Review Paper

Volume - 11 | Issue - 08 | August - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Chemical Science

DIFFERENT TYPES OF BIO ACTIVE COUMARIN DERIVATIVES AS PROMISING CANDIDATES FOR ANTI TUBERCULAR THERAPY AND THEIR STRUCTURE ACTIVITY RELATIONSHIP (SAR) STUDIES

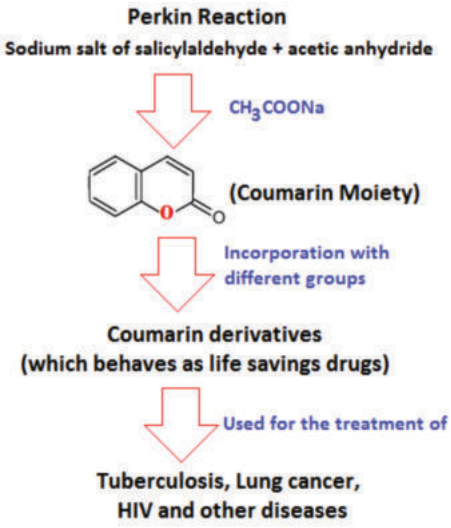
Nilesh Bhattacharya — Department of chemistry, Ramakrishna mission residential college autonomous (Narendrapur).

Suman Bhattacharya* — Ph.D. Senior Scientist, Department of biochemistry and Metabolic Disorders, Sinha Institue Medical Science and Technology, Kolkata-700084, West Bengal, India; Department of Surgery, Columbia University Irving Medical Center, New York, USA. *Corresponding Author

ABSTRACT Tuberculosis is one the most deadliest diseases. In recent years, *Mycobacterium Tuberculosis* showed drug resistance property which is a global threat in recent years. In order to get remedy of this disease, various kinds of novel drugs have been developed. Coumarin is a compound whose chemistry has been widely researched on. Hundreds of its derivatives have been reported from researchers across the globe. Findings amply suggest that coumarin derivatives have novel bioactive utility. Some of them have shown potent anti-TB activity as well. Particularly in a country like India which is still miles away from eradicating TB and the multi-Drug resistant variety, the search for novel compounds continues to attract researchers. This review mainly represents various kinds of bio active Coumarin derivatives as significant anti-TB agents, and their structure activity relationship.

KEYWORDS : Coumarin, Structure activity relationship (SAR), Anti-tubercular derivatives, Minimal Inhibitory Concentrations (MIC), *Mycobacterium tuberculosis* (MTB).

GRAPHICAL ABSTRACT (Structure1)



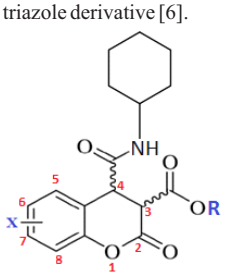
INTRODUCTION:-

Several studies emphasized that natural products are potent and biologically active for the remedy of many diseases. Organic compounds with heterocyclic core shows very good to prominent antimicrobial activity, among which Coumarin is one with oxygen atom showing activity against various diseases like Tuberculosis [1] and others. Coumarin was first isolated from Tonka bean on 1820 by Vogel [2]. In medicinal chemistry, Coumarin is very important molecule, having many biological active derivatives. Some of them showed a very good activity against *Mycobacterium tuberculosis* (MTB). MTB, also known as WHITE PLAGUE which was identified by Robert Koch in 1882 [3]. A person with active tuberculosis disease may be symptom free carrier but once that person comes close to another person then this disease can be spread by cough, sneeze or spit of the active person. Every year a single person with this disease will infect on an average of 10-15 people [4]. It has been reported that there are some frontline agents which have been used for the treatment of TB. Recent development in the formation of different types of Coumarin derivatives also showed good and prominent activity against TB.

