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The review on synthetic study of hydrazine derivatives and their pharmacological activities

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Abstract-

Hydrazine's and their derivatives have found many technical and commercial applications and this is reflected in the immense number of such compounds synthesised to date. In this review an attempt has been made to supplement the existing comprehensive literature by presenting some section of synthesis its analytical studies and the pharmacological activities with some recent approaches. Hydrazine is an inorganic compound with the chemical formula N_2H_4. It is used as the precursor to several pesticides and pharmaceuticals. This requires the conversion of hydrazine to heterocyclic rings such as pyrazole and pyridazines. Examples of commercialized bioactive hydrazine derivatives includes cefazoline, rizatriptan, anastrozole, fluconazole, etc. pharmacological studies includes the antimicrobial, antioxidant, anticancer, anti-Parkinson's, hypertension, etc. also some of the hydrazine's are shown the neuroprotective activity such as anti-Alzheimer's and antidepressant activity.

Keywords: hydrazine, synthesis, antimicrobial, hypertension, antidepressant, antioxidants.

Introduction:

Hydrazine derivatives are widely used compounds in the pharmaceutical, agrochemical, polymer and dye industries and also as precursors in organic synthesis.It is also called as Diamine or diazine or nitrogen hydride and is a strong base. It is an azane and dangerously unstable. Each subunit of H_2N-N is pyramidal, and the N-N bond distance is about 1.45Å. Diamine in its anhydrous form, is colourless. Fuming oily liquid smells like ammonia. It is toxic and corrosive to the tissues [3]. hydrazones are most extensively used chelating coordination ligands in chemistry [4]. They are also important in catalysis and in medicine as antimicrobial, antioxidant and anticancer agents [5]. Many hydrazine derivatives shows significant biological activity and several compounds with hydrazine moiety were shown to be effective for the treatment of tuberculosis, Parkinson's disease and hypertension. In addition, some hydrazines display neuroprotective properties and are used as antidepressant drugs. Hydrazine based peptidomimetics (aza-peptides)were found to be potent agents against hepatitis, AIDS and SARS. Hydrazine derivatives are also being used for the derivatization of nanostructures [2]. The hydrazine and hydrazide derivatives of benzo-y-pyrones with fluorines susubstituents, remain an unexplored group of chemical compounds. Such compounds were shown the antimicrobial strength.[6]

1.1structure with properties:

$H_2N—NH_2$

hydrazine is the inorganic molecule with the chemical formula N_2H_2. (Molecular weight 32.04)

$H_2N—NH_2$

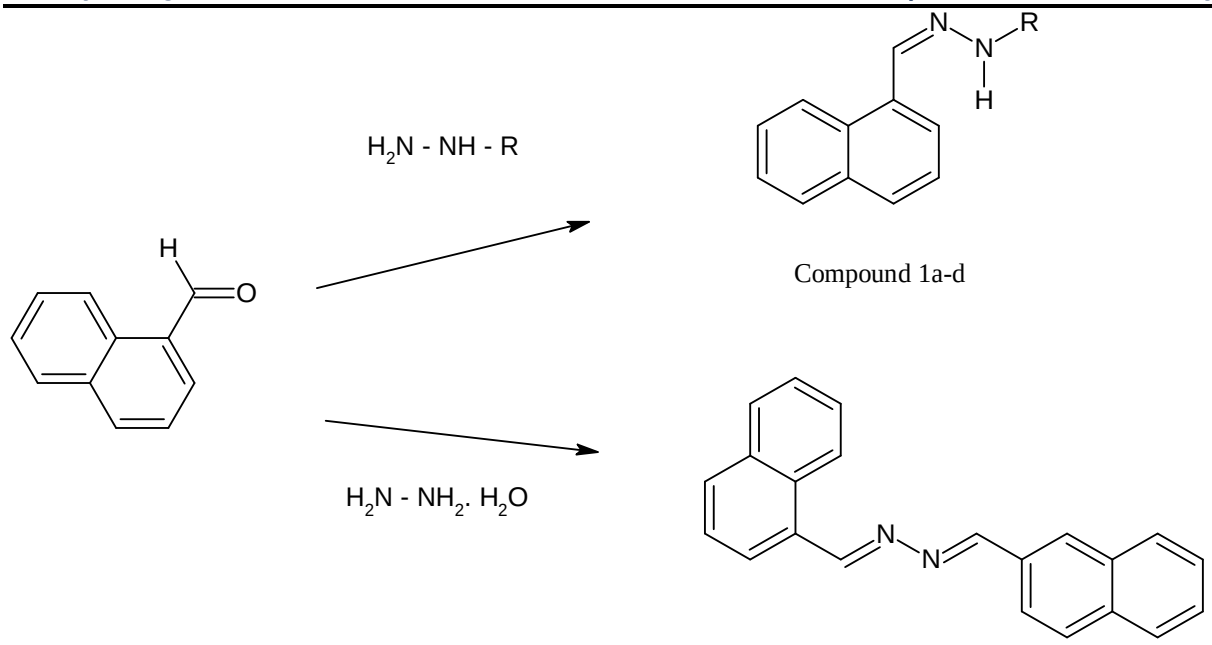
Molecular Formula:	H_4N_2
Formula Weight:	32.04516
Composition:	H(12.58%) N(87.42%)
Molar Refractivity:	9.11 ± 0.3 cm^3
Molar Volume:	35.8 ± 3.0 cm^3
Parachor:	90.2 ± 4.0 cm^3
Index of Refraction:	1.421 ± 0.02
Surface Tension:	39.9 ± 3.0 dyne/cm
Density:	0.892 ± 0.06 g/cm^3
Dielectric Constant:	Not available
Polarizability:	3.61 ± 0.5 $10^{-24}cm^3$
Average Mass:	32.0452 Da

