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RESEARCH ARTICLE

SYNTHESIS, CHARACTERIZATION AND ANTITUBERCULOSIS ACTIVITY OF NOVEL SERIES OF 3[2-oxo-2H-chromen-3yl)amino]- 2 aryl 1,3 Thiazolidine-4-one.

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Abstract

In the present investigation different derivatives of 3(2-aryl methylidene hydrazinyl) –2H-chromene-2-one on condensation with thioglycollic acid yield the corresponding **3[2-oxo-2H-chromen-3yl)amino]- 2 aryl 1,3 Thiazolidine-4-one (IV A_1-D_5).**The newly synthesized heterocycles were characterized on the basis of their chemical properties and spectroscopic data. All newly synthesized compound were evaluated for their antimycobacterial activities against Mycobacterial tuberculosis H37Ra, 10^6 CFU/ml..Some of the compounds exhibited a significant antimycobacterial activity when compared with the drugs such as Rifampicin and streptomycin.

INTRODUCTION

Tuberculosis (TB) is an acute or chronic infectious disease caused by several species of Mycobacterium, collectively called as tubercle bacilli. TB usually attacks the lungs but can also affect the central nervous system, lymphatic system, circulatory system, genitourinary system,gastrointestinal system, bones, joints, and even the skin. It is caused by the bacterium Mycobacterium tuberculosis complex, which includes Mycobacterium tuberculosis (M.tuberculosis, [MTB]) itself, Mycobacterium microti, Mycobacterium pinnipedii Mycobacterium bovis, Mycobacterium caprae, Mycobacterium africanum, and Mycobacterium canettii (Zumla, et al 2013 ; Grange et al.,2009) MTB also known as the "white plague" was identified by Robert Koch in 1882 (Robert Koch, 2006).Many people become symptom-free carriers of the tubercle bacilli bacteria. Although common and deadly in the third world, tuberculosis was almost non-existent in the developed world, but has been making a recent resurgence. Certain drug-resistant strains are emerging and people with immune suppression such as acquired immune deficiency syndrome (AIDS) (Smith and Reynard. (1890, 1992).Person can have active or inactive TB. Active TB disease means the bacteria are active in the body and the immune system is unable to stop them from causing illness. People with active TB in their lungs can pass the bacteria on to anyone they come into close contact with. When a person with active tuberculosis coughs, sneezes or spits, people nearby may breathe in the TB bacteria and become infected. Left untreated, each person with active TB will infect on average between 10 and 15 people every year (Tuberculosis (online), http//www.scidev.net).Therefore, people with latent tuberculosis are increasingly becoming infected with HIV and many more are developing active TB because HIV is weakening their immune system.People who are co-infected with both HIV and latent TB have an up to 800 times greater risk of developing active tuberculosis disease and becoming infectious compared with non HIV people (WHO,2013) . This has spurred for novel efforts to find new anti-TB drug candidates with novel modes of action. Which includes, developing pipelines for drug discovery and development and, in particular, trying to find new regimens that can considerably shorten the duration of effective therapy which would improve patient compliance and slow down the emergence of drug

resistant strains (Spigelman,2013 ; Mdluli and Spigelman, 2006 ; Spigelman and Gillespie,2006 ; Spigelman and Ginsberg, 2007; Duncan,2003; Duncan,2004).

Natural, synthetic and semisynthetic heterocyclic compounds play an important role in drug discovery and chemical biology. The heterocycles are mainly of the classes of alkaloids, flavones, isoflavones, chromans, chromones, coumarins and chromenes. Synthetic compounds of these classes show different biological activity. It has been established that oxygen-containing heterocyclic compounds play an important role in designing new class of structural entities for medicinal applications (Kaur et al.,2013). Among oxygen heterocyclic compounds, coumarin (2H-chromen-2- one) and its derivatives are significant because of their wide spectrum of biological activities.

Inspired by the above facts and in continuation of our ongoing research program in the field of synthesis and characterization of different derivatives of 3(2-aryl methylidene hydrazinyl) –2H-chromene-2-one(1), we hereby report the synthesis and antitubercular activity of 3[2-oxo-2H-chromen-3yl)amino]- 2 aryl 1,3 thiazolidine-4-one derivatives(IV A_1-E_5). The structures of all compounds have been confirmed by spectral analysis (IR, ^{1}H NMR and ^{13}C NMR).