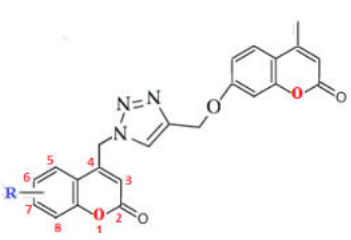
Recently, the report from WHO exhibited that 10.4 million peoples affected and 1.4 million peoples died because of this deadliest disease in the year 2015. This review represents some recent advancement of Coumarin derivatives as anti-TB agents and the structure activity relationship (SAR) studies of these derivatives also could help chemists for making further modification and creating different kinds of Coumarin based anti-TB derivatives.

Coumarin cyclohexyl and Bis-chromenyl triazole compounds against anti TB:-

There are so many cyclohexyl Coumarin derivatives have been synthesized, some of them showed a very much significant antimicrobial activity against *M. bovis*. The structure 1 (i-iii) is the example of cyclohexyl substituted derivative of Coumarin and they are most prominent and most effective among all other cyclohexyl Coumarin derivatives. By considering SAR studies, it has been observed that cyclohexyl substitution at the 4th position showed highest activity against *Mycobacterium Tuberculosis* (MTB). Structue 1 (i,ii,iii) showed anti-TB activity with a same range of MIC level 15.6 µg/ml [5]. In the cyclohexyl Coumarin complex also the R group played an important role as for example if we replaced the isobutyl group by ethyl or methyl group from the structure 1(i) then the activity of the complex towards TB become decreases and the MIC level changes from 15.6 µg/ml to 62.5 µg/ml [5]. As isobutyl group is quite larger as comparison to the methyl or ethyl group, so for the case of isobutyl the lipophilicity and the bio activity of the complex is high in comparison to methyl or ethyl group [5]. Several number of Bis-chromenyl triazole derivatives have been formed among all of them some derivatives showed antimicrobial activity, fungicidal activity and anti tubercular activity [6]. Structure 2 (i-iii) are the example of most active derivatives of Bis-chromenyl triazole, which showed anti tubercular activity in a great way. Synthesis of these derivatives is described by Naik and co-workers. According to the SAR study, it has been observed that benzo fused Coumarin benzo [f] and cholorine (Cl) group at the 6th or 7th position in the Coumarin ring of this derivative produced highly active anti-TB agents (Structure 2. i, ii, iii) [6]. These derivatives showed anti-TB activity with a same MIC level 6.25µg/ml [6]. And this value is exactly comparable with the standard drug streptomycin (STM: MIC level 6.25µg/ml). According to the SAR studies, it can be concluded that chloro and benzo substituents on Coumarin ring boost up anti-TB activity of such kind of choromenyl triazole derivative [6].



1(i-iii)



2(i-iii)

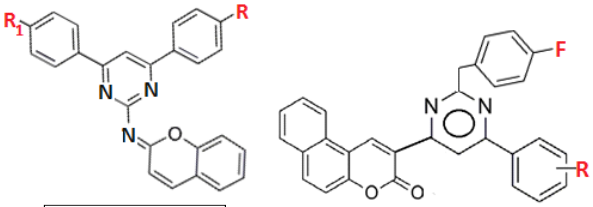
i. X=H, R= Isobutyl; MIC= 15.6 µg/ml
ii. X=6-Br, R= Methyl; MIC = 15.6 µg/ml
iii. X=6-Br, R= 4-Fluorobenzyl; MIC= 15.6 µg/ml

i. R= 6-Cl; MIC = 6.25 µg/ml
ii. R = 7-Cl; MIC = 6.25 µg/ml
iii. R = Benzo [f]; MIC = 6.25 µg/ml

Fig-2: Structure of Coumarin Cyclohexyl 1(i-iii) and Bis-chromenyl triazole 2 (i-iii)