Table No. 1: Physiochemical properties of Hydrazines

Sr. No	Parameters	Properties
1.	Structure	$H_2N—NH_2$
2.	Chemical name	Hydrazine
3.	Synonyms	Diamine, Diazane, Nitrogen hydride
4.	Molecular weight	32.04 g/mol
5.	Appearance	Colourless, Oily liquid
6.	Odour	Ammonia-like
7.	Boilling point	114°C
8.	Log p	0.67

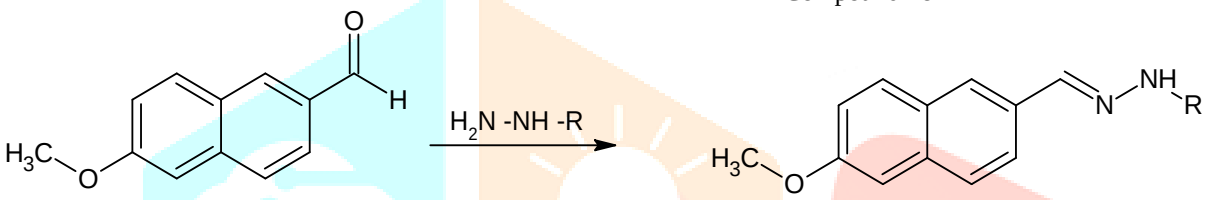
I. Synthesis of hydrazine derivatives:

Scheme 1: 1mmol of 1-naphthaldehyde or 6-Methoxy-2naphthaldehyde and 1,2 mmol of phenyl hydrazine hydrochloride or its derivatives were dissolved in absolute ethanol (20mL) and heated for 60 min on a hot water bath in the presence of CH_3COONa (0.4g). After completion of the reaction, the reaction mixture was cooled to room temperature. The precipitates was collected, washes with cold EtOH to achieve 1a-h (except 1e) with 70.79% - 94% yield.



