IJBPAS, August, 2025, 14(8): X-X

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

A REVIEW ON COUMARIN DERIVATIVES WITH S-TRIAZINE AND SUBSTITUTED THIOUREAS FOR ANTIMICROBIAL ACTIVITY

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Received 20th April 2024; Revised 14th May 2024; Accepted 1st Sept. 2024; Available online 1st Aug. 2025

https://doi.org/10.31032/IJBPAS/2025/14.8.9270

ABSTRACT

The exploration of heterocycles as privileged structures in drug discovery is, beyond doubt, one of the major areas in medicinal chemistry. These privileged structures represent a class of molecules that act as ligands for various biological receptors with a high degree of binding affinity. Problems of multi-drug resistant microorganisms have reached on alarming level in many countries around the world. A series of urea and thiourea derivatives of s-triazine have been developed based on high yielding nucleophilic substitution of 2,4,6-trichloro-1,3,5-triazine by 4-hydroxy coumarin, cyclopropylamine and ammonia at suitable conditions. Most of the synthesized compounds possesses potent antibacterial activities against various Gram-positive and Gram-negative strains of bacteria. A few compounds showed good to superior in vitro antibacterial activity against S.aureus, B.subtilis, E.coli and P. aeruginosa. Infections caused by those microorganisms pose a serious challenge to the medical community and the need for an effective therapy has led to a search for novel antimicrobial agents. Exploitation of these molecules should allow us to rapidly discover new biologically active compounds across a broad range of therapeutic areas in a shorter time scale. In this review article, we have discussed the novel synthesis and antibacterial activity of s-triazinyl urea and thiourea analogues, a class of privileged structures that have a wide range of biological properties.

Keywords: Heterocycles, triazine, thiourea, coumarin, antibacterial

INTRODUCTION

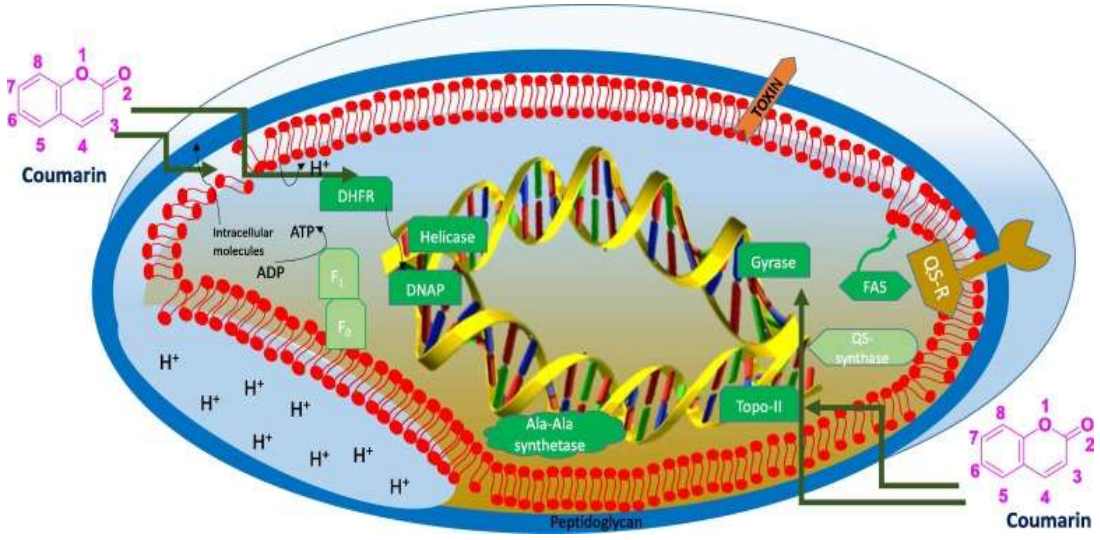
Benzopyran-2-one lactones, often known as coumarins, are a family of naturally occurring lactones that were initially isolated from Tonka beans in 1820. Since the beginning of time, these chemicals have been used as herbal medicines since they are extensively available in nature **[1]**. Over 1300 coumarin derivatives have been found in plants, fungi, and bacteria, mostly from the secondary metabolite. The discovery of this molecule sparked a worldwide quest for its origin and identity **[2].**

Nitrogen containing heterocycles play an important role, not only for life science industry but also in many other industrial fields related to special and fine chemistry **[2, 4]**. Among them 1,3,5-triazines represent a widely used lead structure with multitude of interesting applications in numerous fields **[5]**. Problems of multi-drug resistant microorganisms have reached on alarming level in many countries around the world. A numbers of recent clinical reports describe the increasing occurrence of methicillin-resistant S. aureus and other antibiotic-resistant human pathogenic microorganisms **[6, 7, 8]**. Infections caused by those microorganisms pose a serious challenge to the medical community and the need for an effective therapy has led to a search for novel antimicrobial agents. Exploitation of these molecules should allow us to rapidly discover new biologically active compounds across a broad range of therapeutic areas in a shorter time scale.

Several derivatives of s-triazine show antimicrobial, antibacterial, and herbicidal activities. Some are also used for the treatment of HIV infection **[9]**. Several workers investigated the s-triazine nucleus in the scope of potential therapeutic agents for diseases due to bacteria, malaria, and cancer. The above literature survey led us to consider the s-triazine nucleus as a possible scaffold in the treatment of microbial infections. Coumarin derivatives have revealed new biological activities with interesting potential in therapeutic applications besides their traditional employment as anticoagulants (anti-vitamin-K activity) and suntan agents (photosensitizing action of furocoumarins) **[10]**. Moreover, coumarin (a phytochemical) is chemically the benz[α]pyrone and freely occurring as constituents or could be condensed with carbohydrate said to be glycosides. It is a fused ring system between benzene and lactone known as ‘pyrone ’and structurally resembles to chromone; but the difference in both the positions of carbonyl or ketone system present in individual structures **[11]**. They have yielded important results as antibiotics (Novobiocin and analogues), anti-AIDS agents (Calanolides) and antitumor drugs (Gelparvarin). Some of these drugs derived from 4-hydroxycoumarin have been thoroughly studied.

In the design of new compounds, development of hybrid molecules through the combination of different pharmacophores in one structure may

lead to compounds with increased antimicrobial potency **(Figure 1)**. This would be the



activity. This aim of this review is to have a concise account and detailed highlights of structural derivatives of coumarin with s-triazine and substituted thioureas associated schematic strategies; by the by, to locate candidate(s) with significant antibacterial countenance to diverse groups of chemists, biologists and drug developers, to distinguish and to identity promising structures to be judged for further promotion in the development of newer therapeutic or antibacterial agent(s).

Figure 1 Schematic representation of bacterial cell inhibitory actions of coumarin derivatives

MATERIAL AND METHOD

SARs of coumarin derivatives as antibacterial agents

The exploration of synthetic and semisynthetic coumarin derivatives against inhibitory actions of notorious Gram positive, negative and acid-fast mycobacteria are emphasised here. Evidently, more than twenty-five percent of developed molecules had been seen upstanding antibacterial action(s) and a few more had moderate to less efficacy. In the principle of medicinal chemistry synthetic strategies, molecular hybridization is an established etiquette for development of novel compounds. Indeed, the phytochemical coumarin is natural heterocyclic ring with various biological actions among all; the antibacterial action(s) is more predominant by the intermixing of various components **(Figure 2)**.

