

A REVIEW ON MEDICINAL IMPORTANCE OF ISATIN SCAFFOLDS WITH ANTI-MYCOBACTERIAL ACTIVITY

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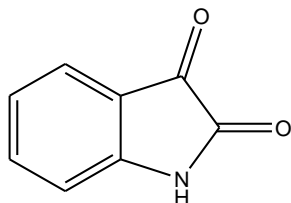
ABSTRACT:-

Isatin consist of 1H indole 2,3diones it is an important class of a heterocyclic compounds. Isatin analogues (or) scaffold have a wide variety of strong interest in synthesis and pharmacological activity. Isatin and its derivatives posses anti-tuberculosis or anti-mycobacterial activity. Tuberculosis is rapid growing diseases. Many Isatin scaffold are more potent then reference drug. This review aims of highlighting the diverse biological activity of Tuberculosis by Isatin scaffold

KEYWORD: ANTI-MYCOBACTERIA,MTB H37Rv, MDR-TB, ISATIN, TUBERCLOSIS,

INTRODUCTION:-

Isatin consist of 1H indole 2,3diones is important class of a heterocyclic compounds. Isatin moiety is privilaged Scaffold's for a chemical modification and is responsible for a broad spectrum and a wide variety of biological and pharmacological activity.¹



According to the latest World Health Organization (WHO) report, tuberculosis (TB) is the ninth leading cause of death throughout the world and the leading cause from a single infectious agent, ranking above HIV/AIDS. There was around 10.4 million people fell ill with TB in the year 2019, resulting 1.67 million deaths TB globally.² The new virulent forms of Mycobacterium tuberculosis (MTB) is a species of pathogenic bacteria in the family Mycobacteriaceae. Mycobacterium tuberculosis has an waxy coatngan its cell surface primarily due to the presence of mycolic acid. Mycobacterium can appear either gram positive and gram negative.

Pathophysiology of tuberculosis:-

The spread of the disease and it is believed that tuberculosis can be spread by sharing food or water, hugging or kissing, sharing toothbrushes, skin contacts like shaking hands, or touching toilets seats.It can spread only through the air droplets containing Mycobacterium that are released by the infected person while coughing, sneezing, singing, or talking. The pathogenesis of Mycobacterium

tuberculosis is illustrated in Fig. 1. M. Tuberculosis from the active TB patient enter the respiratory tract of the host, it crosses the first line mucociliary defence system to reach the alveoli. The second line innate immune mechanism of the alveolar macrophages becomes active and destroys some of the tubercular bacilli, while a few still manage to survive and start replicating at a faster rate, migrating to the other organs. This induces the formation of granulomas where the bacilli are trapped and replicate slowly, thus entering into a latent state of tuberculosis (LTBI). Fig.2.

Reactivation of tuberculosis may occur due to certain factors like HIV infection, smoking addiction, renal failure, diabetes mellitus, drug addiction, chemotherapy, sepsis, malignancy, malnutrition cancer, and immunosuppressive medications that weaken the immunity of the host. When the immune system is weak, the immune cells become unable to hold the uncontrolled bacterial replication, thereby spreading the infection to the bloodstream and other organs including the brain making the host symptomatic, and the patient is said to have active TB disease.³

