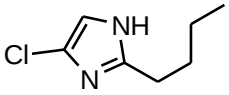
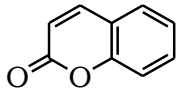
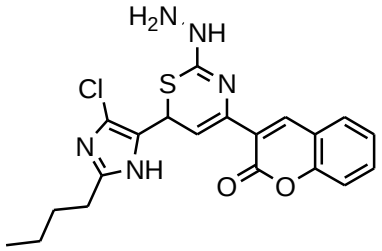
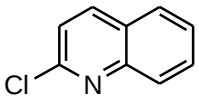
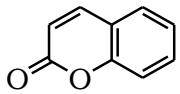
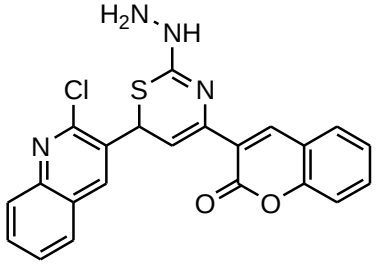
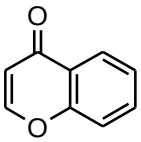
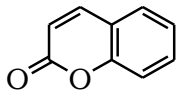
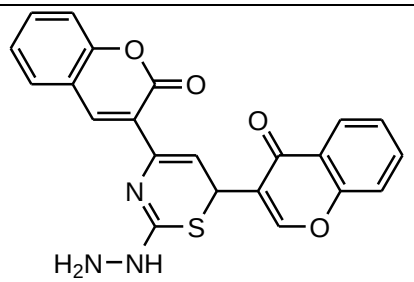
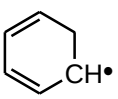
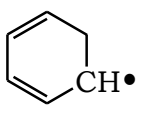
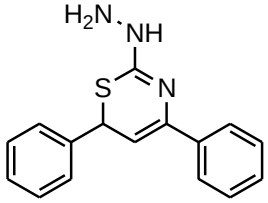
Scheme: Synthesis of 2-Hydazinyl 1,3-Thiazinyl *2H*-Chromen-2-ones

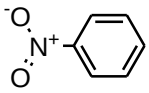
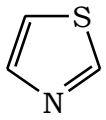
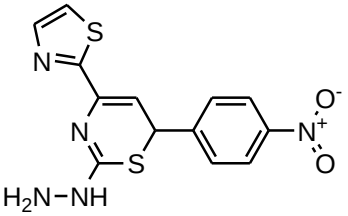
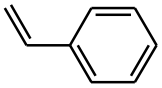
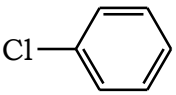
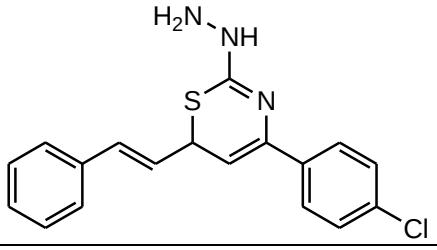
EXPERIMENTAL SECTION

Purchases were made from Fluka or Merck for chemicals and solvents. All of the chemicals used were analytical calibre. With a PerkinElmer spectrum gx FTIR equipment, IR spectra were captured as KBr pellets, and only diagnostic and/or strong peaks are given. Individual ^{1}H NMR spectra were recorded in DMSO-d6 using Varian equipment. The internal standard was provided by signals resulting from left over protonated solvent. As an internal standard, tetramethylsilane was utilized, and all chemical changes were reported in parts per million (ppm).The ^{1}H NMR chemical shifts and coupling constants were discovered to presumptively display first-order behavior. The order of multiplicity is determined by the list of coupling constants (J).A PE Sciex type API 3000 instrument has been used to record mass spectra. Every reaction was carried out in an argon atmosphere.

***Table 1*: Structures of substituents R and R1 and synthesized compounds**

No.	R	R^1	Compound
3a	 3-(1-(2,4-dinitrophenyl)-1H-pyrazol-3-yl)-*2H*-chromen-2-one	 2*H*-chromen-2-one	
3b	 3-(1-phenyl-*1H*-pyrazol-3-yl)-*2H*-chromen-2-one	 2*H*-chromen-2-one	

3c	 3-(1H-pyrazol-3-yl)-*2H*-chromen-2-one	 2*H*-chromen-2-one	 **3c**
3d	 (2R,4R)-pentane-1,2,3,4,5-pentaol	 2*H*-chromen-2-one	
3e	 Thiophene	 2*H*-chromen-2-one	
3f	 2-butyl-4-chloro-1H-imidazole	 2*H*-chromen-2-one	
3g	 2-chloroquinoline	 2*H*-chromen-2-one	
3h	 *4H*-chromen-4-one	 2*H*-chromen-2-one	
3i	 Phenyl	 Phenyl	

3j	 1-nitrobenzene	 Thiazole	
3k	 Styrene	 Chlorobenzene	

Preparation of hydrazinylthiazines: The chalcone (0.01 mole) and thiosemicarbazide (0.01 mole) were dissolved in 15 mL of 30% alcoholic sodium hydroxide and refluxed for two hours. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction-mixture was poured into about 100 ml of cold water, solid was filtered and dried.