Experimental

The purity of the synthesized compounds were checked by thin layer chromatography on silica gel G in various solvent systems using iodine vapours as detecting agent. Melting points were determined by the melting point determination apparatus (TEMPO) in open capillary tubes and are uncorrected.Infra-red spectra were recorded on FTIR Shimedzu-8400S spectrometer using KBr pellets. Proton NMR spectra were recorded on Bruker Avance II 400 NMR Ultra Shield Spectrometer using DMSO-d6 as a solvent and TMS as internal standard.The synthesized compounds were screened for in vitro antituberculosis activity.

chemistry

A series of 3[2-oxo-2H-chromen-3yl)amino]- 2 aryl 1,3 thiazolidine-4-one has been synthesized. Reaction of substituted salicylaldehydes with dimethyl malonate in the presence of a base(piperidine) furnished the corresponding 2-oxo-2H-chromen-3yl-acetate (Ia–c) which on further reaction with hydrazine hydrate afforded 3-hydrazinyl 2H-chromene-2-one(IIa-c) . The compounds (IIa–c) were further reacted with aromatic aldehyde to afford 3(2-aryl methylidene hydrazinyl) –2H-chromene-2-one (IIIa-c). The synthesized compound 3(2-aryl methylidene hydrazinyl) –2H-chromene-2-one (III a-c) were treated with thioglycollic acid to furnish 3[2-oxo-2H-chromen-3yl)amino]- 2 aryl 1,3 thiazolidine-4-one (IV A_1-E_5) were characterized on the basis of their spectral and analytical studies.

General method

The title compounds were prepared in following steps.

2-oxo-2H-chromen-3yl-acetate (Ia-c)

In a 500-ml. round-bottomed flask equipped with a reflux condenser are placed (0.02 mol) of salicylaldehyde, (0.03 mol) of ethyl malonate, and 20 ml. of absolute ethanol. To this mixture add 1 ml. of piperidine and 0.5 ml. of glacial acetic acid and the solution is heated under reflux for 3 hr. The mixture was cooled and the solid obtained was separated by filtration and recrystallized from ethanol to give the corresponding compounds.

Synthesis of 3-hydrazinyl-2H-Chromen-2-one (IIa–c)

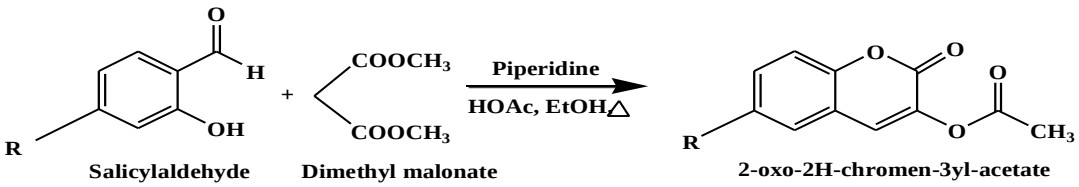
In a 20ml of hydrazine hydrate (98%) was refluxed 0.02mol of compound (Ia-c) for 2 h. The precipitate formed after cooling was filtered, washed with water, dried and recrystallized from ethanol.

Synthesis of 3(2-aryl methylidene hydrazinyl)-2H-Chromene-2-one (III a-c)

For 2-6 h, 0.01mol of compound (IIa-c) and 0.011mol of appropriate aromatic aldehydes and 25ml of ethanol (96%) were refluxed. The solid that separate was filtered and recrystallized from ethanol.

Synthesis of 3[2-oxo-2H-chromen-3yl)amino]- 2 aryl 1,3 thiazolidine-4-one (IV A_1-D_5)

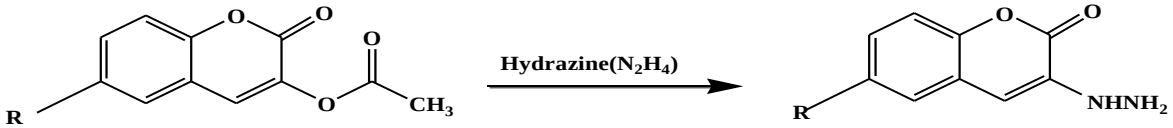
A mixture of compound (IIIa-c) i.e 0.011 mole of thioglycollic acid($SHCH_2COOH$) was heated under reflux for 4hrs in dry benzene using Dean Stark trap.Excess benzene was evaporated in vaccum.The residue was triturated with saturated $NaHCO_3$ until CO_2 evaluation ceased and was then left to stand overnight.The solid thus obtained was filtered and washed with water. By adopting similar type of procedures, and employing equimolar quantities of reactants, different derivatives of **3[2-oxo-2H-chromen-3yl)amino]- 2 aryl 1,3 thiazolidine-4-one(IV A_1-D_5)** were synthesized. Synthetic pathway for preparation of title compound is shown in **Scheme 1**. Physical data of synthesized compounds is given in **Table 1**. Elemental analysis of compounds (IVA_1-E_5) is given in **Table 2.**



Salicylaldehyde **Dimethyl malonate** **2-oxo-2H-chromen-3yl-acetate**

I a-c

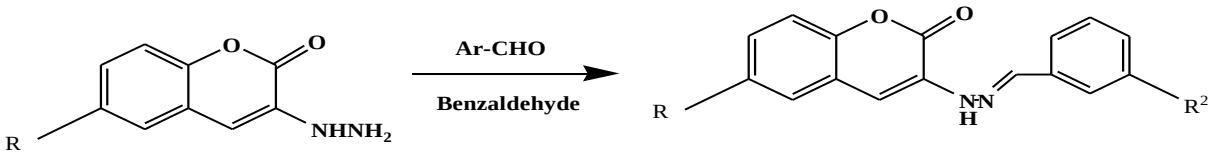
Synthesis of 2-oxo-2H-chromen-3yl-acetate