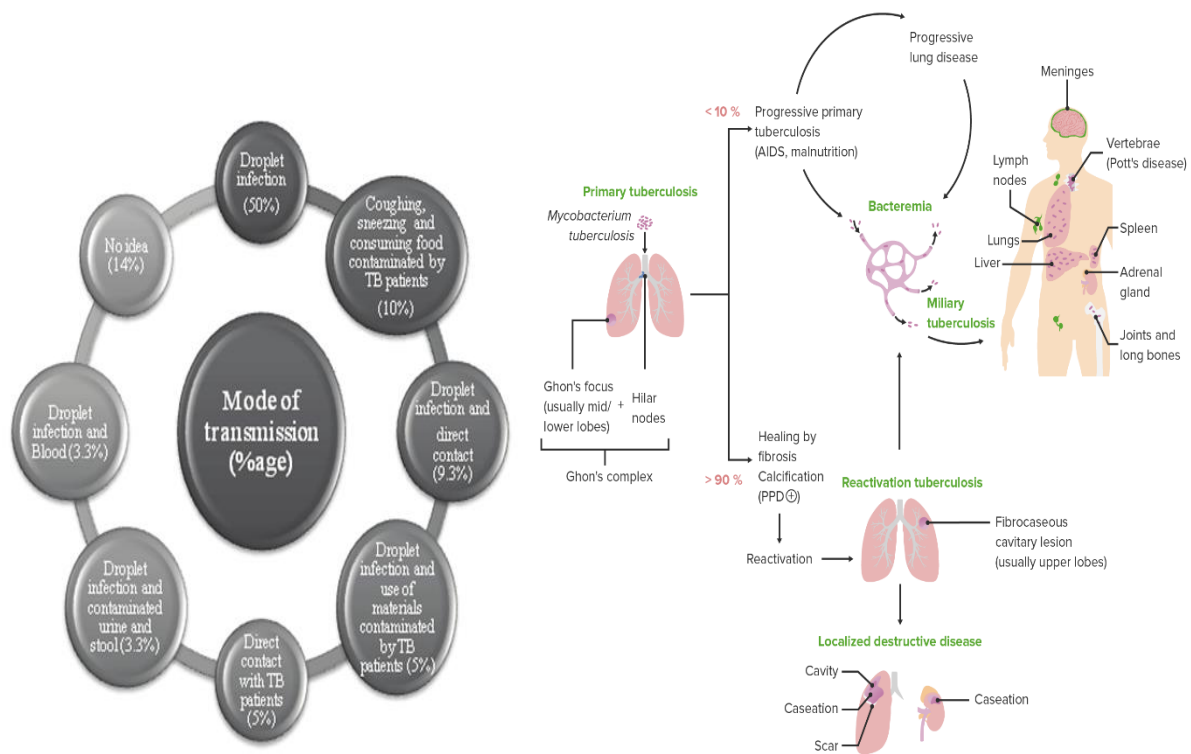


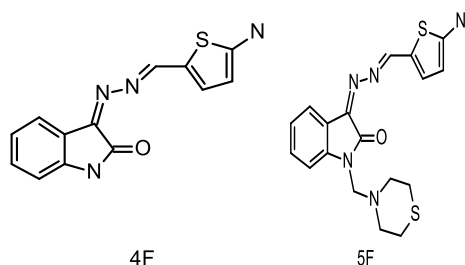
Fig1:- Transmission of Tuberculosis

Fig2:- Entering mycobacterium tuberculosis in humanbody

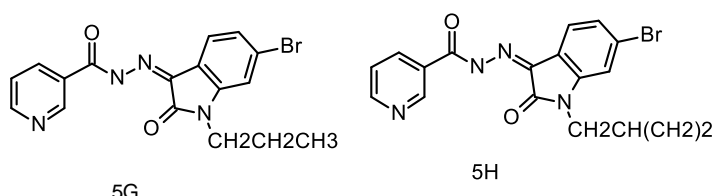
MEDICINAL IMPORTANCE OF ISATIN SCAFFOLDS WITH ANTI-MYCOBACTERIAL ACTIVITY:-

SivanandhanKarunanidhi et al (2021)⁴The compounds were initially screened for their anti-mycobacterial activity against the H37Rv strain of Mycobacterium tuberculosis (MTB) under level-I testing. 4f and 5f emerged as the most potent compounds with IC50 of 3.6 μM and 1.9 μM against RIFR1 MTB strain, followed by INH-R1 MTB strain with IC50 of 3.5 μM and 3.4 μM, respectively.

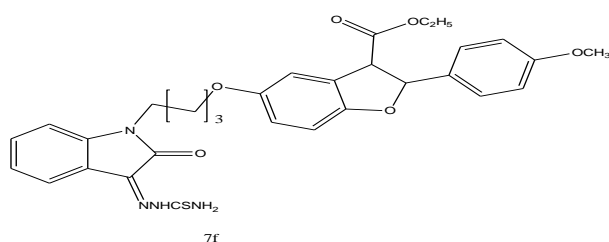
Against FQ-R1 MTB strain, the lead compounds 4f and 5f displayed excellent inhibition at IC₅₀ 5.9 μ M and 4.9 μ M, it indicating broad spectrum of activity.