Compound 1a-d

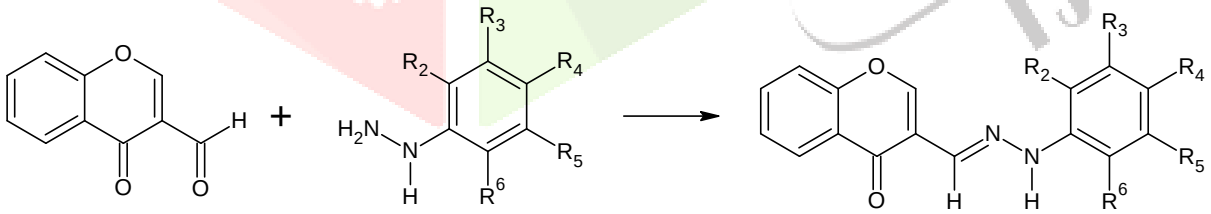
Compound 1e



Compound 1f-h

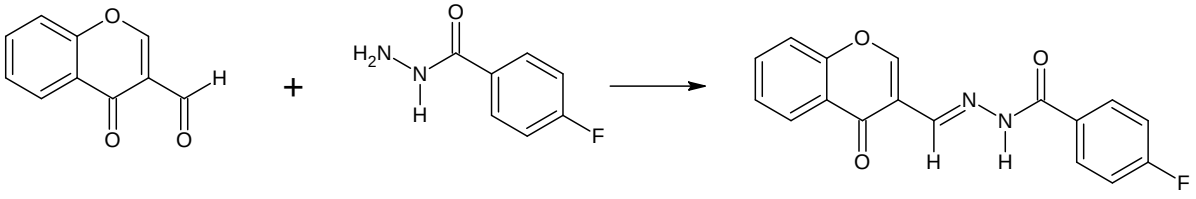
For the synthesis of 1e compound, the solution of 1 naphthaldehyde (2mmol) and hydrazine hydrate (1mmol) in EtOH (25ml)was heated for 4 hr on a hot water bath . after cooling the precipitates was collected then washed with cold EtOH to give 1,2-bis(naphthalen-1-tmethylene) hydrazine (1e) in 40.90% yield.[7]

Scheme 2:

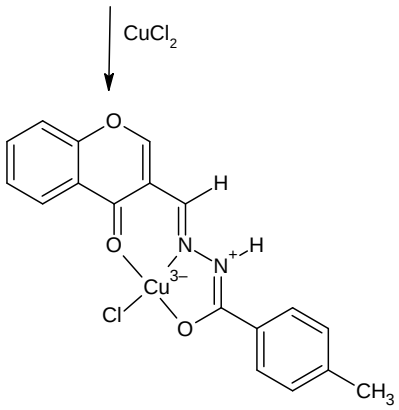


3-Formyl chromone

Hydrazine derivative 1,3,,4,6,7,8,9,10



Hydrazine derivative 5



Complex with Cu (II) 11

Synthesis of hydrazine and hydrazide derivatives of 3-formylchromone.

Reaction conditions: solvent: CH3COOC2H5, time: 48h, temperature: reflux temperature, crystallization from 50:50 acetone/ethanol.

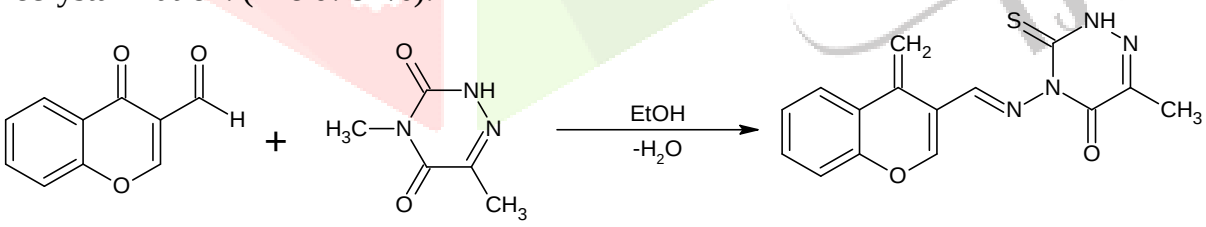
Hydrazine derivatives of 3-formylchromone:

1: R2=R5=F, R3=R4=R6=H; **3:** R4=CF3, R2=R3=R5=R6=H; **4**: R3=R5=CF3, R2=R4=R6=H; **6:** R2=R3=R5=R6=F, R4=H; 7: R2=CH3, R5=F, R3=R4=R6=H; **8**: R2=R4=R6=F, R3=R5=H; **9:** R2=R3=R4=R5=R6= F, **10**: R2=CF3, R3=R4=R5=R6=H [6]

Scheme 3:

3.1 Synthesis of hydrazone ligands

The synthesis of HL is by mixing hot ethanolic solution of 4-amino-6methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one (1.58g, 10.0 mmol) and chromone-3-carboxaldehyde (1.74 g, 10.0mmol). The reaction mixture was refluxed for 30 min. The yellow crystals were collected after the reaction mixture was fully cooled to room temperature. The product has been filtered off; fine crystals have been obtained from ethanol recrystallization. (Yield: 81%).