2-oxo-2H-chromen-3yl-acetate **3-hydrazinyl 2H-chromen-2-one**

II a-c

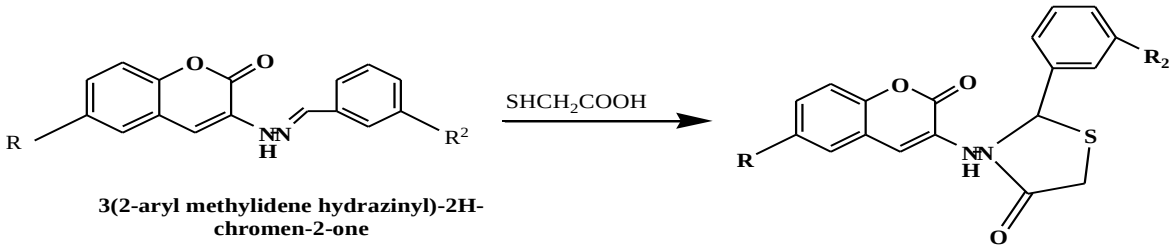
Synthesis of 3-hydrazinyl 2H-chromen-2-one.



3-hydrazinyl 2H-chromen-2-one **3(2-aryl methylidene hydrazinyl)-2H-chromen-2-one**

III a-c

Synthesis of 3(2-aryl methylidene hydrazinyl)-2H-chromen-2-one.



3(2-aryl methylidene hydrazinyl)-2H-chromen-2-one **3[2-oxo-2H-chromen-3yl)amino]- 2 aryl 1,3 Thiazolidine-4-one**

IV A_1-D_5

Synthesis of 3[2-oxo-2H-chromen-3yl)amino]- 2 aryl 1,3 Thiazolidine-4-one

Spectral data

3-(2-oxo-2H-chromen-3yl-amino)-2-phenyl-thiazolidine-4-one. (IV A_1)

FTIR (KBr) (V_{max} cm^{-1}):– 1590 (NH_2), 1550(N-N), 1100(C-N), 1675 (C=C), 3030(C-H), 1575 (C-C), 1735 (C=O). ^{1}H NMR data - (ppm, 300MHz,TMS, δppm): 7.06-7.62 (m, 8H, Ar-H), 2.2 (s, 1H,NH), 6.48 (s, 1H, CH), 3.29(s, 2H, CH_2).^{13}C NMR data- (ppm, 100MHz, DMSO) δppm: 162 (C=O), 120-128 (C=C), 167-168 (C=0) five membered , 57.2 (CH aliphatic), 38.6 (CH_2 aliphatic).

2-(3-Chloro-phenyl)-3-(2-oxo-2H-chromen-3yl-amino) - thiazolidine-4-one. (IVA_2)
FTIR (KBr) (V_{max} cm^{-1}):– 1590 (HN_2), 1550 (N-N), 1100 (C-N) , 1675(C=C), 850-550 (C-Cl), 1575 (C-C) .^{1}H NMR data - (ppm, 300MHz,TMS)-6.94-7.63 (m,8H, Ar-H), 2.02 (s, 1H,NH), 6.49 (s, C-H), 3.30 (s, 2H, CH_2)**.** ^{13}C NMR data- (ppm, 100MHz, DMSO) δppm: 162 (C=O), 120-128 (C=C), 32.2 (CH_2 aliphatic)

3-(2-oxo-2H-chromen-3yl-amino)-2-tolyl-thiazolidine-4-one. (IV A_3)

FTIR (KBr) (V_{max} cm^{-1}):– 1590 (NH_2), 1550(N-N), 1100(C-N) , 1675 (C=C), 1575(C-C), 1735 (C=O) , 3030(C-H).^{1}H NMR data - (ppm, 300MHz,TMS)-7.4(m, 8H,Ar-H), 2.36 (s, 1H,NH), 6.62 (s, C-H), 3.30 (s, 2H, CH_2), 2.30(s,3H,CH_3). ^{13}C NMR data- (ppm, 100MHz, DMSO) δppm: 162 (C=O), 120-128 (C=C benzene), 20.9 (CH_3 aliphatic), 37.9 (CH_2 aliphatic)

2-(3-Nitro-phenyl)-3-(2-oxo-2H-chromen-3yl-amino) - thiazolidine-4-one (IV A_4)

FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 1575 (C-C), 1590-1450 (N-O stretching) , 1735 (C=O) , 3030(C-H). ^{1}H NMR data - (ppm, 300MHz,TMS)-7.10(m,8H, Ar-H), 2.50 (s, 1H,NH), 6.22 (s, C-H), 3.30 (s, 2H, CH_2). ^{13}C NMR data- (ppm, 100MHz, DMSO) δppm:162(C=O), 120-128(C=C), 56.2(CH aliphatic) , 38.1 (CH_2 aliphatic)