In this SAR study of coumarin had briefly emphasized on integument of active sites of the congener for properties of inhibitory actions. 2-(furan-2-ylmethyleneamino)-6-coumarinyl-4-substituted nicotinic nitriles 1 had been notable antibacterial inhibitory properties, due to the presence of electron donating substituents, –OCH3, –CH3 of phenyl ring and electron withdrawing NO2, halogen groups respectively. Similarly, metal complexes bearing coumarinyl carbohydrazide

with indole Schiffbase derivatives 2 had exhibited remarkable antibacterial activity due to the presence of withdrawing chloro substituents incomplexes, which have better zone of inhibition than methylated ligand. Indeed, the increases antibacterial efficacy is directly proportionate to lipophilic character of metal chelate ions, which could favour to permeation by lipid layer of bacterial cell membrane. Moreover, substituted ribofuranosyl coumarinyl 1,2,3-triazole derivatives 3 had been reported as potent candidates against clinical isolates of MDR human pathogenic bacterial strains. The structure bearing ribosylfuranosyl 1,2,3-triazole nucleus connected to 4-methyl-7-hydroxycoumarin at C-7 position through oxymethylene (–OCH2) linker. Concomitantly, the coumarinyl linked pyrazole carbaxamide derivatives 4 had been reported as good antibacterial bacterial agent as inhibitors of Topoisomerase II and Topoisomerase IV. On the N-(4-chloro phenyl) pyrazole 5-carboxamide 4 structure of coumarin at C-3 position, an attachment of diethyl amino or bromo may lead inhibitory effect on bacterial growth.

Furthermore, monocarbonylcurcumin-coumarin ring linker with 1,2,3-triazole nucleus through two carbon chain compounds due to the presence of 4-methoxy substitution at curcumin-coumarin hybrids 5 may have showed good antibacterial actions. Similarly, coumarin flouroquinolone hybrids 6 were reported as having good antimycobacterial actions due to flouro quinolone ring, which is essential for any antibacterial action. Thus, the developed molecules may have greater degrees of inhibitory actions on bacterial DNA gyrase or topoisomerase. Ruthenium(II)-DMSO complexes of substituted coumarin 3-acylhydrazone 7 had been reported from 7-diethylamino- coumarin hydrazide. These complexes had shown greater inhibitory action due to the presence of hydrazide group and metal ion Ruthenium(II) in structural frame. On the structure of compound 8, where the presence of 1,2,3-triazolyl substituted coumarin ring which makes the molecules had exhibited significant antibacterial actions.

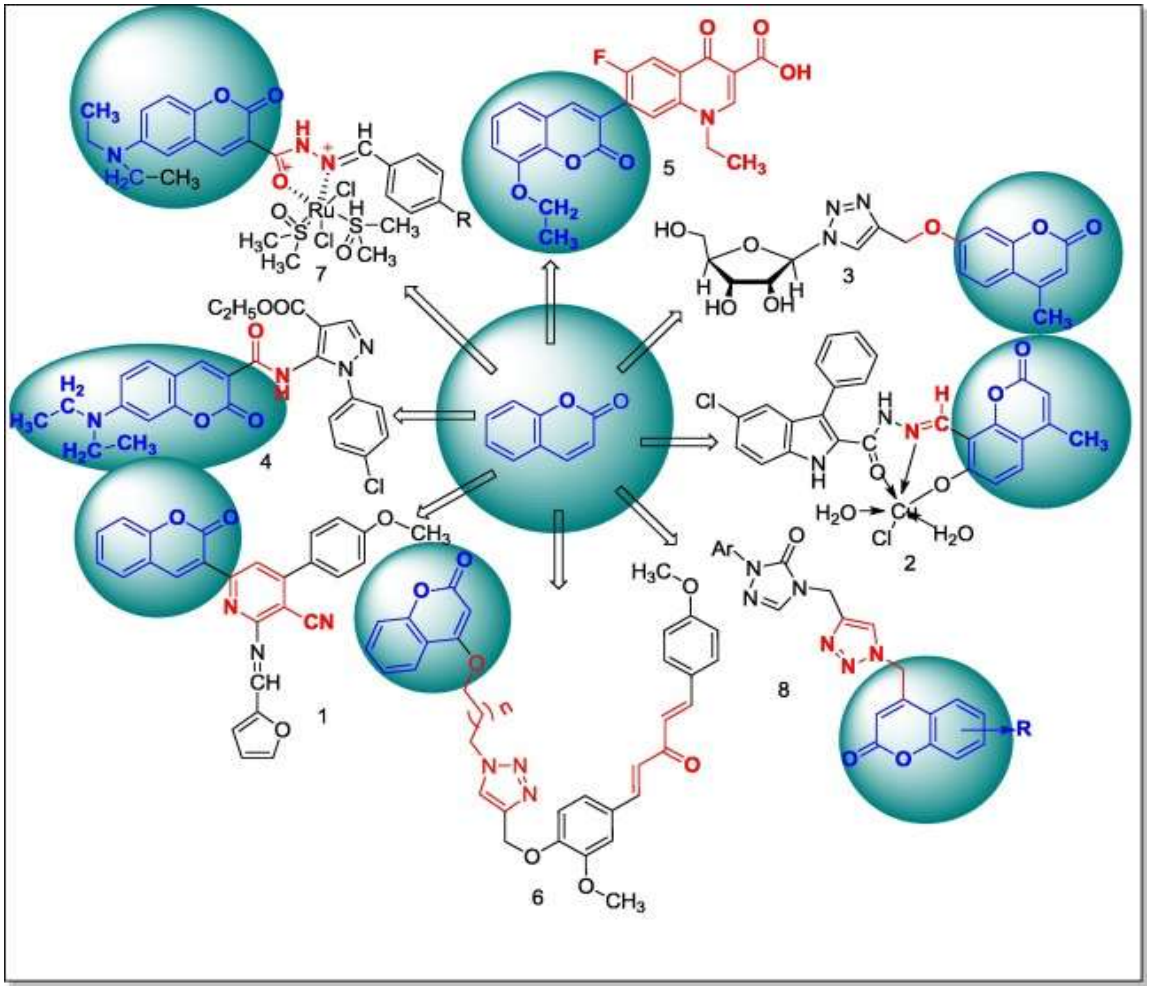
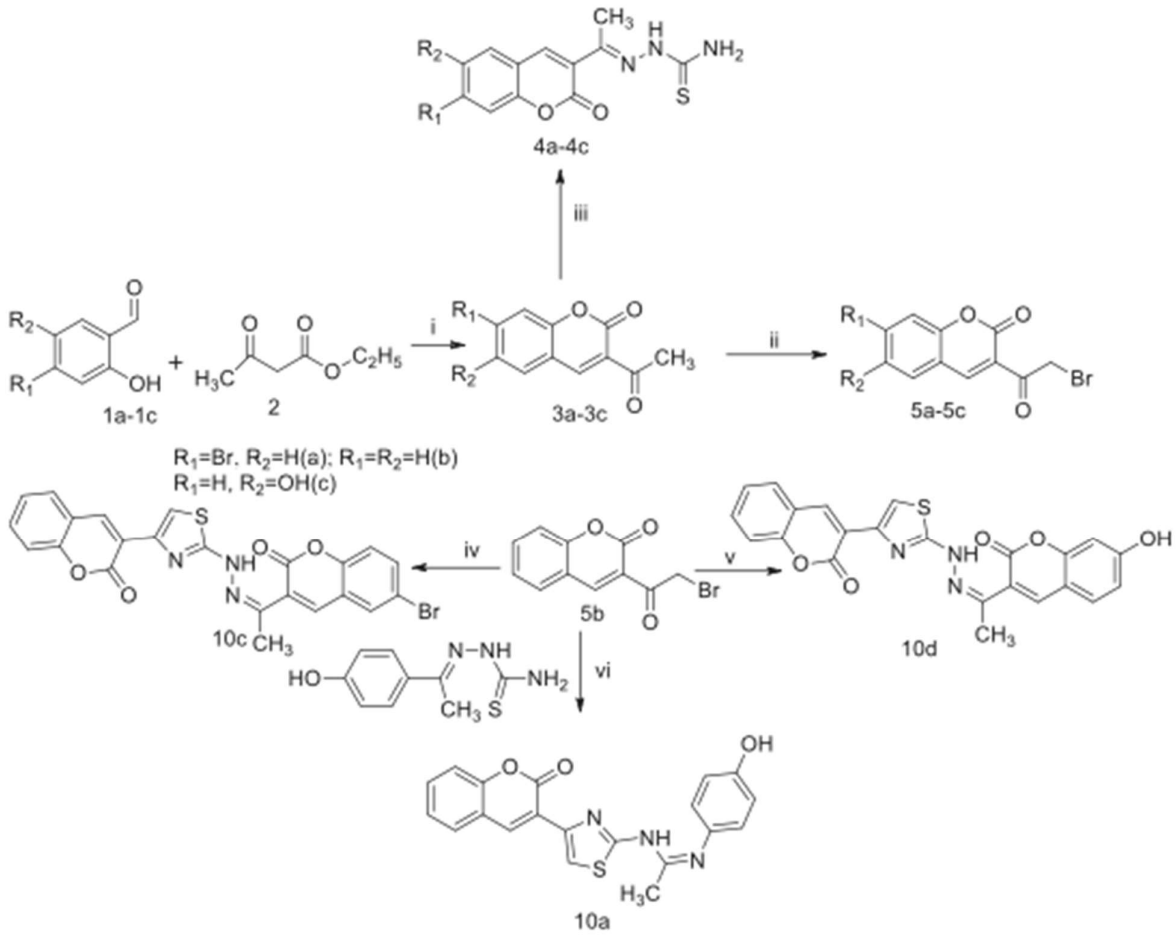