Coumarin based Pyrimidine hybrids as anti-TB agents:-

There are so many different kinds of Pyrimidine derivatives have been synthesized and it has been observed that these derivatives have biological activity including anti tubercular, antibacterial activity [7,8]. There are several number of pyrimidine Coumarin derivatives have been formed and some of them showed excellent anti-TB activity. As for example Structure 3 is the example of pyrimidine Coumarin derivative and it has the growth inhibitory rate 65% against MTB $H_{37}Rv$ at a concentration 6.25 µg/ml [9]. Structure 4, is an example of benzo Coumarin pyrimidine hybrids with fluoro substituent. In structure 4, the R group mention in the ring is methoxy (-OMe) group. SAR studies revealed that according to the position of the methoxy group in the ring, the activity of this derivative become changes. When the methoxy group present at the 4th position of the ring then this derivative (structure 4) shows highest activity [10]. Along with that if some electron withdrawing groups like nitro or any halogen present in the phenyl ring of this derivative then it also showed a great activity against MTB with a MIC level 1.12-3.12 µg/ml [10]. Flourine atom in a drug or fluorinated group into drugs allows simultaneous modulation of electronic, steric, lipophilic parameters which can influence both the pharmacodynamics and pharmacokinetics properties of drugs [10,11] as for example the structure 4 is a benzo Coumarin Pyrimidine derivative with fluorine substituent. This derivative also showed a great activity against MTB $H_{37}Rv$ [10].



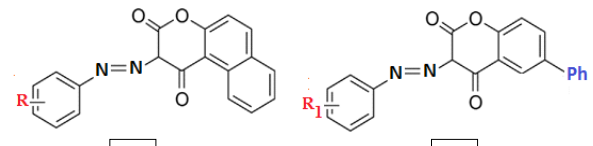
3
R= OMe, R1= NO_2

4
R = 4- OMe

Fig-3: Structure of Coumarin based pyrimidine Derivatives.

Coumarin hydrazide derivatives as anti-TB agents:-

Some hydrazide derivatives of Coumarin are biological active and showed antimicrobial activity. The molecule 5 and 6 were synthesized to examine their Anti TB by Shah et al [12]. SAR studies revealed that when some electron withdrawing groups like nitro (-NO_2) or chlorine (-Cl) present at the 4th position of the phenyl ring then it produce highly active anti tubercular agents. The structure 5 showed activity against MTB $H_{37}Rv$ with a rate of growth inhibitory 94% on the other hand compound 6 showed anti-TB activity against MTB $H_{37}Rv$ with a rate of growth inhibitory 88% [12]. These result are slightly lesser than the front line anti-TB drugs rifampicin (RIF ; growth inhibitory rate 97%). But on the other hand if the electron withdrawing group is replaced by some electron donating groups like methoxy (-OMe) or methyl (-Me) groups from the structure 5 then the activity of this derivative decreases largely [12]. The derivative 6 is obtained by changing benzo fused ring from the structure 5, and this compound (structure 6) is synthesized or modified to observe the activity against TB. So in the new structure 6, there is a substitution of phenyl ring at the 6th position of the Coumarin ring. Further it has been observed that in structure 6, by placing different groups like (nitro, methyl, chlorine) in the phenyl ring in the position of R_1, no fruitful results were found [12]. This indicates for this particular compound present of bulky groups in Coumarin moiety is not effective against tuberculosis.