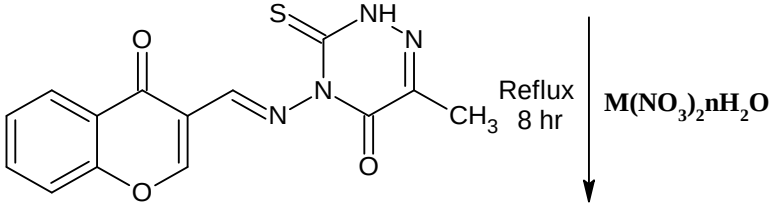


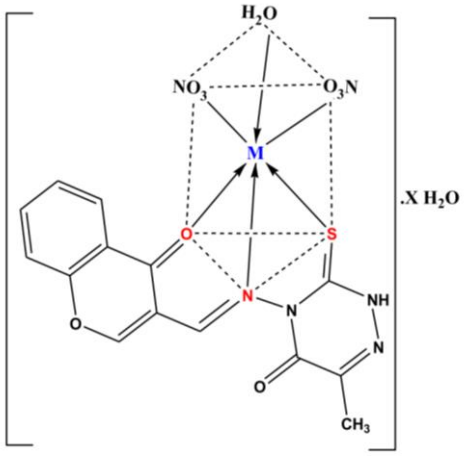
Chromone-3-carboxaldehyde

4-amino-6methyl-3thioxo-3,4 dihydro-1,2,4-triazin-5(2H)-one

3.2 Synthesis of Cu^{2+} and Zn^{2+} nanocomplex

A methanolic solution of HL (0.92g, 3mmol) was added to metal salts (3mmol) namely, $Cu(NO_3)_2..3H_2O$ and $Zn(NO_3)_2.6H_2O$. The reaction mixture was refluxed for 8 hr. The precipitate was filtered and washed several times with 50% (v/v) methanol-water to remove any traces of unreacted starting materials. Finally, the precipitate was dried in vacuum dessicators over anhydrous $CaCl_2$ overnight. The dried complexes are $[Cu(HL)(NO_3)_2(H_2O)].H_2O$;Yield: 63%.[8]



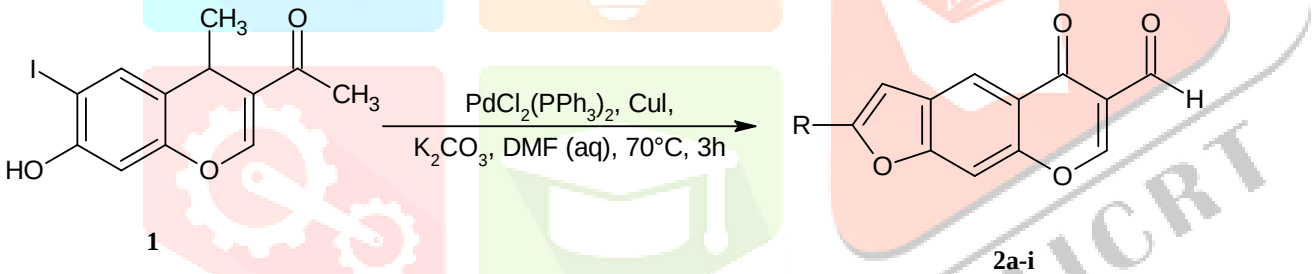


$M = Cu^{2+}$ n= 3, X = 1
$M = Zn^{2+}$ n= 6, X = 0.5

Scheme 4:

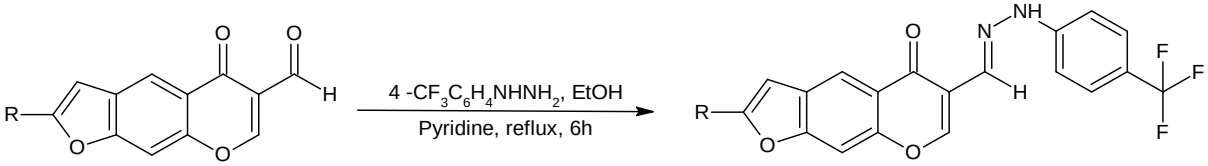
cross-coupling and cycloisomerization of 7-hydroxy-6-iodo-4-oxo-4H-chromene-3-carbaldehyde (1) with terminal acetylenes followed by transformation of the intermediate furochromone-6-carbaldehydes (2) into hydrazono derivatives (3) as shown in Scheme 1. Compound 1 was prepared in 68% yield by treatment of 2,4-dihydroxy-5-iodoacetophenone with phosphoryl oxychloride–dimethyl formamide (POCl3/DMF) mixture at room temperature (RT) for 12 h.