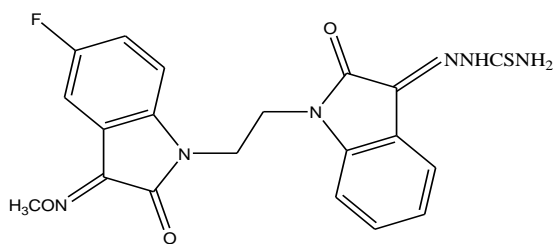
Zainab M. Elsayed et.al (2021)⁵The novel isatin-nicotinohydrazide hybrids as promising anti-tubercular. where compounds 5g and 5h showed excellent activity (MIC $\frac{1}{4}$ 3.9 mg/mL). Moreover, the target hybrids were examined against six bronchitis causing-bacteria. K. pneumonia emerged as the most sensitive strain with MIC range: 0.49–7.81 mg/mL.



Yaohuan Zhang et.al (2018)⁶A series of novel of all benzofuran-isatin-hydroxyimine/-thiosemicarbazide hybrids exhibited considerable in vitro anti-mycobacterial activities against the tested three MTB strains, and all hybrids (MIC: <0.06–0.062 μ g/mL) except 7i were more potent than the first-line anti-TB agents INH and RIF (MIC: 0.078 μ g/mL), and nine of them 7a, 7b, 7e–h and 7j–l (MIC: <0.06 μ g/mL) were comparable to the parent compound TAM16 (MIC: <0.06 μ g/mL). The most active hybrid 7f (MIC: <0.06, 0.22 and 0.86 μ g/mL, respectively) was >4.8 folds more potent than RIF and INH against both drug-sensitive MTB H37Rv and MDR-TB isolates.

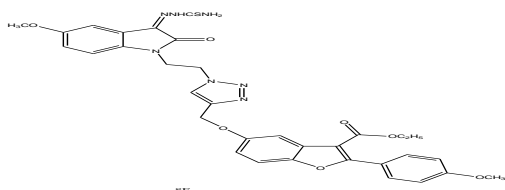


Yan Xua et.al (2018)⁷A series of novel homonuclear and heteronuclearbis-isatin derivatives tethered through ethylene were designed, evaluated for their in vitro anti-mycobacterial activities against MTB H37Rv and MDR-TB. All hybrids exhibited potential anti-mycobacterial activities against MTB H37Rv and MDR-TB with MIC ranging from 16 to 256 μ g/mL. In particular, the heteronuclearbis-isatin 4i (MIC: 25 and 16 μ g/mL) was most active against MTB H37Rv and MDR-TB strains, and could act as a lead for further optimization.



4i

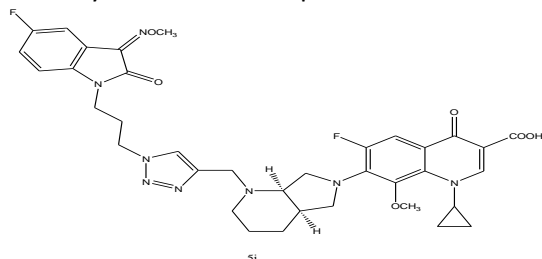
Feng Gao et.al (2018)⁸ A novel benzofuran-isatin hybrids, and in vitro evaluation of their anti-mycobacterial activity against both drug-susceptible and multi-drug resistant (MDR) Mycobacterium tuberculosis (MTB) strains. In parallel, cytotoxicity of these hybrids was also tested in VERO cells. Preliminary results indicated that all hybrids with acceptable cytotoxicity in VERO cells (CC50: 128- >1,024 $\mu\text{g}/\text{mL}$) exhibited considerable anti-mycobacterial activities against MTB H37Rv and MDR-TB with MIC ranging from 0.25 to 8 $\mu\text{g}/\text{mL}$. It is worth noting that hybrid 8f with no cytotoxicity towards VERO cells (CC50: >1,024 $\mu\text{g}/\text{mL}$) was found to be the most active compound (MIC: 0.25 and 0.5 $\mu\text{g}/\text{mL}$) against MTB H37Rv and MDR-TB strains. Comparing to the first-line anti-tuberculosis agents rifampicin and isoniazid, hybrid 8f has shown over two magnitude more active against MDR-TB.