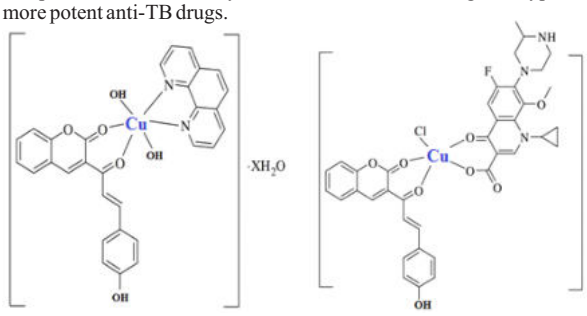
5 **6**

Fig-4: Pictorial representation of Coumarin hydrazide derivatives

Coumarin derivatives coordinate with metal ions formed anti-TB agents:-

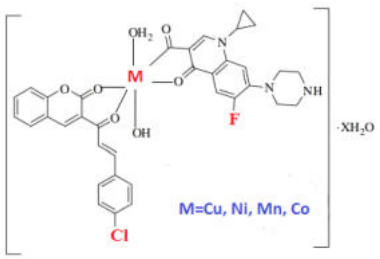
There are so many metal ions are present in the different kinds of Coumarin complex and it is evident that the metal ion increases the activity of the complex [13]. Coumarin as well as different kinds of heterocyclic group behaves as ligand and coordinates with the metal ions [14]. According to the literature data, it has been observed that Coumarin with attachment of some transition metals formed some coordinate complex and which was extremely bio active more specifically they have antimicrobial activity. Patel and co workers described the synthesis of some Coumarin based mixed ligand complex with copper ion. In structure no 7 there is an example of Coumarin based ligands and 1,10-phenanthroline coordinates with copper metal and which showed moderate effect against TB and these results were compared with some frontline anti-TB drugs like isoniazid (INH), rifampicin (RIF) and ethambuthol (EMB). Here the copper metal enhances the activity of the Coumarin based complex molecule against MTB $H_{37}Rv$ with a MIC of 30 µg/ml (structure 7). And such kind of Coumarin derivative with the metal ion copper(II) showed growth inhibitory 86% [15]. The structure 8 is an example of Coumarin based mixed ligand and gatifloxacin both are coordinate with the metal ions and form complexes which showed anti-TB activity [15]. In this kind of complex, Copper or Nickel metal can be present as metal ions. But in this case the Coumarin derivative with copper metal showed more activity against MTB as comparison to the complex with Ni metal, structure 8 with copper ion showed anti-TB activity with 99% growth inhibitory at a concentration 0.25 µg/ml and the same complex coordinates with nickel ion showed anti-TB activity with 98% growth inhibitory at a concentration 0.35 µg/ml [16]. Further in the structure 9, a Coumarin based mixed ligand and Ciprofloxacin coordinate with different kinds of metal ion like Ni(II), Cu(II), Mn(II), Co(II) and all of them are quite effective antimicrobial drugs and very much potent against TB [15].

So here some of the Coumarin based derivatives were mentioned and it is observed that their activity increases with the presence of different kind of metal ions and such kind of enhancement in activity may be due to increase in lipophilicity of the complex [17]. Here also it is observed that some ligands specially Coumarin based ligands coordinate with different metal ions and formed highly potent anti tubercular agents. So as a whole synthesis of such kind of derivatives is quite interesting and it gives a fruitful results and it is obvious that such types of complexes would definitely attract chemists for making new types of more potent anti-TB drugs.



7
MIC (MTB)= 30 µg/mL

8
MIC (MTB)= 0.25µg/mL



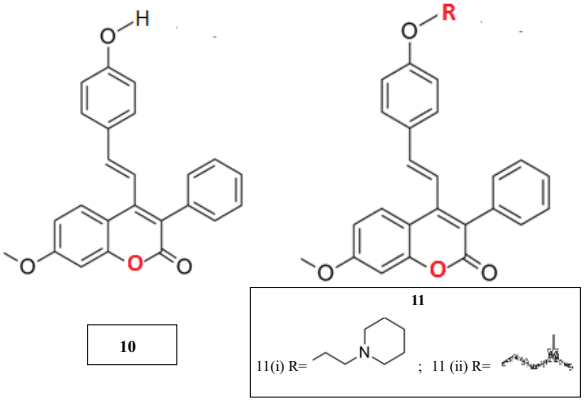
9
MIC (MTB)= 25 µg/mL

Fig-5: Different structures of Coumarin derivative coordinate with transition metal ions