Figure 2: Structural-activity-relationships of coumarin derivatives

Synthesis of thiazolyl hydrazonyl substituted coumarin derivatives

Twelve derivatives bearing hydrazonyl thiazolyl substituted coumarin were synthesised by the reflux condensation of 3-bromoacetyl coumarin 5b, and substituted phenyl/substituted 3-acetylcoumarin thiosemicarbazone 4a-4c in chloroform and ethanol (2:1) yield thiazolyl linked coumarin analogues. By the principle of Hanztsch's reaction, the formation of thiazole ring, which was incorporated in structure between bromoacetyl group and the corresponding thiosemicarbazone congener, in the presence of mixed solvents ethanol and chloroform. The insertion of hydroxyl group and bromo substituents of benzylidene imine residue had resulted in significant antimycobacterial activity. The compound 6-bromo-3-(1-(2-(4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)hydrazono)ethyl)–2H-chromen-2-one 10c was reported as a good antimycobacterial agent with 15 µM as the MIC value in comparison to Isoniazid (INH) **[12]**.

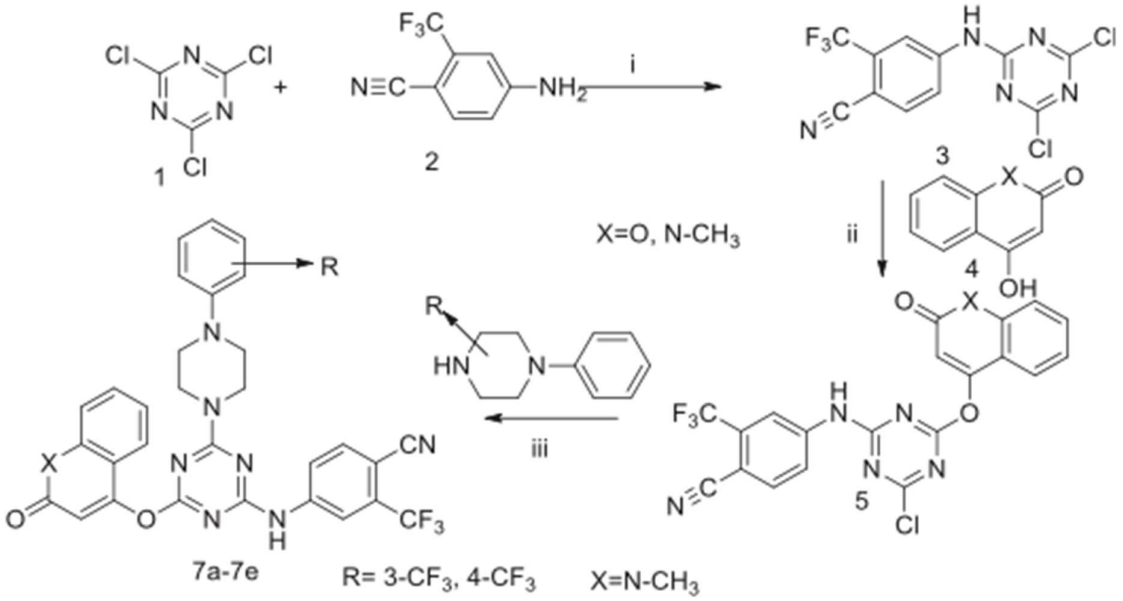


Scheme 1 Hydrazonyl thiazolyl substituted coumarin derivatives

Synthesis of coumarin bearing triazine derivatives

Two series of quinolonyl/ coumarinyl triazine derivatives 7a-7e and 8a-8d were synthesized. In this synthesis, an intermediate subtract, 4-((4,6-dichloro-1,3,5-triazin-2-yl)amino)-2-(trifluoromethyl)benzonitrile 3 was synthesized by the reaction mixture of 4-amino- 2-trifluoromethyl benzonitrile 1 and trichloro-1,3,5-triazine 2 in the presence of triethylamine by nucleophilic displacement of chlorine atom from triazine nucleus. The obtained product further reacted with either 4-hydroxy coumarin or 1-methyl quinolone in the presence of sodium hydride in THF to produce another precursor of title compound 5. Finally, the desired compounds corresponding 4-((4-chloro-6-((1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)-1,3,5-triazin-2-yl)amino)-2-(trifluoromethyl)benzonitrile 7 and 4-((4-((2-oxo-2H-chromen-4-yl)oxy)-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-