3-(6-(1-(2,4-dinitrophenyl)-3-(2-oxo-*2H*-chromen-3-yl)-1*H*-pyrazol-4-yl)-2-hydrazinyl-6H-1,3-thiazin-4-yl)-2H-chromen-2-one(3a):
^{1}H NMR (DMSO, δ, ppm): 4.5 (d, 1H, -C*H*-S), 6.0 (t, 1H, -N*H*), 6.1 (s, 1H, =C*H*-), 7.4 (m, 4H, Ar-H), 7.5 (s, 1H, =C*H*-), 7.6 (m, 2H, Ar-H), 7.8 (m, 2H, Ar-H), 8.0 (s, 1H, =C*H*-), 8.1 (d, 2H, NH_2), 8.2 (d, 1H, Ar-H), 8.3 (s, 1H, Imidazole Ar-H), 8.8-8.9 (m, 2H, Ar-H); Mass=650 [M+H]+Yield: 72%.

3-(4-(2-hydrazinyl-4-(2-oxo-*2H*-chromen-3-yl)-*6H*-1,3-thiazin-6-yl)-1-phenyl-1H-pyrazol-3-yl)-*2H*-chromen-2-one(3b):
^{1}H NMR (DMSO, δ, ppm): 4.5 (d, 1H, -C*H*-S), 6.0 (t, 1H, -N*H*), 6.1 (s, 1H, =C*H*-), 7.4 (m, 5H, Ar-H), 7.5 (s, 3H, =C*H*-), 7.6 (m, 4H, Ar-H), 7.8 (m, 2H, Ar-H), 8.0 (s, 1H, =C*H*-), 8.1 (d, 2H, NH_2), 8.3 (s, 1H, Imidazole Ar-H); Mass=560 [M+H]+ : Yield: 74%.

3-(4-(2-hydrazinyl-4-(2-oxo-*2H*-chromen-3-yl)-*6H*-1,3-thiazin-6-yl)-1H-pyrazol-3-yl)-*2H*-chromen-2-one(3c):
^{1}H NMR (DMSO, δ, ppm): 4.5 (d,1H, -C*H*-S), 6.0 (t, 1H, -N*H*), 6.1 (s, 1H, =C*H*-), 7.4 (m, 4H, Ar-H), 7.5(s, 1H, Imidazole, Ar), 7.6 (s, 1H,=C*H*-), 7.7 (m, 2H, Ar-H), 7.8 (m, 2H, Ar-H), 8.0 (s, 1H,=C*H*-), 8.1 (d, 2H, NH_2),12.5 (1H, Imidazole NH); Mass=484 [M+H]+: Yield: 68%.

3-(2-hydrazinyl-6-((1R,2S,3R,4R)-1,2,3,4,5-pentahydroxypentyl)-*6H*-1,3-thiazin-4-yl)-*2H*-chromen-2-one(3d):
^{1}H NMR (DMSO, δ, ppm): 3.3-3.4 (d, 5H, C*H*OH), 3.5 (d, 4H, -(O*H*)$_4$), 3.6 (m, 2H, C(*H*)$_2$O), 4.5 (d, 1H, -C*H*-S), 6.0 (t, 1H, -N*H*), 6. 7 (s, 1H,=C*H*-), 7.4 (m, 2H, Ar-H), 7.5 (s, 1H, =C*H*-), 7.6 (m, 2H, Ar-H), 8.1 (d, 2H, NH_2); Mass=423 [M+H]+:Yield: 73%.

3-(2-hydrazinyl-6-(thiophen-2-yl)-*6H*-1,3-thiazin-4-yl)-*2H*-chromen-2-one(3e):
^{1}H NMR (DMSO, δ, ppm): 4.5 (d,1H, -C*H*-S), 6.0 (t,1H, -N*H*), 6.1 (s, 1H, =C*H*-), 6.8- 6.9 (m, 2H, Thiazole, Ar-H), 7.4 (d, 1H, Thiazole, Ar-H), 7.5 (m, 3H, Ar), 7.6 (s, 1H, =C*H*-), 7.8 (d, 1H, Ar-H), 8.1 (d, 2H, NH_2). Mass=356 [M+H]+:Yield: 80%.