Coumarin Chalcones as anti-TB agents:-

Chalcone Coumarin hybrids are effective biological active compounds

exhibiting anti tumor [18], anti bacterial [19], anti malarial [20], anti TB [21] etc. Structure 10 is an example of chalcone Coumarin it showed a moderate activity against MTB with MIC level 30µg/ml [22]. Further by using SAR studies, structure 11(i) and 11(ii) have been synthesized by aminoalkylation in the structure 10. It has been observed that structure 11(i) and 11(ii) showed a promising activity against MTB. Structure 11(i) active against TB with a MIC level 3.5µg/ml and structure 11(ii) showed anti-TB activity with a MIC level 7.5µg/ml [22]. This result is quite comparable with some frontline anti TB drugs like rifampicin (RIF) and streptomycin (STM), but this kind of chalcone Coumarin showed some amount of cytotoxicity in kidney cell line (HEK-293) [22]. According to the SAR studies it has been observed that structure 11(i) is more prominent and most active Coumarin chalcone derivative with a very high selectivity rate. On the other hand structure 10 is a conformationally restricted chalcones and it has a greater selectivity rate. So as a whole chalcone Coumarin derivatives showed a significant activity against MTB. Also such kind of synthesis, modifications and their structure activity relationship studies may further help chemists to make more potent anti-TB drugs.

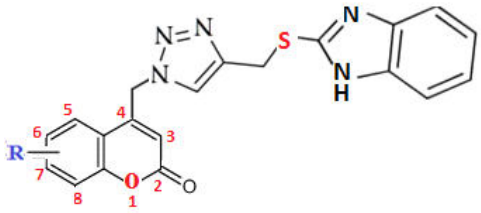


10

Fig-6: Chalcone-Coumarin derivative

Imidazole Coumarin derivatives as anti-TB agent:-

Imidazole Coumarin hybrids have some biological properties and also this kind of derivatives played a great role on anti-TB activity [23,24]. By considering SAR studies, different types of imidazole Coumarin derivatives have been synthesized by adding different groups in Coumarin moiety. Among them some derivatives have in vitro anti-TB activity against MTB $H_{37}Rv$. Fig 7 Structure-12 (i-v) are the example of imidazole Coumarin derivatives. These derivatives showed a significant ant-TB activity. SAR studies revealed that the activity of the imidazole Coumarin derivatives depends on the R group present in the Coumarin ring of the complex. When the R group is methyl (-Me), may be present at the 6^{th} or 7^{th} position (structure 12. i, ii) of the coumarin ring in the complex, then this derivative showed anti-TB activity with same MIC level 7.7×10^{-6}mol/Lit [25]. When two methyl groups present in the Coumarin ring at the 5^{th}, 7^{th} or 7^{th}, 8^{th} (structure 12. iii, iv) position of this derivative, then this compound showed better activity than the previous mono methylated imidazole Coumarin compound. The di-methylated imidazole Coumarin complex showed anti-TB activity with a MIC level 3.8×10^{-6}mol/Lit [25].



12

i)R= 6-Me; ii) R= 7-Me

iii)R= 5,7-Me; iv)R= 7,8-Me; v)R= 7-Cl

Fig-7: Structure of Imidazole-Coumarin derivative

And this result is far better than the standard drug pyrazinamide (PZA). There is another good example of imidazole Coumarin derivative that is chlorine (Cl) at the 7^{th} position of the Coumarin ring example structure 12(v). This derivative also showed a prominent activity against MTB $H_{37}Rv$ with a MIC level 7.3×10^{-6} mol/Lit but in place of chlorine if we placed any donating group like methoxy (-OMe) then the activity of the derivative decreases in a high rate [25]. Except these highly active derivatives there are so many imidazole Coumarin derivatives have been synthesized but they all have moderate activity against MTB.

CONCLUSION:-

Tuberculosis which is caused by the Tubercle Bacilli bacteria is one of the most dangerous diseases throughout the world. Various TB strains exhibit resistant property. In this context, it should be mentioned here that due to this resistant property of various TB strains, which is exemplified by MDR-TB, XDR-TB, TDR-TB the so called first line anti TB drugs are still ineffective. Several researchers have found that the second line of anti-TB agents exhibit more toxic effects rather than its efficacy against the drug resistant strains. So here in this review article, we are trying to emphasized that synthesis or development of new anti-TB agents could be widely use for the treatment of both drug-susceptible and drug resistance TB strains.