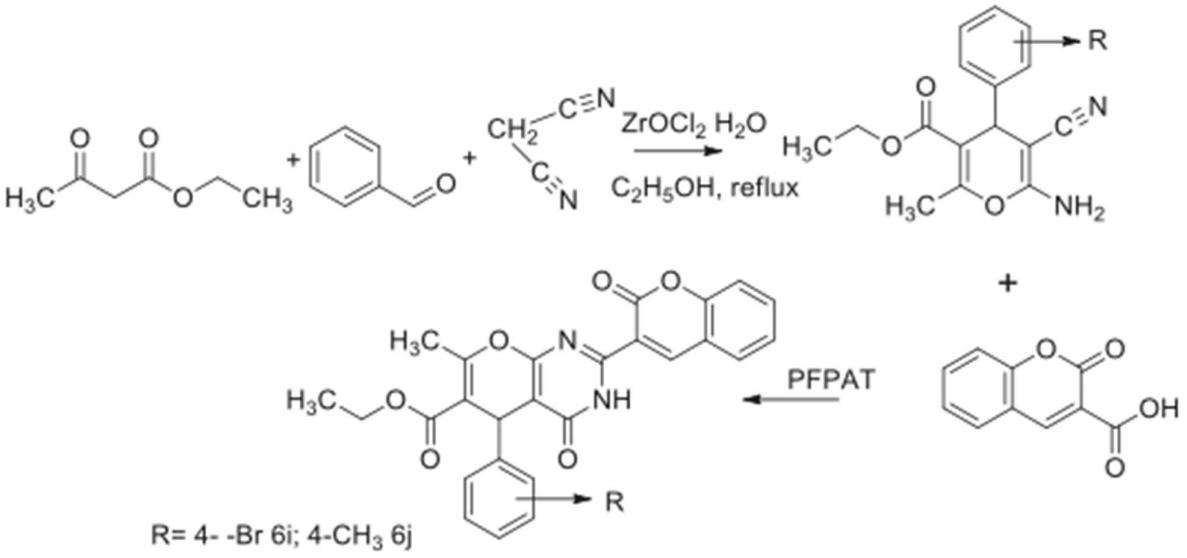
yl)amino)-2-(trifluoromethyl)benzonitrile 8 were prepared by nucleophilic displacement of another chlorine atom of product 5 with 4-substituted aryl piperazinyl 6 in the presence of 1,4-dioxane and potassium carbonate. The compounds bearing quinolone as 7c and 7d had hown good antibacterial activity against S. aureus as 27 mm ZOI with the MIC value 6.25 µg/mL in comparison to the standard Ciprofloxacin. Moreover, these derivative 8d contain coumarin ring in structure had shown good antibacterial action against E. coli at the MIC value 12.5 µg/mL **[13]**.



Scheme 2 Coumarin bearing triazines derivatives

Synthesis of thiazolyl-pyrazoline coumarin derivatives

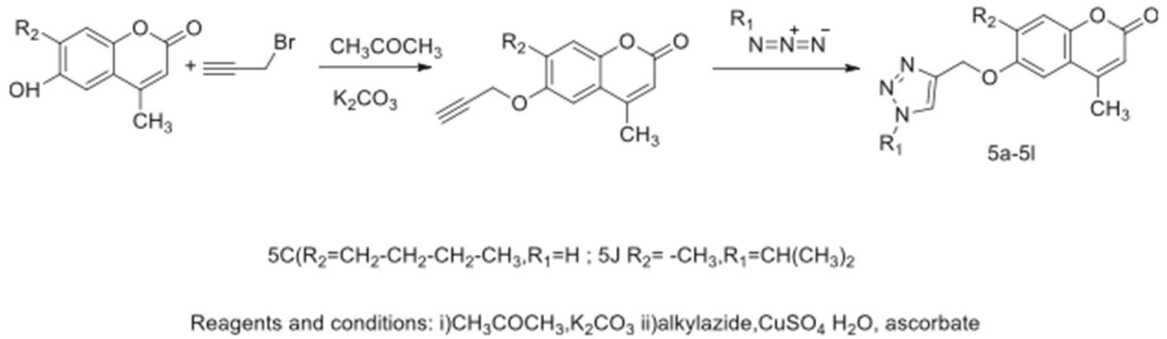
A novel series of coumarin compounds bearing thiazolyl and pyrazolone linked derivatives were synthesized by the reflux condensation of alcoholic solution of 6-bromo 3-bromoacetyl coumarin 1 with another intermediate reactant 5-hydroxy-3,5-bis(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carboxamide 2. The intermediate trifluoromethyl pyrazolone carboxamide 2 was synthesized by the reaction of 2,2,2-trifluoroethyl 4,4,4-trifluoro-3-oxobutanoate with thiosemicarbazide. Moreover, the compound 6c had notable activity against B. subtilis and S. epidermidis at 25 and 20 mm as ZOI in comparison to Cefixime **[14]**.



Scheme 3 Thiazolyl- pyrazoline coumarin derivatives

Synthesis of 1,2,3-triazolyl substituted coumarin derivatives

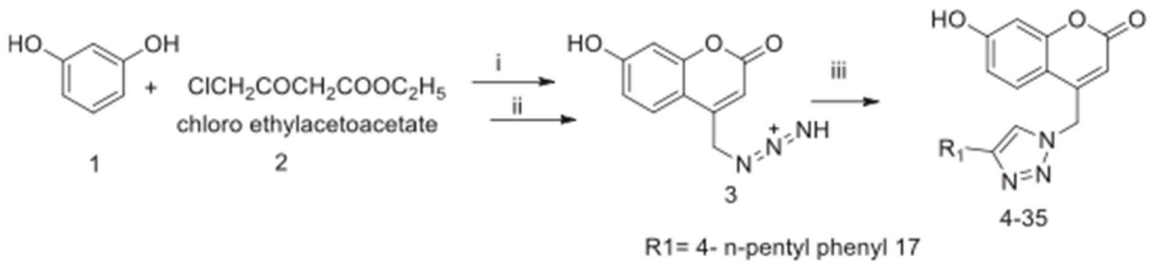
A series of twelve triazolylmethyloxy substituted alkyl coumarin analogues, 5a-5 l were synthesized by reacting with 4-methyl-6-(prop-2-ynyloxy)-2H-chromen-2-one and substituted alkyl azide in the principle, 'click reaction', and the obtained compound 4-methyl-6-((1-subst. alkyl-1H-1,2,3-triazol-4-yl)methoxy)-2H-chromen-2-one yielded 5a-5 l. The compound 5c having n-butyl substituted coumarin linked with triazolyloxymethyl at C-6 position and isopropyl substituted coumarin linked with triazolyloxymethyl 5j had been reported as a good in vitro antibacterial agent against E. coli and S. aureus at MIC values 8 and 7 µg/mL, respectively **[15]**.



Scheme 4 1,2,3-Triazolyl substituted coumarin derivatives

Synthesis of coumarin bearing triazole derivatives

In this scheme, coumarin derivatives having substituted triazole ring attached were designed and synthesized using copper(I) catalysed by 'Huisgen 1,3-dipolar 'reaction of terminal alkyne with treatment azide. In the scheme, intermediate 4-azidomethyl coumarin derivatives were liberated as sodium azide with 4-chloromethyl- 7-hydroxy coumarin and 4-chloromethyl- 7-methyl coumarin, then these were prepared by the reaction of 3-hydroxy phenol and 3-methyl phenol with chloro ethyl acetoacetate under cyclisation in the presence of dehydrating agents concentrated sulfuric acid. Furthermore, these 1,2,3-triazole-coumarin hybrids were obtained by 'click chemistry 'of 4-azidomethyl coumarin derivative and substituted alkynes in the presence of catalyst Cu(I), which generally was prepared in situ by copper sulfate and metallic copper. Moreover, the synthesis of 1,2,3-triazolyl substituted aryl sulfonamide of coumarin azide and the corresponding N-propargylated aryl sulfonamides were prepared. The compound 7-hydroxy-4-((4-(4-pentylphenyl)-1H-1,2,3-triazol-1-yl)methyl)-2H-chromen-2-one17 had shown as a good antibacterial agent against E. faecalis at MIC value 8 µg/mL **[16]**.