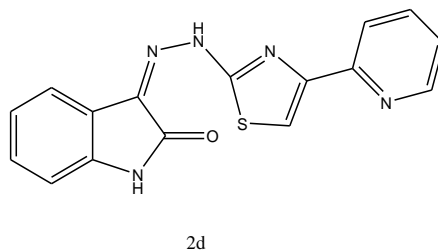
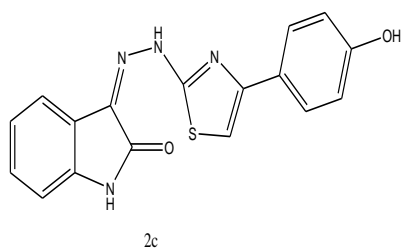
8f

Xinjia Yan et.al (2017)⁹ novel substituted isatin-propylene-1H-1,2,3-triazole-4-methylene-moxifloxacin hybrids 5a-l were designed. Mycobacterium tuberculosis as well as cytotoxicity in VERO cell line. All hybrids exhibited excellent activities against two Mycobacterium tuberculosis strains with minimum inhibitory concentration in the range from 0.05 to 2.0 $\mu\text{g}/\text{mL}$. The most active hybrid 5i was 2-8 times more potent than the reference agents (moxifloxacin and rifampicin) in vitro against Mycobacterium tuberculosis H37Rv, while 2->2,048 times more potent than the reference agents (moxifloxacin, rifampicin and isoniazid) in vitro against multidrug-resistant Mycobacterium tuberculosis. However, all hybrids (the 50% cytotoxic concentration/CC50: 2-32 $\mu\text{g}/\text{mL}$) were much

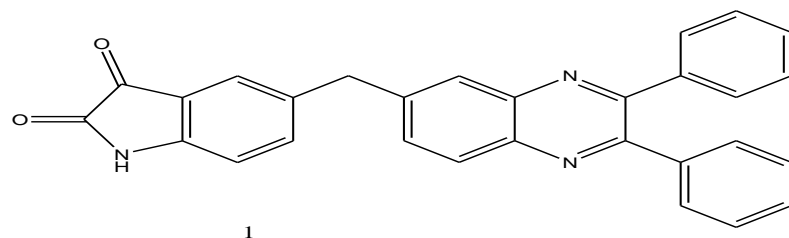
more cytotoxic than the parent moxifloxacin (CC50: 128 $\mu\text{g}/\text{mL}$) against VERO cell line



Leyla Yurttas et.al (2017)¹⁰A series of 3-[(4-aryl-2-thiazolyl)hydrazone]-1H-indol-2,3-dione derivatives (2af) were designed and synthesized using isatin as starting material. The obtained thiazole compounds were screened to investigate their antituberculosis activity against Mycobacterium tuberculosis H37RV (ATCC 27294). Among them, two compounds 2c and 2d were displayed antitubercular potential two-fold greater than standard drugs.

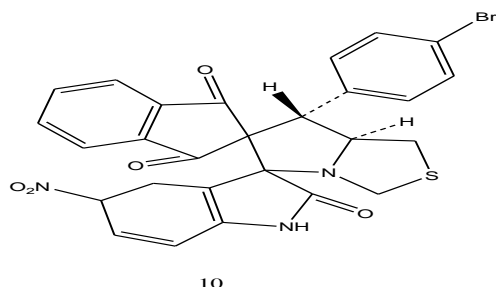


U. Usha Rani et.al (2017)¹¹Heterocyclic compounds are very much used as therapeutic agents. Indole, an important class of nitrogen, containing heterocyclic with wide variety of biological activities. Isatin is a derivative of indole which is indole-2, 3 Dione. Isatin is reported for antitubercular activity. Quinoxaline is also reported for various biological activities. So, a scheme was designed and isatin incorporated quinoxaline were prepared to improve biological activity. In the present research isatin incorporated quinoxaline (1, 1A, 1B and 1C) were prepared, and were characterized by using TLC, IR, NMR and MASS spectral data. They were evaluated for anti-tubercular activity. Among those derivatives, compound 1 showed good activity.