Several number of Coumarin derivatives have been synthesized by using Coumarin moiety which includes cyclohexyl Coumarin derivative [5], Pyrimidine Coumarin,[9,10], Coumarin hydrazide [12], Chalcone Coumarin [22], Imidazole Coumarin,[23,24,25]. Among them some are extremely good against TB whereas some of the derivatives showed moderate activity against TB. Several studies also investigated that further modification in these Coumarin derivatives could be more potent and effective against both the drug-susceptible and drug-resistant TB strains. By using these modified Coumarin derivatives it could be possible to reduce the length of the TB therapy.

Here, we seek to highlight various types of Coumarin derivatives which are not only more potent but also exhibit the anti-TB activity through the inhibition of growth rate against MTB and also discussed structure activity relationship of these various Coumarin derivatives, this SAR studies will be very much helpful to chemists for new thoughts or new modification in the Coumarin derivatives to make them more potent and more active against tuberculosis.

ABBREVIATIONS:

TB	tubercle bacillus
MTB	mycobacterium tuberculosis
MDR-TB	multi-drug resistant tuberculosis
MIC	minimal inhibitory concentration
MDR	multidrug resistant
M. bovis	mycobacterium bovis
INH	isoniazid
EMB	ethambuthol
PZA	pyrazinamide
RIF	rifampicin
STM/SM	streptomycin
R-MTB	replicating mycobacterium tuberculosis
NR-MTB	non replicating mycobacterium tuberculosis
XDR-TB	extensively drug-resistant tuberculosis
TDR-TB	totally drug resistant tuberculosis
WHO	world health organization
SAR	structure activity relationship
HIV	human immunodeficiency virus
SI	selectivity index

REFERENCES

1. P. Kaur, R. Arora, N.S Gill, Review on oxygen heterocycles, Indo Am. J. Pharma. Res. 3 (2013) 9067-9084.
2. G. Feuer in "Progress In medicinal Chemistry" Edited by G.P. Eillis and G.B. West North Holland (NY), 1974, 10, 86.
3. J.M. Grange, eds Schaaf S, Zumla AI. In *Tuberculosis*: A Comprehensive Clinical Reference.Saunders 2009; 44-59.
4. Tuberculosis (online), http//www.scidev.net, TB and HIV Coinfection, CDC NCHSTP Division of Tuberculosis Elimination.
5. A. H. Rezayan, P. Azerang, S. Sardari, A. Sarvary, Synthesis and biological evaluation of coumarin derivatives as inhibitors of *mycobacterium bovis* (BCG), Chem. Biol. Drug Des. 80 (2012) 929-936.
6. R. J. Naik, M. V. Kulkarni, K. S. R. Pai, P. G. Nayak, Click chemistry approach for bis-chromenyl triazole hybrids and their antitubercular activity, Chem. Biol. Drug Des. 80 (2012) 516-523.
7. A.A. Siddiqui, R. Rajesh, M.U. Islam, V. Alagarsamy, S.N. Meyyanathan, B.P. Kumar, B. Suresh, Acta Pol. Pharm. 64 (2007) 17e26.
8. A.H. Bacelar, M.A. Carvalho, M.F. Proença, Eur. J. Med. Chem. 45 (2010) 3234e3239.
9. A.A. Siddiqui, R. Rajesh, M.U. Islam, V. Alagarsamy, E.D. Clercq, Arch. Pharm. Chem. Life Sci. 340 (2007) 95e102.
10. D.S. Reddy, K.M. Hosamani, H.C. Devarajegowda, Eur. J. Med. Chem. 101 (2015) 705e715.
11. R. Ruzziconi, F. Buonerba, J. Fluor. Chem. 152 (2013) 12e28.
12. A. Manvar, A. Bavishi, A. Radadiya, J. Patel, V. Vora, N. Dodia, K. Rawal, A. Shah,. Bioorg. Med. Chem. Lett. 21 (2011) 4728e4731.
13. Z. A. Siddiqi, M. Khalid, S. Kumar, M. Shahid, S. Noor, Antimicrobial and SOD