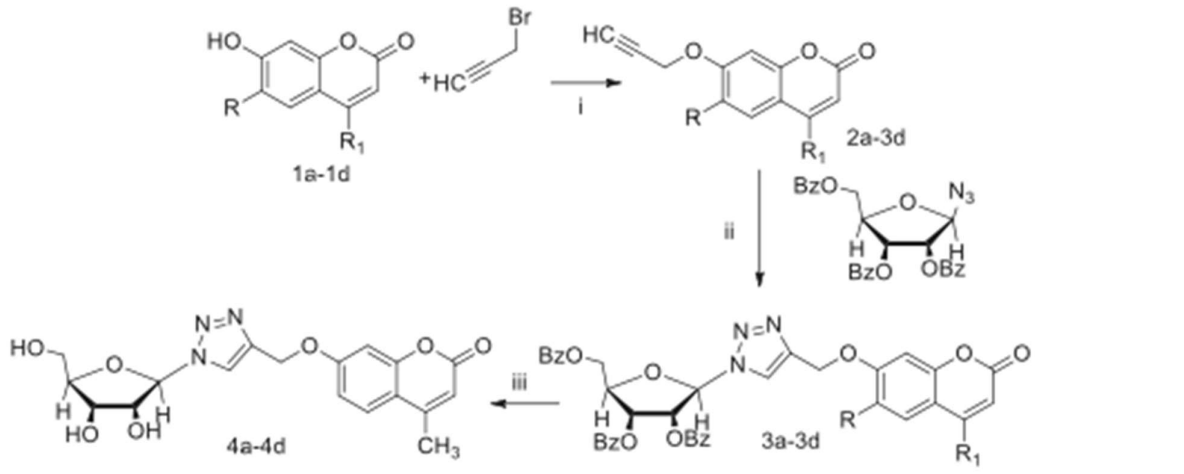
Reagents and conditions: i)Conc,H_2SO_4,-5°C ii)NaN_3,CH_3CN.reflux iii)correspomding azide1M $CuSO_4$, tert.butanol:H_2O(1:1), DMF, 80°C

Scheme 5 Coumarin bearing triazole derivatives

Synthesis of ribofuranosyl –coumarinyloxy bearing 1,2,3-triazole derivatives

A series of substituted ribofuranosyl coumarinyl 1,2,3-triazole 4a-4d had been synthesized by cycloaddition reaction between azido sugar and 7-alkynated 4-methyl coumarin 2a-2d in presence of Cu(I) with good yields. During synthesis of these compounds, initially with an intermediate 7-hydroxy substituted coumarin 1a-1d were treated with propargyl bromide in the presence of potassium carbonate to produce corresponding 7-propargyloxy substituted coumarin in an 85% yield. Then after, 7-propargyloxy coumarin was reacted with the corresponding 2-azido-2,3,5-tribenzoyl-β- D-ribofuranose in the presence of ascorbate-CuSO4 in THF through Cu(I) mediated cycloaddition reaction to afford

resultant N'-2,3,5-tribenzoyloxy β- D-ribofuranosyl-4-coumarinyl-7-oxymethyl-1,2,3-triazole in 70% yield. Then debenzoylation of the resulted targeted ribofuranosyl coumarinyl 1,2,3-triazole derivatives. The compound N'-2,3,5-tribenzoyloxy β- D-ribofuranosyl-4-methylcoumarinyl-7-oxymethyl-1,2,3-triazole and N'-2,3,5-tribenzoyloxy β- D-ribofuranosyl-4-coumarinyl-7-oxymethyl-1,2,3-triazole had been reported having a good inhibitory action against M. tuberculosis at MIC 5.1 μM **[17]**.

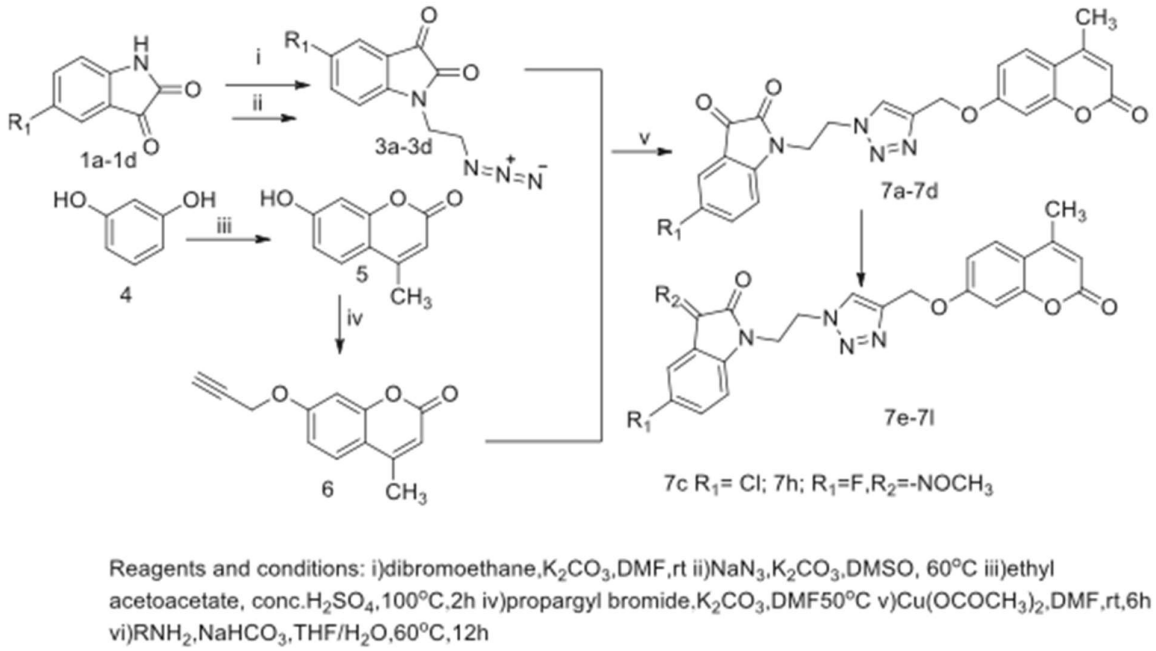


Scheme 6 Ribofuranosyl-coumarinyloxy bearing 1,2,3- triazole derivatives

Synthesis of isatin-linked 1,2,3-triazole with coumarin

A series of newly synthesized compounds 1, 2, 3-triazole tethered indolinone-coumarin hybrids 7a-7l from two reactant substrates such as, 4-methyl 7-(prop-2-ynyloxy) coumarin 6 and azidoethyl substituted isatin 3a-3d. In the synthesis the corresponding hybrids, initially 7-hydroxy 4-methyl coumarin 5 was prepared by Pechmann condensation of ethyl acetoacetate and resorcinol 4 in acidifying agent; and the compound 4, being heated with 7-hydroxy 4-methyl coumarin and propargyl bromide in the presence of potassium carbonate at 50 °C. Another intermediate 1-(2-azidoethyl)indoline-2,3-dione was prepared by the reaction between isatin and 1,2-dibromoethane in the presence of potassium carbonate yield N-(2-bromoethyl isatin). Consequently, this product reacted with sodium azide at 60 0C to afforded 1-(2-azidoethyl)indoline-2,3-dione. These two precursors were further used for the synthesis of the triazole tethered coumarin isatin hybrids through cupper(I)-promoted alkyne-azide cyclo addition in the presence of DMF and copper acetate. Finally the desired products were condensed with appropriate amine hydrochloride to obtain respective (Z)-3-

(methoxyimino)-1-(2-(4-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethyl)indolin-2-one derivatives 7e-7l. The compound 5-chloro-1-(2-(4-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethyl)indoline-2,3-dione 7c and (Z)-3-(methoxyimino)-1-(2-(4-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethyl)indolin-2-one 7h had exhibited as a good antibacterial agent against M. smegmatis at MIC value 50 µg/mL in comparison to standard drugs, Rifampicin and Isoniazid **[18, 19]**.