2-(3-Methoxy-phenyl)-3-(2-oxo-2H-chromen-3yl-amino) - thiazolidine-4-one (IV A_5)

FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 3030(C-H) ,1395-1440(C-O-H),1210-1320(O-C)**,**1575(C-C). ^{1}H NMR data - (ppm, 300MHz,TMS)-7.16(m,8H, Ar-H), 2.72 (s, 1H,NH), 6.32 (s, C-H), 3.30 (s, 2H, CH_2, 3.78 (s,OCH_3). ^{13}C NMR data- (ppm, 100MHz, DMSO) δppm:162(C=O), 120-128(C=C), 56.2(CH aliphatic), 38.1 (CH_2 aliphatic), 54-60 (CH_3 aliphatic)

3-(6-Chloro-2-oxo-2H-chromen-3yl-amino)-2-phenyl-thiazolidine-4-one. (IV B_1)

FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 3030(C-H) , 910-630 (C-Cl) **,** 1575 (C-C).^{1}H NMR data - (ppm, 300MHz,TMS)-7.7(m, 8H,Ar-H), 2.44 (s, 1H,NH), 6.55 (s, C-H), 3.30 (s, 2H, CH_2).^{13}C NMR data- (ppm, 100MHz, DMSO) δppm:162 (C=O), 120-128 (C=C), 56.2(CH aliphatic), 38.1 (CH_2 aliphatic).

3-(6-Chloro-2-oxo-2H-chromen-3yl-amino)-2-(3-Chloro-phenyl)-thiazolidine-4-one. (IV B_2)
FTIR (KBr) (V_{max} cm^{-1}):– 1590 (HN_2), 1550 (N-N), 1100 (C-N) , 1675 (C=C), 3030 (C-H), 850-550 (C-Cl), 1575 (C-C). ^{1}H NMR data - (ppm, 300MHz,TMS)-7.2-8.6(m,8H, Ar-H), 2.52 (s, 1H,NH), 6.43(s, C-H),3.28(s, 2H, CH_2)**.** ^{13}C NMR data- (ppm, 100MHz, DMSO) δppm: 162 (C=O), 120-128 (C=C), 38.2 (CH_2 aliphatic)

3-(6-Chloro-2-oxo-2H-chromen-3yl-amino)-2m-tolyl-thiazolidin -4-one (IV B_3)
FTIR (KBr) (V_{max} cm^{-1}):– 1590 (HN_2), 1550 (N-N), 1100 (C-N) , 1675(C=C), 3030(C-H), 850-550 (C-Cl), 1575 (C-C) . ^{1}H NMR data - (ppm, 300MHz,TMS)-7.2-8.6(m,8H, Ar-H), 2.52 (s, 1H,NH), 6.43(s, C-H),3.30 (s, 2H, CH_2) **,** 2.22(s,3H,CH_3). ^{13}C NMR data- (ppm, 100MHz, DMSO) δppm: 162 (C=O), 120-128 (C=C), 38.8 (CH_2 aliphatic), 21.2 (CH_3 aliphatic).

3-(6-Chloro-2-oxo-2H-chromen-3yl-amino)-2(3-Nitro-phenyl)-thiazolidine-4-one. (IV B_4)
FTIR (KBr) (V_{max} cm^{-1}):– 1590(HN_2), 1550(N-N), 1100(C-N) , 1675(C=C), 3030(C-H), 850-550(C-Cl), 1575(C-C) , 1590-1455(N-O stretching).^{1}H NMR data - (ppm, 300MHz,TMS)-7.2-8.6(m,8H, Ar-H), 2.50 (s, 1H,NH), 6.43(s, C-H), 3.30(s, 2H, CH_2) **.**^{13}C NMR data- (ppm, 100MHz, DMSO) δppm: 162 (C=O), 120-128 (C=C), 57.2 (CH aliphatic), 38.2 (CH_2 aliphatic).

3-(6-Chloro-2-oxo-2H-chromen-3yl-amino)-2(3-Methoxy-phenyl)-thiazolidine-4-one.. (IV B_5)
FTIR (KBr) (V_{max} cm^{-1}):– 1590 (HN_2), 1550 (N-N), 1100 (C-N) , 1675(C=C), 3030(C-H), 850-550 (C-Cl), 1575 (C-C) .^{1}H NMR data - (ppm, 300MHz,TMS)-7.16(m,8H, Ar-H), 2.72 (s, 1H,NH), 6.32 (s, C-H), 3.30 (s, 2H, CH_2, 3.78 (s,OCH_3).^{13}C NMR data- (ppm, 100MHz, DMSO) δppm:162(C=O), 120-128(C=C), 56.2(CH aliphatic), 38.1 (CH_2 aliphatic), 54-60 (CH_3 aliphatic).