activities of novel transition metal complexes of pyridine-2,6-dicarboxylic acid containing 4-picoline as auxiliary ligand, Eur. J. Med. Chem. 45 (2010) 264-269.
14. S. Delaney, M. Pascaly, P.K. Bhattacharya, K. Han, J.K. Barton, Oxidative damage by ruthenium complexes containing the dipyridophenazine ligand or its derivatives: A focus on intercalation, Inorg. Chem. 41 (2002) 1966-1974;
15. Rangappa S Keri , B S Sasidhar , Bhari Mallanna Nagaraja , M Amélia Santos. Recent progress in the drug development of coumarin derivatives as potent antituberculosis agents. Eur J Med Chem 2015 Jul 15;100:257-69.
16. J. Patel, H. Dholariya, K. Patel, J. Bhatt, K. Patel, Cu(II) and Ni(II) complexes of coumarin derivatives with fourth generation flouroquinolone: Synthesis, characterization, microbicidal and antioxidant assay, Med. Chem. Res. 23 (2014) 3714-3724
17. K. S. Patel, J. C. Patel, H. R. Dholariya, V. K. Patel, K. D. Patel, Synthesis of Cu(II), Ni(II), Co(II), and Mn(II) complexes with ciprofloxacin and their evaluation of antimicrobial, antioxidant and antitubercular activity, Open. J. Metal 2 (2012) 49-59.
18. P.S. Bhale, H.V. Chavan, S.B. Dongare, S.N. Shringare, Y.B. Mule, S.S. Nagane, B.P. Bandgar, Bioorg. Med. Chem. Lett. 27 (2017) 1502e1507.
19. R. Kant, D. Kumar, D. Agarwal, R.D. Gupta, R. Tilak, S.K. Awasthi, A. Agarwal, Eur. J. Med. Chem. 113 (2016) 34e49.
20. A.W. Salae, O. Chairerk, P. Sukkoet, T. Chairat, U. Prawat, P. Tuntiwachwuttikul, P. Chalermglin, S. Ruchirawat, Photochem. 135 (2017) 135e143.
21. R.H. Hans, E.M. Guantai, C. Lategan, P.J. Smith, B.J. Wan, S.G. Franzblau, J. Gut, P.J. Rosenthal, K. Chibale, Bioorg. Med. Chem. Lett. 20 (2010) 942e944.
22. I. Ahmad, J.P. Thakur, D. Chanda, D. Saikia, F. Khan, S. Dixit, A. Kumar, R. Konwar, A.S. Negi, A. Gupta, Bioorg. Med. Chem. Lett. 23 (2013) 1322e1325.
23. X. L. Hu, Z. Xu, M. L. Liu, L. S. Feng, G. D. Zhang. Recent developments of coumarin hybrids as anti-fungal agents. *Curr. Top. Med. Chem.* 17 (2017) 3219-3231
24. XiaohongJin , Yan Xu , Xuhong Yang , Xiuling Chen , Minghu Wu , Jianguo Guan , Lianshun Feng. Design, Synthesis and In Vitro Anti-microbial Evaluation of Ethylene/ Propylene-1H-1,2,3-Triazole-4-Methylene-tethered Isatin-coumarin Hybrids. Curr Top Med Chem 2017;17(29):3213-3218.
25. A. Anand, M. V. Kulkarni, S. D. Joshi, S. R. Dixit. One pot Click chemistry: A three component reaction for the synthesis of 2-mercaptobenzimidazole linked coumarinyl triazoles as anti-tubercular agents. Bioorg. Med. Chem. Lett. 26 (2016) 4709-4713.