various terminal acetylenes in the presence of dichlorobis(triphenyl)phosphine(II) as a source of active Pd(0) species and CuI as co-catalyst using potassium carbonate as a base in aqueous dimethyl formamide (DMF) at RT for 3 h.



1 **2a-i**

Compounds 2a–i were treated with 4-(trifluoromethylphenyl)hydrazine in the presence of pyridine as a base in ethanol under reflux followed by aqueous work-up and purification by column chromatography on silica gel to afford the corresponding hydrazono derivatives 3a–i in high yield and purity. [9]



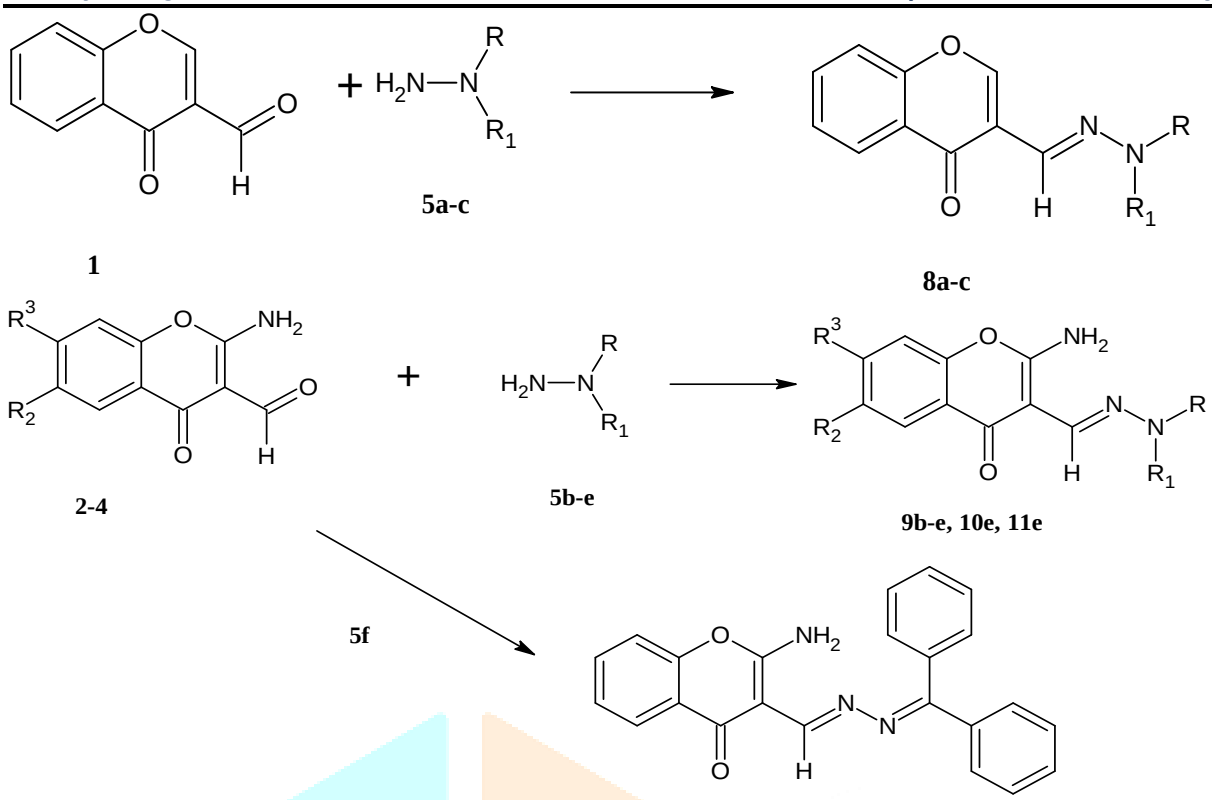
2a-i **3a-i**

Scheme 5:

3-Formylchromone is a very reactive compound and its reactions with nitrogen nucleophiles give a variety of products. The primary amino group can react at three electrophilic sites (C-2, C-4, CHO) of 3-formylchromones. The reaction of equimolar quantities of 3-formylchromone and an aromatic primary amine leads to a mixture of anil and a 1,4-adduct.