3-(6-Bromo-2-oxo-2H-chromen-3yl-amino)-2-Phenyl-thiazolidin -4-one. (IV C_1)
FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 690– 515 (C-Br), 3030 (C-H) **,** 1575(C-C).^{1}H NMR data - (ppm, 300MHz,TMS)-7.1-7.8 (m, 8H,Ar-H), 2.60(s, 1H,NH), 6.57 (s, C-H). 3.30 (s, 2H, CH_2).^{13}C NMR data- (ppm, 100MHz, DMSO) δppm:162(C=O),120-128(C=C), 57.1(CH aliphatic), 38.3 (CH_2 aliphatic).

3-(6-Bromo-2-oxo-2H-chromen-3yl-amino)- 2-(3-Chloro-phenyl)-thiazolidine-4-one. (IV C_2)
FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 3030 (C-H) **,** 1575(C-C), 850-550 (C-Cl) , 690– 515 (C-Br).^{1}H NMR data - (ppm, 300MHz,TMS)-7.1-7.8 (m, 8H,Ar-H), 2.60(s, 1H,NH), 6.51 (s, C-H). 3.24(s, 2H, CH_2).^{13}C NMR data- (ppm, 100MHz, DMSO) δppm:162(C=O),120-128(C=C), 56.9(CH aliphatic), 38.5 (CH_2 aliphatic)

3-(6-Bromo-2-oxo-2H-chromen-3yl-amino)- 2-m-tolyl-thiazolidin-4-one. (IV C_3)
FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 690– 515 (C-Br), 3030 (C-H) **,** 1575(C-C).^{1}H NMR data - (ppm, 300MHz,TMS)-7.2-8.6(m,8H, Ar-H), 2.49 (s, 1H,NH), 6.43(s, C-H), 3.28(s, 2H, CH_2) **,** 2.21(s,3H,CH_3). ^{13}C NMR data- (ppm, 100MHz, DMSO) δppm: 162 (C=O), 120-128 (C=C), 57.2(CH aliphatic), 38.2 (CH_2 aliphatic), 20.9 (CH_3 aliphatic).

3-(6-Bromo-2-oxo-2H-chromen-3yl-amino)- 2-(3-Nitro-phenyl)-thiazolidin-4-one. (IV C_4)
FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 690– 515 (C-Br), 3030 (C-H) **,** 1575(C-C), 1590-1455 (N-O stretching). ^{1}H NMR data - (ppm, 300MHz,TMS)-7.2-8.6(m,8H, Ar-H), 2.51 (s, 1H,NH), 6.53(s, C-H), 3.30(s, 2H, CH_2) **,** 2.20(s,3H,CH_3). ^{13}C NMR data- (ppm, 100MHz, DMSO) δppm: 162 (C=O), 120-128 (C=C), 57.5(CH aliphatic), 37.9 (CH_2 aliphatic).

3-(6-Bromo-2-oxo-2H-chromen-3yl-amino)- 2-(3-Methoxy-phenyl)-thiazolidin-4-one. (IV **C_5)**
FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 690– 515 (C-Br), 3030 (C-H) **,** 1575(C-C).^{1}H NMR data - (ppm, 300MHz,TMS)-7.16(m,8H, Ar-H), 2.72 (s, 1H,NH), 6.32 (s, C-H), 3.30 (s, 2H, CH_2, 3.78 (s,OCH_3). ^{13}C NMR data- (ppm, 100MHz, DMSO) δppm:162(C=O), 120-128(C=C), 56.2(CH aliphatic), 38.1 (CH_2 aliphatic), 54-60 (CH_3 aliphatic).

3-(6-Nitro-2-oxo-2H-chromen-3yl-amino)- 2-phenyl-thiazolidin-4-one. (IV **D_1)**
FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 3030 (C-H) **,** 1575(C-C).
1590-1455 (N-O stretching).^{1}H NMR data - (ppm, 300MHz,TMS)-7.1-7.8 (m, 8H,Ar-H), 2.60(s, 1H,NH), 6.53 (s, C-H). 3.26 (s, 2H, CH_2).^{13}C NMR data- (ppm, 100MHz, DMSO) δppm:162(C=O),120-128(C=C), 57.4(CH aliphatic), 38.5 (CH_2 aliphatic).

2-(3-Chloro-phenyl)-3-(6-nitro-2-oxo-2H-chromen-3-yl-amino) - thiazolidine-4-one (IV **D_2)**
FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 3030 (C-H) **,** 1575(C-C).

1590-1455 (N-O stretching), 850-550 (C-Cl).^{1}H NMR data - (ppm, 300MHz,TMS)-7.2-8.6(m,8H, Ar-H), 2.1 (s, 1H,NH), 6.50(s, C-H),3.29(s, 2H, CH_2) **.**^{13}C NMR data- (ppm, 100MHz, DMSO) δppm: 162 (C=O), 120-128 (C=C), 57.2(CH aliphatic), 38.2 (CH_2 aliphatic).