3-(6-(2-butyl-4-chloro-*1H*-imidazol-5-yl)-2-hydrazinyl-*6H*-1,3-thiazin-4-yl)-*2H*-chromen-2-one(3f):
^{1}H NMR (DMSO, δ, ppm): 1.0 (d, 3H, CH_3), 1.3 (m, 2H, CH_2), 1.5 (m, 2H, CH_2), 2.8 (d, 2H, CH_2), 4.5 (d, 1H, -C*H*-S), 6.0 (t, 1H, -N*H*), 6. 1 (s, 1H, =C*H*-), 7.5 (m, 3H, Ar), 7.6 (s, 1H,

=C*H*-), 7.8 (d, 1H, Ar-H), 8.1 (d, 2H, NH_2), 13.0 (s, 1H, Imidazole NH); Mass=430 [M+H]+:Yield: 75%.

3-(6-(2-chloroquinolin-3-yl)-2-hydrazinyl-*6H*-1,3-thiazin-4-yl)-*2H*-chromen-2-one(3g):
^{1}H NMR (DMSO, δ, ppm): 4.5 (d, 1H, -C*H*-S), 6.0 (t, 1H, -N*H*), 6.1 (s, 1H, =C*H*-), 7.4 (m, 2H, Ar), 7.5 (s, 1H, =C*H*-), 7.6-7.7 (s, 3H, =C*H*-), 7.8-7.9 (d, 2H, Ar-H), 8.0 (d, 1H, Ar-H), 8.1 (d, 2H, NH_2), 8.2 (s, 1H, Ar-H); Mass=435 [M+H]+:Yield: 76%.

3-(2-hydrazinyl-6-(4-oxo-*4H*-chromen-3-yl)-*6H*-1,3-thiazin-4-yl)-2H-chromen-2-one(3h):
^{1}H NMR (DMSO, δ, ppm): 4.5 (d, 1H, -C*H*-S), 6.0 (t, 1H, -N*H*), 6.4 (s, 1H, =C*H*-), 7.1 (s, 1H, =C*H*), 7.4 (m, 3H, Ar-H), 7.5 (d, 2H, Ar-H), 7.8-8.0 (m, 4H, Ar-H), 8.1 (d, 2H, NH_2). Mass= 418 [M+H]+: Yield:78 %.

2-hydrazinyl-4,6-diphenyl-*6H*-1,3-thiazine(3i):
^{1}H NMR (DMSO, δ, ppm): 4.5 (d, 1H, -C*H*-S), 6.0 (t, 1H, -N*H*), 6.7 (s, 1H, =C*H*-), 7.2-7.3 (m, 4H, Ar-H), 7.5 (m, 4H, Ar-H), 8.0 (m, 2H, Ar-H), 8.1 (d, 2H, NH_2); Mass= 282 [M+H]+:Yield: 82%.

2-hydrazinyl-6-(4-nitrophenyl)-4-(thiazol-2-yl)-*6H*-1,3-thiazine(3j):
^{1}H NMR (DMSO, δ, ppm): 4.5 (d, 1H, -C*H*-S), 6.0 (t, 1H,-N*H*), 6.7 (s, 1H, =C*H*-), 7.5 (d, 2H, Ar-H), 7.6- 7.8 (m, 2H, Thiazole, Ar-H), 8.1 (d, 2H, NH_2), 8.2 (d, 2H, Ar); Mass= 334 [M+H]+:Yield: 70%.

(E)-4-(4-chlorophenyl)-2-hydrazinyl-6-styryl-*6H*-1,3-thiazine(3k):
^{1}H NMR (DMSO, δ, ppm): 4.5 (d, 1H, -C*H*-S), 6.0 (t, 1H, -N*H*), 6.3 (d, 2H, -C*H*=C*H*-), 6.4 (s, 1H, =C*H*-), 7.2-7.4 (m, 7H, Ar-H), 7.5 (d, 2H, Ar-H), 8.1 (d, 2H, NH_2); Mass= 342 [M+H]+:Yield: 79%.

CONCLUSION

As part of our ongoing work, we used a synthetic approach to create more adaptable, development of an eco-friendly, and efficient technique for the synthesis of heterocyclic compounds, Our approach has several significant benefits, such as higher selectivity, simplicity, catalyst-free reaction and environmental pollution free conditions over conventional methods.

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