3-Formylchromones with aromatic amino carboxylic acids yield enamines of 2-hydroxy(alkoxy)-chroman-4-ones or 3-(aryliminomethyl)-chromones, depending on the reaction conditions.

The preparation of hydrazones 8b–c, 9b–e, 10e, 11e, 12 was carried out by stirring and heating the mixture of 3-formylchromone (1) or 2-amino-3-formylchromones (2–4) with substituted aromatic and aliphatic hydrazines in dry ethanol or toluene[10]

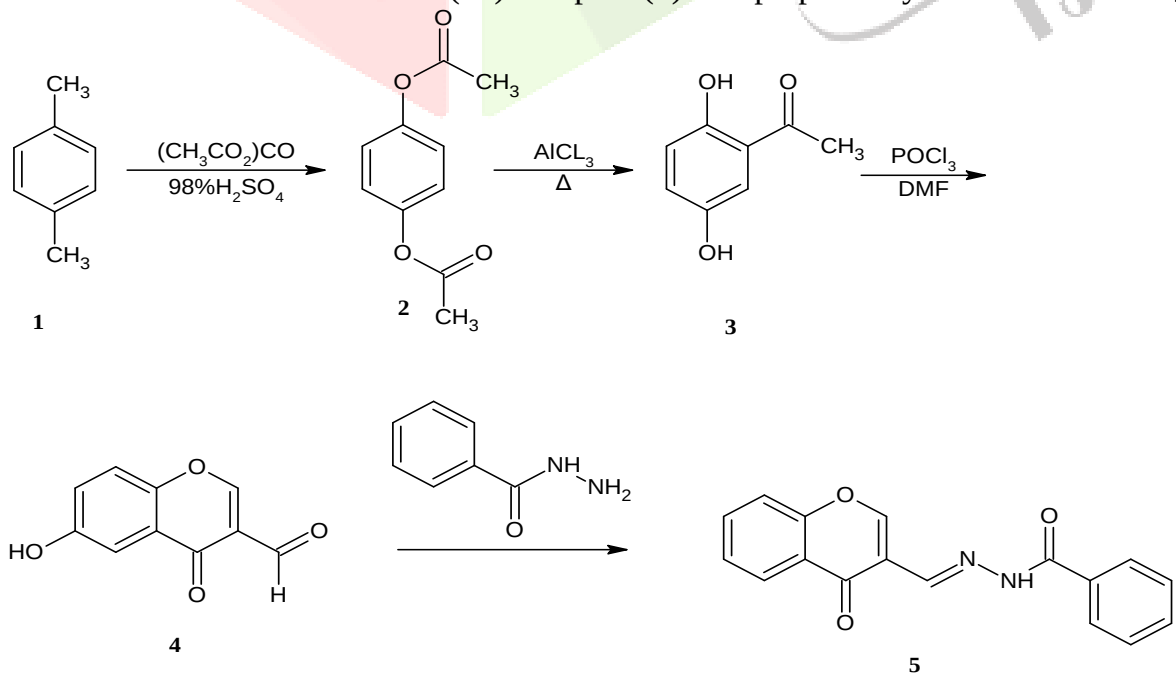


Scheme 6:

2: R^2=R^3= H
3: R^2=R^3= CH_3
4: R^2= Cl, R^3= H
5f: H_2N-N=C(C_6H_5)$_2$

a: R= CH_3, R^1= P(S)(OCH_3)$_2$
b: R= H, R^1= 2,5-dichlorophenyl
c: R= H, R^1= $COOCH_3$
d: R= H, R^1= C_6H_5COOH
e: R= H, R^1= $(CH_2)_2OH$

The ligand (1.0 mmol, 0.308 g) and the La(III) nitrate (0.5 mmol, 0.217 g) were added to ethanol (10 mL). The mixtures were stirred at 60 °C. After 5 min, the mixtures were filtered to remove any insoluble residues and then stirring was continued for 24 h at room temperature. A white precipitate, the La(III) complex (1), was separated from the solution by suction filtration, purified by washing several times with ethanol, and dried for 24 h under vacuum. The Sm(III) complex (2) was prepared by the same method.[11]