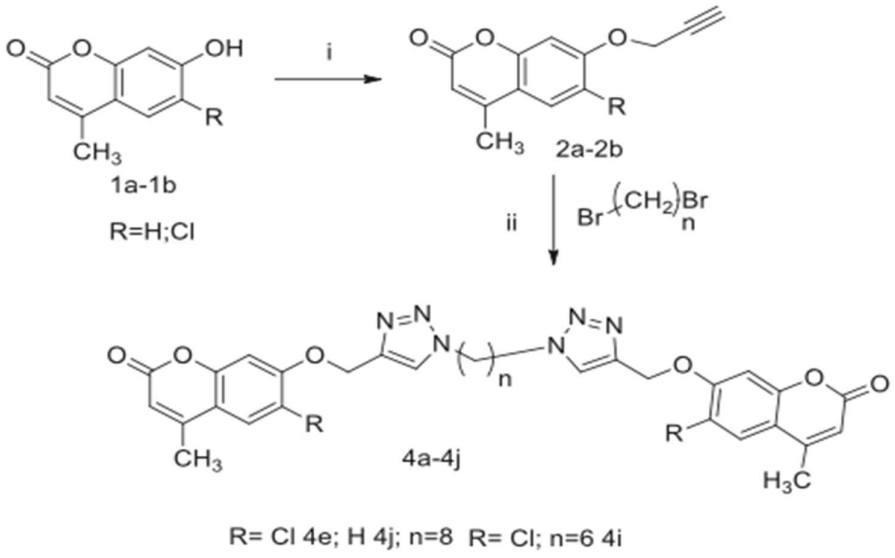


Scheme 7 Isatin- linked 1, 2, 3-triazole with coumarin

Synthesis of bis 1,2,3-triazolyl methyloxy coumarin derivatives

A series of dimer compounds containing bis 1,2,3-triazolyl methoxy linked with 4-methyl-7-hydroxy coumarin derivatives under microwave irradiation methods was synthesized and the obtained products had antimycobacterial and antibacterial activities. Initially an intermediate 4-methyl-7-(prop-2-yn-1-yloxy)-2H-chromen-2-one 2 was prepared by a two step reaction, firstly 4-methyl 7-hydroxy coumarin derivative 1 was prepared by the Pechmann condensation of substituted resorcinol and ethyl acetoacetate in the presences of acidifying agent, then after the compound 1 was reacted with propargyl bromide in the presence of dry acetone and potassium carbonate for yielding 2. In the synthesis of dimer of triazole-coumarin derivatives initially, nucleophilic substitution of dibromoalkane with sodium azide liberated azidoalkane and coupled with 4-methyl-7-(prop-2-yn-1-yloxy)-2H-chromen-2-one in the presence of cupper catalysed by 1,3-

cycloaddition via azido-alkyne reactions. The title compounds were optimised by CuI in DMF:H2O (1:3) under microwave irradiation at 180 W for 10 min. All the desired target molecules were screened for their antimycobacterial action using resazurin microtiter assay (REMA) in comparison to standard Rifampin and isoniazid (INH). Moreover, the compound 7,7′-(((1,1′-octane 1,8-diyl) bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene)) bis(oxy))bis(6-chloro-4-methyl-2H-chromen-2-one) 6j had shown good antibacterial action against *B. subtilis, S. aureus, E. coli* at MIC doses 3.125 µg/mL for each; and the compound 7,7′-(((1,1′-methylenebis(1H-1,2,3-triazole-4,1-diyl))bis(methylene))bis(oxy))bis(4-methyl-2H-chromen-2-one) 6e had in vitro control over B. subtilis, S. aureus and P. vulgaris at MIC doses 6.25 µg/mL. Consequently, compounds 6i and 6j had excellent antimycobacterial action with MIC 1,56 µg/mL. In SAR studies, it was known that electron-negative chlorine substituted coumarin at C-6 position and longer lipophilic alkyl chain linker between two ring systems play an important role for significant antibacterial action **[20]**.



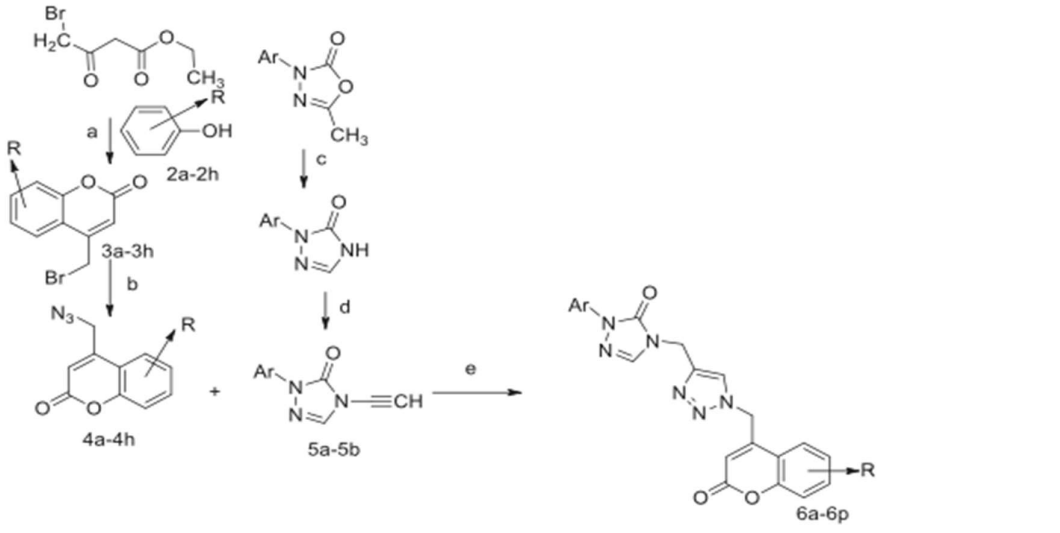
Reagents and conditions: i)propagryl bromide, anhydrous K_2CO_3,acetone,reflux,18h; ii)NaN_3,CuI,DMF:H_2O,80°C,24h