3-(6-Nitro-2-oxo-2H-chromen-3yl-amino)- 2-m-tolyl-thiazolidin-4-one (IV **D_3)**

FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 3030 (C-H) **,** 1575(C-C). 1590-1455 (N-O stretching).^{1}H NMR data - (ppm, 300MHz,TMS)-7.2-8.6(m,8H, Ar-H), 2.2 (s, 1H,NH), 6.43(s, C-H), 3.28(s, 2H, CH_2) **,** 2.21(s,3H,CH_3). ^{13}C NMR data- (ppm, 100MHz, DMSO) δppm: 162 (C=O), 120-128 (C=C), 57.2(CH aliphatic), 38.2 (CH_2 aliphatic), 20.9 (CH_3 aliphatic).

3-(6-Nitro-2-oxo-2H-chromen-3yl-amino)- 2-(3-nitro-phenyl)-thiazolidin-4-one. (IV **D_4)**

FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 3030 (C-H) **,** 1575(C-C). 1590-1455 (N-O stretching).^{1}H NMR data - (ppm, 300MHz,TMS)-7.2-8.6(m,8H, Ar-H), 2.0 (s, 1H,NH), 6.47(s, C-H), 3.30(s, 2H, CH_2)**.**^{13}C NMR data- (ppm, 100MHz, DMSO) δppm: 162 (C=O), 120-128 (C=C), 56.2(CH aliphatic), 38.7 (CH_2 aliphatic).

2-(3-Methoxy-phenyl)-3-(6-nitro-2-oxo-2H-chromen-3-yl-amino) - thiazolidine-4-one (IV **D_5)**

FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 3030 (C-H) **,** 1575(C-C). 1590-1455 (N-O stretching).^{1}H NMR data - (ppm, 300MHz,TMS)-7.16(m,8H, Ar-H), 2.72 (s, 1H,NH), 6.32 (s, C-H), 3.38 (s, 2H, CH_2, 3.80 (s,OCH_3).^{13}C NMR data- (ppm, 100MHz, DMSO) δppm:162(C=O), 120-128(C=C), 56.5(CH aliphatic), 38.4(CH_2 aliphatic), 54-60 (CH_3 aliphatic).

3-(6-Methoxy-2-oxo-2H-chromen-3yl-amino)- 2-phenyl-thiazolidin-4-one. (IV **E_1)**

FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 3030 (C-H) **,** 1575(C-C). ^{1}H NMR data - (ppm, 300MHz,TMS)-6.96-7.14 (m,8H, Ar-H), 2.1 (s, 1H,NH), 6.48 (s, C-H), 3.32 (s, 2H, CH_2), 3.74 (s,OCH_3).^{13}C NMR data- (ppm, 100MHz, DMSO) δppm:162(C=O), 120-128(C=C), 56.9(CH aliphatic), 38.6 (CH_2 aliphatic), 54-58 (CH_3 aliphatic).

2-(3-Chloro-phenyl)-3-(6-methoxy-2-oxo-2H-chromen-3-yl-amino) - thiazolidine-4-one. (IV **E_2)**

FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 3030 (C-H) **,** 1575(C-C), 850-550 (C-Cl).^{1}H NMR data - (ppm, 300MHz,TMS)-6.94-7.16 (m,8H, Ar-H), 2.72 (s, 1H,NH), 6.32 (s, C-H), 3.38 (s, 2H, CH_2) , 3.83 (s,OCH_3).^{13}C NMR data- (ppm, 100MHz, DMSO) δppm:162(C=O), 120-128(C=C), 56.5 (CH aliphatic), 38.4(CH_2 aliphatic), 54-60 (CH_3 aliphatic).

3-(6-Methoxy-2-oxo-2H-chromen-3yl-amino)- 2-m-tolyl-thiazolidin-4-one.. (IV **E_3)**

FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 3030 (C-H) **,** 1575(C-C), 850-550 (C-Cl).^{1}H NMR data - (ppm, 300MHz,TMS)-6.86-7.16 (m,8H, Ar-H), 2.1 (s, 1H,NH), 6.48 (s, C-H), 3.32 (s, 2H, CH_2), 3.74 (s,OCH_3) ,2.21(s,3H,CH_3). ^{13}C NMR data- (ppm, 100MHz, DMSO) δppm:162(C=O), 120-128(C=C), 56.9(CH aliphatic), 38.6 (CH_2 aliphatic), 54-58 (CH_3 aliphatic).

3-(6-Methoxy-2-oxo-2H-chromen-3yl-amino)- 2-(3-nitro-phenyl)-thiazolidin-4-one.. (IV **E_4)**

FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 3030 (C-H) **,** 1575(C-C), 1590-1455 (N-O stretching).^{1}H NMR data - (ppm, 300MHz,TMS)-6.94-7.14 (m,8H, Ar-H), 2.13 (s, 1H,NH), 6.32 (s, C-H), 3.38 (s, 2H, CH_2) , 3.83 (s,OCH_3).^{13}C NMR data- (ppm, 100MHz, DMSO) δppm:162(C=O), 120-128(C=C), 56.5 (CH aliphatic), 38.4(CH_2 aliphatic), 54-60 (CH_3 aliphatic).