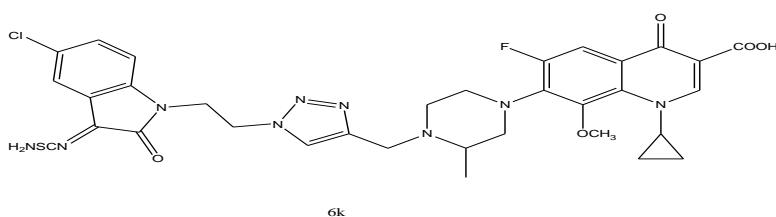


Ruslan Gr. Redkin et.al (2017)¹²The interaction of isatins, α -amino acids and 1,6-bismaleimido-hexane has been studied. This method has the advantages of mild reaction conditions, high atom economy and excellent yields. The most suitable conditions for this reaction are boiling alcohol-water

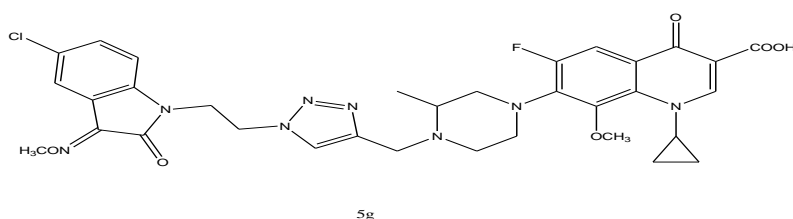
medium. The obtained compounds showed a weak selective antimicrobial activity for the Micrococcaceae family

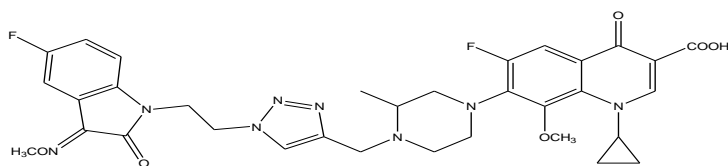


ZhiXu et.al (2017)¹³ A Set of novel gatifloxacin -1H -1,2,3-triazole-isatin hybrid 6a-L was designed, Synthesized and evaluated for their invitroantimycobacterial activity against M.Tuberculosis (MTB) H₃₇Rv And MDR-TB as well as cytotoxicity. The results showed that all the targets (MIC:0.025-3.12µG/ml) exhibited excellent inhibitory activity against MTB H₃₇Rv and MDR-TB, but were much more toxic (CC₅₀ 7.8-62.5 µg/ml) was 2-32 times more potent invitro then the reference compound.



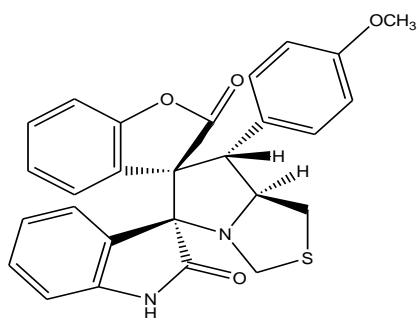
ZhiXua et.al (2017)¹⁴ Twelve novel 1H-1,2,3-triazole-tethered gatifloxacin (GTFX) isatin conjugates 5a-l with greater lipophilicity compared with GTFX were designed, synthesized and evaluated for their in vitro anti-mycobacterial activities against M. tuberculosis (MTB) H37Rv and MDR-TB as well as cytotoxicity. The preliminary results showed that all the targets (MIC: 0.10-8 µg/mL) exhibited excellent inhibitory activity against MTB H37Rv and MDR-TB, but eight of them (CC50: 7.8-62.5 µg/mL) were much more toxic than the parent GTFX (CC50: 125 µg/mL). Among them, 5g (MIC: 0.10 µg/mL) was 4-8 times more potent in vitro than the references GTFX (MIC: 0.78 µg/mL) and RIF (MIC: 0.39 µg/mL) against MTB H37Rv, but less active than INH (MIC: 0.05 µg/mL). The most potent 5g and 5h (MIC: 0.25 µg/mL) were 4->512 times more active than the three references (MIC: 1.0->128 µg/mL) against MDR-TB.