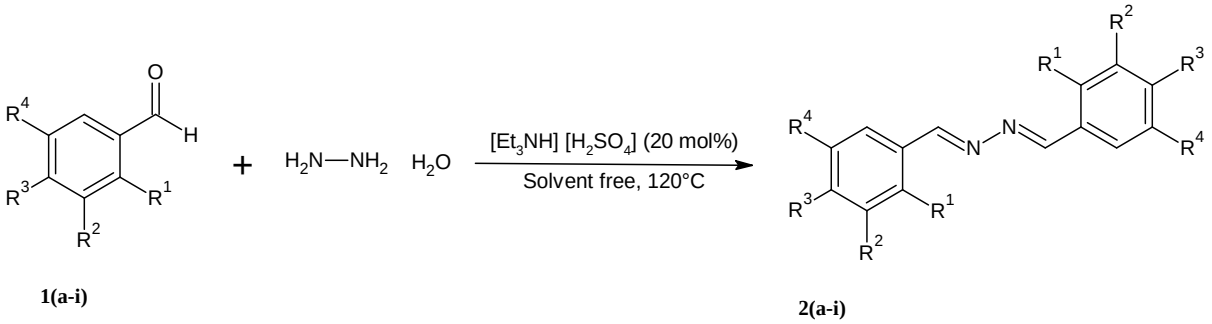


Scheme of the synthesis of ligands

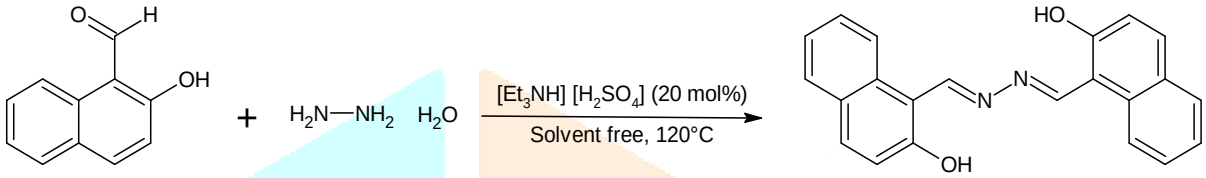
Scheme 7:

The synthetic pathways of a series of hydrazone derivatives 2(a–j) and 4(a–e) are shown in Schemes 1 and 2, respectively. Herein, each series was typically accessed via a nucleophilic addition between hydrazine hydrate and appropriately substituted aromatic aldehydes 1(a–j) and 3-formylchromones 3(a–e) to yield target hydrazone derivatives. All the compounds were obtained in excellent yields (90–98%) with high purity.[12]

7.1 Synthetic pathway for the synthesis of hydrazone derivatives of substituted aromatic aldehydes 2(a–j).



1(a-i) 2(a-i)



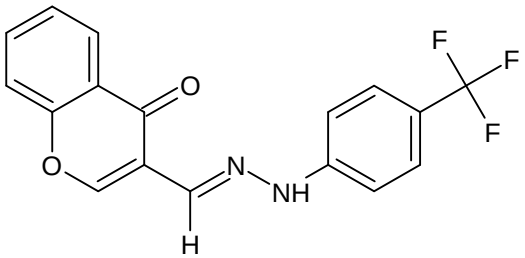
1 (j) 2 (j)

7.2 Synthetic pathway for the synthesis of hydrazone derivatives of substituted 3-formylchromone derivatives 4(a–e).

II. PHARMACOLOGICAL ACTIVITY

1. Anti-Alzheimer's activity

Malose J. Mphahlele 1, Samantha Gildenhuys 2, and Emmanuel N. Agbo 1, et al (2019) [28] reported the Replacement of the 6-carbaldehyde group of 2b with 6-hydrazono functionality in 3b, on the other hand, reduced the anticholinesterase, anti-lipoxygenase, and antioxidant activities, but enhanced activity against β-secretase.