3-(6-Methoxy-2-oxo-2H-chromen-3yl-amino)- 2-(3-methoxy-phenyl)-thiazolidin-4-one..(IV **E_5)**

FTIR (KBr) (V_{max} cm^{-1}):–1590(NH_2), 1550(N-N), 1100(C-N), 1675(C=C), 3030 (C-H) **,** 1575(C-C). ^{1}H NMR data - (ppm, 300MHz,TMS)-6.92-7.1 (m,8H, Ar-H), 2.02 (s, 1H,NH), 6.52 (s, C-H), 3.38 (s, 2H, CH_2, 3.32 (s,OCH_3).^{13}C NMR data- (ppm, 100MHz, DMSO) δppm:162(C=O), 120-128(C=C), 57.5(CH aliphatic), 38.7(CH_2 aliphatic), 54-60 (CH_3 aliphatic).

The Anti mycobacterial evaluation

The antimycobacterial activity of the synthesized compounds (IV A_1-D_5) were assessed against Mycobacterium tuberculosis in MB7H9 broth media supplemented with ADC by MABA (Resazurin) assay. Given compounds were dissolved in DMSO (Stock con. 10 mM), then compounds were seeded in MB7H9 media (100 µl volume) enriched with ADC (10% v/v) with decreasing double dilutions starting with 50 µM (for 250 µl volume) in 96 well plate.After that 150µl of culture (Mycobacterium tuberculosis H37Ra, 10^6 CFU/ml) was added to each well except blank (negative control).Culture control, Blanks (media alone), Rifampin and streptomycin were taken as test control.Plate was incubated for 5 days at 37^{o} C incubator.On 6th day, 25 µl Resazurin (0.01% w/v, stock con.) was

added and plate was incubated further till pink colour in control wells.The color change from purple to pink was assessed visually and fluorescence was measured at 530±25 nm and 590±25 nm for excitation and emission respectively in Synergy Biotek plate reader. All the antitubercular results are shown in Table 3.

Result and discussion

In this study different novel derivatives of 3[2-oxo-2H-chromen-3yl)amino]- 2 aryl 1,3 thiazolidine-4-one (IVA_1-D_5) have been synthesized and evaluated for antimycobacterial activity. We described here a convenient and efficient protocol for the preparation of 3[2-oxo-2H-chromen-3yl)amino]- 2 aryl 1,3 thiazolidine-4-one (IV A_1-D_5). All compounds were synthesized according to Scheme 1. At the first stage, condensation of substituted salicylaldehydes was done with dimethyl malonate in the presence of a base (piperidine) to yield 2-oxo-2H-chromen-3yl-acetate. Further 2-oxo-2H-chromen-3yl-acetate was reacted with hydrazine hydrate to furnish 3-hydrazinyl 2H-chromene-2-one.Then these compounds were treated with different aromatic aldehydes to give 3(2-aryl methylidene hydrazinyl)-2H-chromene-2-one.Then (2-aryl methylidene hydrazinyl)-2H-chromene-2-one condensed with thioglycollic acid and different aldehydes to form different derivatives of 3[2-oxo-2H-chromen-3yl)amino]- 2 aryl 1,3 thiazolidine-4-one (IV A_1-D_5).

Compounds (IV A_1-D_5) was screened for their in vitro antitubercular activity against Mycobacterium tuberculosis in MB7H9 broth media supplemented with ADC by MABA (Resazurin) assay.The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to completely inhibit the bacterial growth.

In the series (IV A_1-D_5), the compounds **IVA_3**, **IVB_3**, **IVB_5**, **IVC_3**, **IVC_5**, **IVE_3**, **IVE_5** showed excellent activity with MIC 3.125 µg/Ml.Whereas the compounds **IVA_5**, **IVB_4**, **IVC_4**, **IVD_3**, **IVD_5** showed moderate avtivity with MIC 6.25 µg/Ml. The very weak activity were observed by compounds **IVA_1**, **IVC_1**, **IVD_1**, **IVD_4**, **IVE_4** with MIC 25 µg/Ml and 50 µg/Ml.

Table 1. Physical data of 3[2-oxo-2H-chromen-3yl)amino]- 2 aryl 1,3 thiazolidine-4-one derivatives.

Compound	R	R2	Molecular formula	Molecular weight	Melting point	Yield (%)
IVA_1	H	H	$C_{18}H_{14}N_2O_3S$	338	217-222	67.32
IVA_2	H	Cl	$C_{18}H_{13}ClN_2O_3S$	373	252-263	72.40
IVA_3	H	CH_3	$C_{19}H_{16}N_2O_3S$	352	242-248	68.34
IVA_4	H	NO_2	$C_{18}H_{13}N_3O_5S$	383	265-272	70.26
IVA_5	H	OCH_3	$C_{19}H_{16}N_2O_4S$	368	211-220	73.20
IVB_1	Cl	H	$C_{18}H_{13}ClN_2O_3S$	373	209-210	69.89
IVB_2	Cl	Cl	$C_{18}H_{12}Cl_2N_2O_3S$	407	274-278	72.87
IVB_3	Cl	CH_3	$C_{19}H_{15}ClN_2O_3S$	387	234-244	68.76
IVB_4	Cl	NO_2	$C_{18}H_{12}ClN_3O_5S$	418	279-280	70.09
IVB_5	Cl	OCH_3	$C_{19}H_{15}ClN_2O_4S$	403	187-188	69.85
IVC_1	Br	H	$C_{18}H_{13}BrN_2O_3S$	417	277-279	66.95