Scheme 8 Dimer of Triazole-coumarin hybrids derivatives

Synthesis of triazole substituted coumarin derivatives

1,2,3-triazole derivatives were prepared by the Cu(I)ions catalysed [2 + 3]cycloaddition reaction between organic azides and terminal alkynes at an ambient temperature. In this synthesis, a series of triazolyl bearing coumarin derivatives 6a-6p were performed via., azide-

alkyne cycloaddition reaction. The substituted 4-azidomethyl coumarins were synthesized by two step reaction, substituted 4-bromomethyl coumarin were prepared by Pechmann cyclisation of bromoethyl acetoacetate and the substituted phenol in acidifying agent. Then the obtained products were reacted with sodium azide in aqueous. Additionally,an intermediate compounds 4-ethynyl-1-substituted phenyl-1H-1,2,4-triazol-5(4H)-one 5a-5b were prepared by the reaction of 1-substituted phenyl-1H-1,2,4-triazol-5(4H)-one with prop-1-yne using potassium carbonate in anhydrous acetone solution. This reaction was followed by azide-alkyne cycloaddition of ethynyl-1-substituted phenyl-1H-1,2,4-triazol-5(4H)-one and substituted 4-ethyl azido coumarin 4a-4h in presence of copper ascorbate in THF/water 1:1 for yield of 4-((1-((2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-1-substituted phenyl-1H-1,2,4-triazol-5(4H)-one 6a-6p (coumarinyl-1,2,3-triazolyl-1,2,4-triazolone) and recrystallized from suitable solvents. SARs of these derivatives indicated that the presence of electron donating groups in coumarin ring and phenyl attached 1,2,4-triazole compounds were enhanced the antimycobacterial action against M. tuberculosis. The compounds 4-((1-((6-methyl-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-1-phenyl-1H-1,2,4-triazol-5(4H)-one 6e was recorded as a good antimycobacterial agent against M. tuberculosis at MIC value 1.60 µg/ml individually in comparison to standard drug Pyrazinamide **[21]**.



6e(Ar- phenyl R= 7-CH_3 ; ,6f Ar= phenyl , R=5,6-benzo; 6i Ar= 4-Anisyl ,R= 6-CH_3 ;6j (Ar=4-Anisyl R= 6-Cl; ,6k(Ar=4-Anisyl R= 6-'t'-butyl; ,6l (Ar=4-Anisyl R= 7-CH_3; ,6n(Ar=4-Anisyl R= 5,6-benzo);

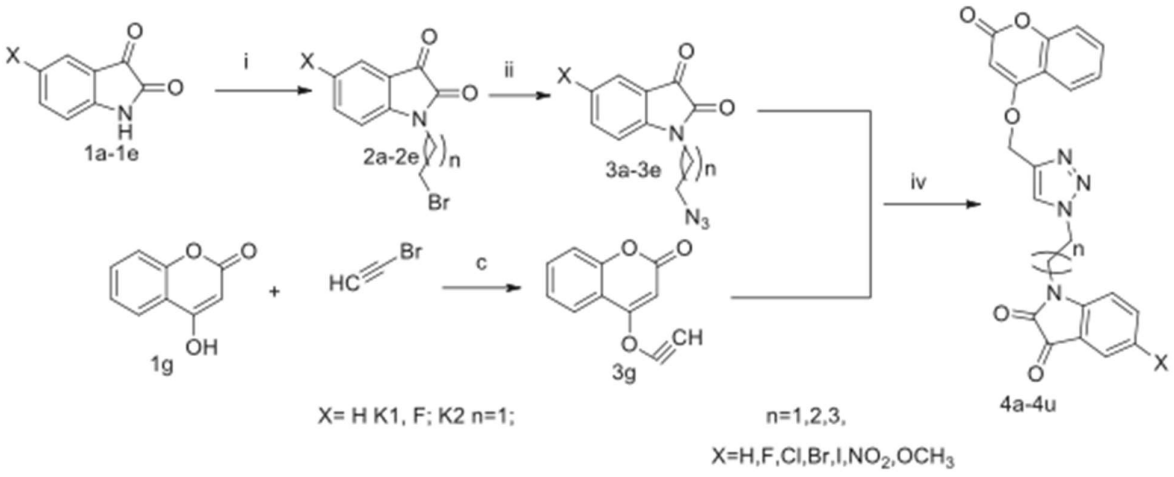
Reagents and conditions: a)Conc.H_2SO_4,0-5^oC b)NaN_3,acetone,water,rt c)NH_2CHO,180^oC d)propargyl bromide, anhydrous K_2CO_3, acetone,rt

Scheme 9 1,2,3-Triazole substituted coumarin derivatives

Synthesis of isatin-triazolyl coumarin derivatives

A series of triazolyl linker isatin-coumarin hybrid molecules were synthesized. In this reaction, the substituted isatin 1a-1e reacted with 1,2-dibromo alkanes using potassium carbonate as base DMF solvent then after resultant intermediate 2a-2e was react with sodium azide in DMF produce 1-(4-azidoalkyl)-substituted isatin 3a-3e. Another reactant 4-(prop-2ynyloxy)-coumarin 3g was further reacted with various derivatives of 1-(4-azidoalkyl)-indolin-2,3-dione in presence of copper sulfate pentahydrate with sodium ascorbate in DMF solution to yield desired target candidates 1-(2-(4-(((2-oxo-2H-chromen-4-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethyl) substituted indoline-2,3-dione hybrids 4a-4u. SARs of these desired derivatives indicate that electron density of the fifth position of isatin remarkable influence of antibacterial action and activity is directly proportional to increase the electronegativity on same position of isatin so order of potency substitution

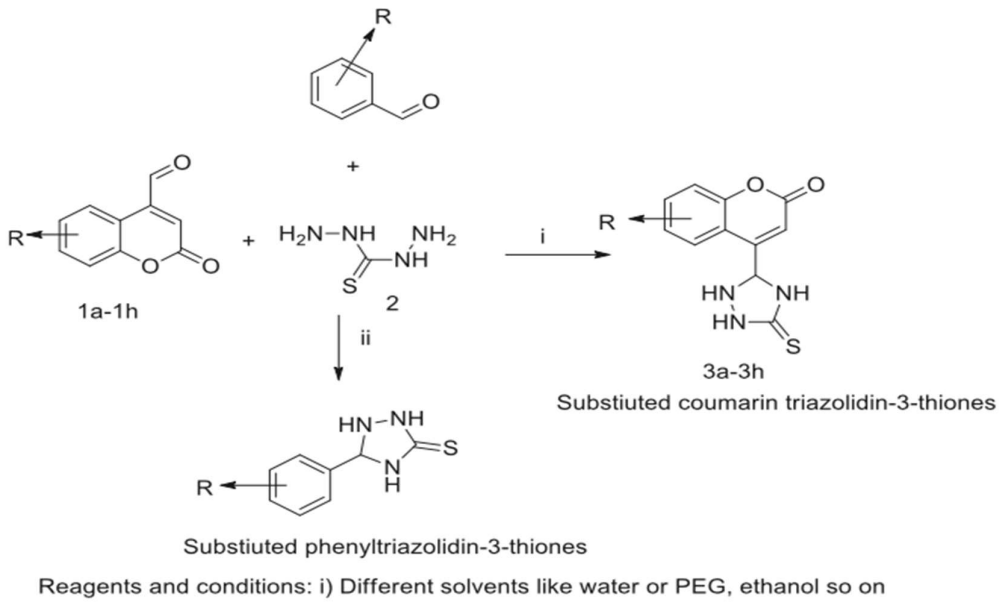
fluro > chloro > bromo > iodo > nitro > metho xy > hydrogen and concerned for linker space carbon length n = 1 > 2 > 3. All the synthesized products were evaluated for their antibacterial potential against bacterial strains E. coli, S. enteric, S. aureus. The compound 1-(2-(4-(((2-oxo-2H-chromen-4-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethyl) indoline-2,3-dione 4a and 1-(2-(4-(((2-oxo-2H-chromen-4-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethyl) 5-fluoro- indoline-2,3-dione 4b had shown as good antibacterial action against S. aureus at the MIC value 30 and 312 µg/mL **[22]**.