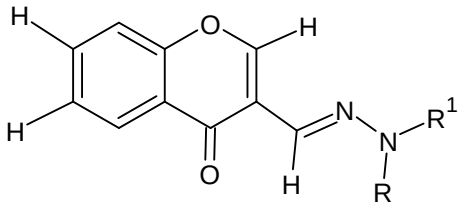
3-[(*E*)-{2-[4-(Trifluoromethyl)Phenyl]Hydrazinylidene}Methyl]-4*H*-1-Benzopyran-4-One

(3)

2. Anticancer Activity

Łazarenkow j. Nawrot-modranka brzezin´ska , et al,(2011) reported Synthesis, preliminary cytotoxicity evaluation of new chromone hydrazone derivative and phosphor-hydrazone derivatives of coumarin and chromone. Better biological activity is displayed by the compounds with aliphatic substituents in the

hydrazone moiety. Additionally, the presence of Cl in chromone system at position 6, considerably improve the cytotoxic activity of the studied aliphatic compound.

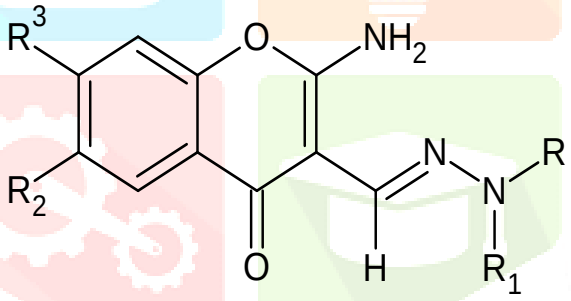


3-[(e)-(disubstituted-hydrazinylidene) methyl]-4H-1-benzopyran-4-one (4)

3. Analgesic, antipyretic, and anti-inflammatory activity

Mehtab Parveen, Shaista Azaz (2014) Solvent-free, [et3nh] [hso4] catalyzed facile synthesis of hydrazone derivatives.

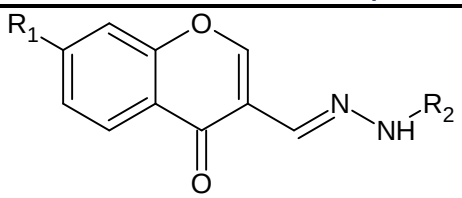
Documented in the literature that hydrazone derivatives exhibit a wide spectrum of biological properties such as anti-inflammatory, analgesic antipyretic as well as chelating properties towards various metal ions. To develop an eco-friendly approach for the synthesis of biologically active hydrazone derivatives, they explored the efficacy of [Et3NH] [HSO4] by carrying out the reaction of substituted aromatic aldehydes and 3formylchromones with hydrazine hydrate in (2: 1) molar ratio.



3,30 - [(1e,10 E)-Hydrazine-1,2-Diylidenebis(Methanyl-Ylidene)] Bis(4H-Chromen-4-One) (5)

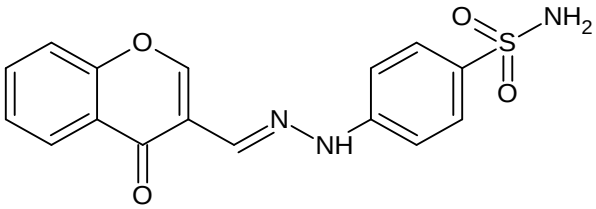
4. Molecular docking

Guangcheng Wang, Ming Chen and his co-workers (2017) reported the studies of chromone hydrazone derivatives as a-glucosidase inhibitors. 4-sulfonamide substitution at phenyl part of hydrazide was found to be the most active compound. The binding interactions of the most active analogues were confirmed through molecular docking studies.



3-[(E)-(2-Emethyl]-7-Methyl-4H-1-Benzopyran-4-One

(5)



4-{(2e)-2-[(4-Oxo-4h-1-Benzopyran-3-Yl) Methylidene] Hydrazinyl} Benzene-1-Sulfonamide

(6)

5. Antifungal activity:

Anca-Elena Dascalua, Alina Ghineta, Emmanuelle Lipka, (2020) reported the study of hydrazone derivatives as antifungal agents. The natural compound containing the hydrazone moieties were tested the *in vitro* antifungal activities. The activities wwre evaluated using the micro-dillution method by using hymexazol. Canazole and ketoconazole as positive controls, The inhibition activity of 28 new compounds mixing the structure of hydrazine with a pyrrolidinone ring were evaluated against a large panel of fungal strains and they shows the 'fungicide-like' properties.[18]

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