IVC_2	Br	Cl	$C_{18}H_{12}BrClN_2O_3S$	452	287-288	67.48
IVC_3	Br	CH_3	$C_{19}H_{15}BrN_2O_3S$	431	256-260	66.70
IVC_4	Br	NO_2	$C_{18}H_{12}BrN_3O_5S$	462	280-282	64.32
IVC_5	Br	OCH_3	$C_{19}H_{15}BrN_2O_4S$	447	265-266	72.40
IVD_1	NO_2	H	$C_{18}H_{13}N_3O_5S$	383	230-234	69.22
IVD_2	NO_2	Cl	$C_{18}H_{12}ClN_3O_5S$	418	277-279	61.42
IVD_3	NO_2	CH_3	$C_{19}H_{15}N_3O_5S$	397	187-188	69.87
$IIID_4$	NO_2	NO_2	$C_{18}H_{12}N_4O_7S$	428	287-289	69.33
IVD_5	NO_2	OCH_3	$C_{19}H_{15}N_3O_6S$	413	269-278	65.58
IVE_1	OCH_3	H	$C_{19}H_{16}N_2O_4S$	368	157-168	63.48
IVE_2	OCH_3	Cl	$C_{19}H_{15}ClN_2O_4S$	403	207-218	69.27
IVE_3	OCH_3	CH3	$C_{20}H_{13}N_2O_4S$	382	187-188	69.54
IVE_4	OCH_3	NO_2	$C_{19}H_{15}N_3O_6S$	413	247-258	62.18
IVE_5	OCH_3	OCH_3	$C_{20}H_{18}N_2O_5S$	398	187-192	59.02

Table 2. Elemental analysis of compounds (IV A_1-D_5).

Compound	Carbon(%)	Hydrogen(%)	Oxygen(%)	Nitrogen(%)
IVA_1	63.89	4.17	14.18	8.28
IVA_2	57.99	3.51	12.87	7.51
IVA_3	64.76	4.58	13.62	7.95
IVA_4	56.39	3.42	20.87	10.96
IVA_5	61.94	4.38	17.37	7.60
IVB_1	57.99	3.51	12.87	7.51
IVB_2	53.08	2.97	11.79	6.88
IVB_3	58.99	3.91	12.41	7.24
IVB_4	51.74	2.89	19.15	10.06
IVB_5	56.65	3.75	15.89	6.95
IVC_1	51.81	3.14	11.50	6.71
IVC_2	47.86	2.68	10.63	6.20
IVC_3	52.91	3.51	11.13	6.50
IVC_4	46.77	2.62	17.31	9.09
IVC_5	51.02	3.38	14.31	6.26

IVD_1	56.39	3.42	20.87	10.96
IVD_2	51.74	2.89	19.15	10.06
IVD_3	57.42	3.80	20.13	10.57
IVD_4	50.47	2.82	26.14	13.06
IVC_5	55.20	3.66	23.22	10.16
IVE_1	61.94	4.38	17.37	7.60
IVE_2	56.65	3.75	15.89	6.95
IVE_3	62.81	4.74	16.73	7.33
IVE_4	55.20	3.66	23.22	10.11
IVE_5	60.29	4.55	20.08	7.03

Table 3. In vitro antitubercular activity of the title compounds (IVA_1-D_5)

Compound	MIC(μ g ml−1)
IVA_1	>25
IVA_2	>12.5
IVA_3	>3.125
IVA_4	>12.5
IVA_5	>6.25
IVB_1	>12.5
IVB_2	>12.5
IVB_3	>3.125
IVB_4	>6.25
IVB_5	>3.125
IVC_1	>25
IVC_2	>50
IVC_3	>3.125
IVC_4	>6.25
IVC_5	>3.125
IVD_1	>25
IVD_2	>12.5
IVD_3	>6.25
IVD_4	>12.5
IVD_5	>6.25
IVE_1	>25
IVE_2	>12.5
IVE_3	>3.125
IVE_4	>25
IVE_5	>3.125
Rifampcin	0.25
Strepomycin	0.60

Conclusion.

In this paper we report the synthesis of some 3[2-oxo-2H-chromen-3yl)amino]- 2 aryl 1,3 thiazolidine-4-one (IV A_1-D_5) derivatives and the antitubercular evaluation of some of the novel compounds. . The preliminary in vitro antitubercular data demonstrated that the compound **IVA_3**, **IVB_3**, **IVB_5**, **IVC_3**, **IVC_5**, **IVE_3**, **IVE_5** has the most potent activity against Mycobacterium.

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