Scheme 10 Isatin-triazolyl coumarin derivatives

Synthesis of 4-triazolidin-thione coumarin derivatives

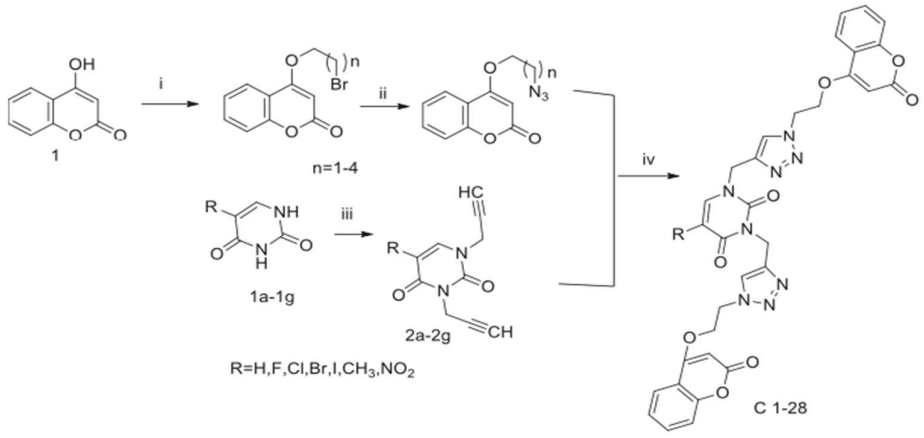
Two series of substituted coumarin containing 1,2,4-triazolidin −3-thione derivatives 3a-3j were synthesised, by the formation of respective semithiocarbazone in nucleophilic addition reaction of semithiocarbazide to electron deficient carbon atom of carbonyl compound of substituted 4- formyl coumarin/benzaldehyde and followed by intramolecular nucleophilic attack of amine (NH2) of thiosemicarbazone to azomethine to liberate the desired target molecules substituted coumarin and phenyl triazolidin-2-thiones. SAR studies of these compounds revealed that substituted phenyl ring replaced by substituted coumarin triazolidin thiones enhanced the antitubercular activity, where as various mono substituted electron donating group like methoxy, methyl, attached either phenyl triazolidine thione or respective coumarin triazolidine thione derivatives had been reported as more potent than disubstituted system. Mono substitution of phenyl ring and coumarin bearing triazolidine thion had been shown a good antimycobacterial action, as the substituted coumarin triazolidin thione methyl, methoxy, 5,6-benzo and 7,8 benzo moderate increases the antibacterial action whereas in phenyl triazolothiones the substituted hydroxy, 5,6-benzo in the phenyl ring enhanced the significant antibacterial action. The compound 7-methoxy-4-(5-thioxo-1,2,4-triazolidin-3-yl)–2H-chromen-2-one 3d was reported as good antibacterial agent against B. subtilis at MIC 0.8 µg/mL in comparison to the standard drug ciprofloxacin **[23]**.



Scheme 11 4-Triazolidin-thione coumarin derivatives

Synthesis of bis triazole uracil based coumarin derivatives

Incorporation of 1,2,3-triazole ring in several drug designing strategies due to its better aromatic stabilization, good binding affinity, isostere of carboxylic group and resistant towards both oxidation and reduction in acidic and alkaline medium. 1,2,3- triazole and its derivatives had been shown with a wide range pharmacological actions. Thus, researchers had more attentions as 1,2,3-triazole ring is tethering agent in drug design. A series of compounds of bis coumarinyl alkyloxy 1,2,3-triazole linker with uracil hybrids C1-28 were designed and synthesized. Antibacterial potentials of these obtained analogues were studied. These compounds were synthesized from 4-(2-azidoethoxy)–2H-chromen-2-one 1. Initially the 4-hydroxy coumarin was dissolved DMSO and followed by addition of dibromoethane in presence of potassium carbonate to obtain alkylated coumarin, which further react with sodium azide in DMSO solution to give 4-(2-azidoethoxy)–2H-chromen-2-one 1. Another reactant, 5-substituted-1,3-di(prop-2-yn-1-yl)pyrimidine-2,4(1H,3H)-dione 2a-2g was prepared by the reaction of substituted uracil 1a-1g with propargyl bromide in the presence of DMF solution as solvent and was used as potassium carbonate at a room temperature. Finally, 3-azidoalkylated coumarin were treated with propargylated uracil in the presence of copper sulfate and sodium ascorbate in DMF solution at room temperature to get the desired target analogues triazole tethered coumarin-uracil hybrids C 1–28. SAR studies of these compounds indicated that the analogues containing substituted uracil were more potent with antibacterial actions than compounds without non-substituted uracil. Thus, compound poses electron withdrawing substituent had shown more inhibitory action, whereas potency decreased with increasing chain carbon length in between two nuclei. Among all the tested candidates, the compound bearing chloro uracil substituted triazolyl ethoxy coumarin C-3 had reported as good antibacterial agent(s) against *E. faecalis, S. aureus, P. aeruginosa and E. coli* at MIC values, 7.23 µg/ml in comparison to the standard drug Levofloxacin **[24]**.



Reagents and conditions: i)Dibrmoalkane, K_2CO_3,DMF, 2h, stir, rt ii)NaN_3,DMF, 1h, stir, rt, iii)propargyl bromide, K_2CO_3,DMF,2h, stir, rt iv)sodium ascorbate, $CuSO_4$,DMF,15min, stir, rt

Scheme 12 Bis-Triazole uracil based coumarin derivatives

DISCUSSION

The present paper is focused on the synthesis of novel heterocyclic compounds as possible antibacterial agents.

The evolving of MDR bacterial strains have spiraled to unbridled notorious standards, due to the accumulation of multidrug resistance in them; surprisingly, one would hardly find a more vivid illustration of any commensal like, the Gram-positive Staphylococcus aureus, which is now the methicillin-resistant S. aureus (MRSA), transforming into a perilous MDR-MRSA with an armamentarium of multidrug resistance, Today 'MDR-MRSA 'is regarded as the ghoulish superbug of the health domain! Thus, the necessity of some newer antibacterial agents to overcome the grievous resistance pattern of MRSA and other bacterial infective agent(s). Additionally, the SAR studies are the coveted corollary, as highlighted in detail.

CONCLUSION

This phyto-compound coumarin, with its congeners would provide a frame for pharmacophore-based drug discovery against bacterial diseases. Herein, a comprehensive review of the various reaction strategies such as, Schiffbase, Azo-dye, Mannich-base, transitional metal complexes, Pechmann condensation and a few more synthetic principles for antibacterial activities are described. These are expected to be beneficial to control MDR bacterial pathogens in the rising demands of antibacterial candidates, from clinicians today. Indeed, these synthetic/semi-synthetic approaches of additions of newer phyto-based modified chemical entities with in vitro inhibitory actions against pathogenic microorganisms; particularly, against MRSA, mycobacteria and several other ghoulish infectious bacteria. Further work is necessary to understand the various signalling unknown mechanisms with mode of administration and pharmacokinetics and dynamic properties in drug development cascades.

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