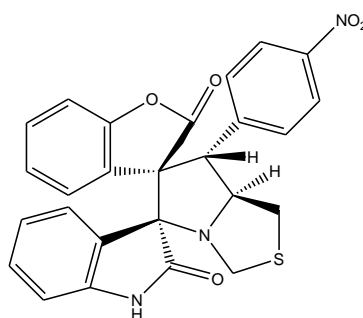


5h

ChouroukMhiri et.al (2015)¹⁵ A new potent antitubercular agents, a series of novel dispirooxindolopyrrolidines and dispirooxindolopyrrolothiazoles have been synthesized via a three-component 1,3-dipolar cycloaddition of (Z)-3-arylidenebenzofuran-2-ones, substituted isatin derivatives and α -aminoacids. All the target heterocycles were evaluated for in vitro antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain and the most active compounds were subjected to cytotoxicity studies against (RAW 264.7) cell lines. Among them, The compounds showed potent anti-tubercular activity with MIC ranging from 1.56 to 6.25 $\mu\text{g}/\text{mL}$. In particular dispirooxindolopyrrolothiazole derivatives 5c and 5f were found to be the most active (MIC of 1.56 $\mu\text{g}/\text{mL}$) with a good safety profile (27.53 and 20.74% at 50 μM , respectively). This is the first report demonstrating the benzofuranoneoxindole hybrids as potential antimycobacterial agent

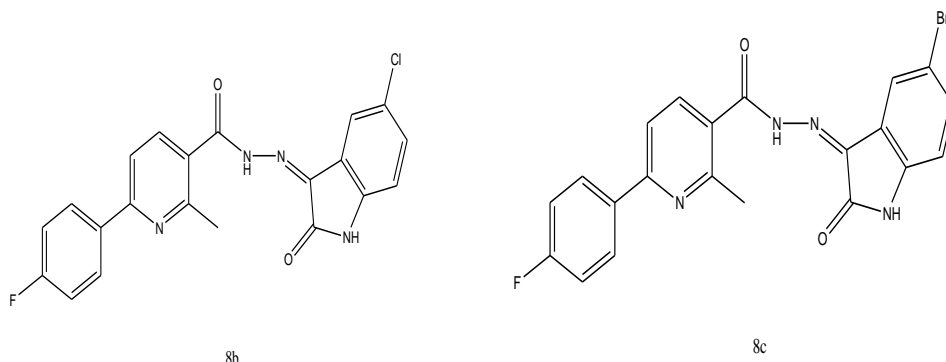


5c

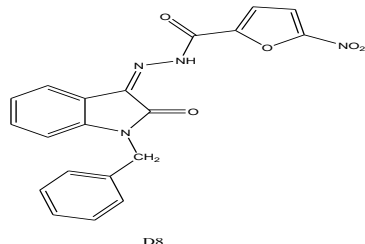


5f

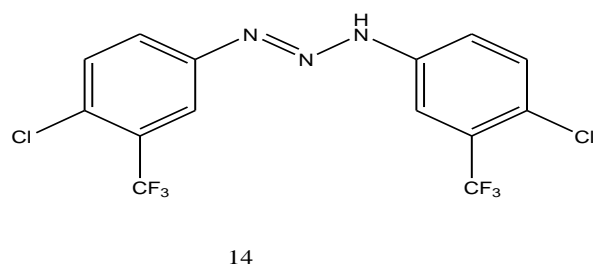
Wagdy M. Eldehna et.al (2015)¹⁶ Three series of 6-aryl-2-methylnicotinohydrazides 4a–i, N'-arylidene-6-(4-bromophenyl)-2-methylnicotino hydrazides 7a–f, and N'-(un/substituted 2-oxindolin-3ylidene)-6-(4-fluorophenyl)-2-methylnicotinohydrazides 8a–c were synthesized and evaluated for their potential in vitro antimycobacterial activity against *M. tuberculosis*. The results showed that isatinhydrazides 8a–c are remarkably more active than the parent hydrazide 4c. Hydrazides 8b and 8c exhibited the highest activity among all the tested compounds (MIC = 12.5 and 6.25 $\mu\text{g}/\text{mL}$, respectively. Besides, 8b and 8c showed good drug-likeness scores of 0.62 and 0.41, respectively. Those two isatinhydrazides could offer an excellent framework for future development to obtain more potent antitubercular agents. The SAR study suggested that lipophilicity of the synthesized derivatives is a crucial element that accounts for their antimycobacterial.



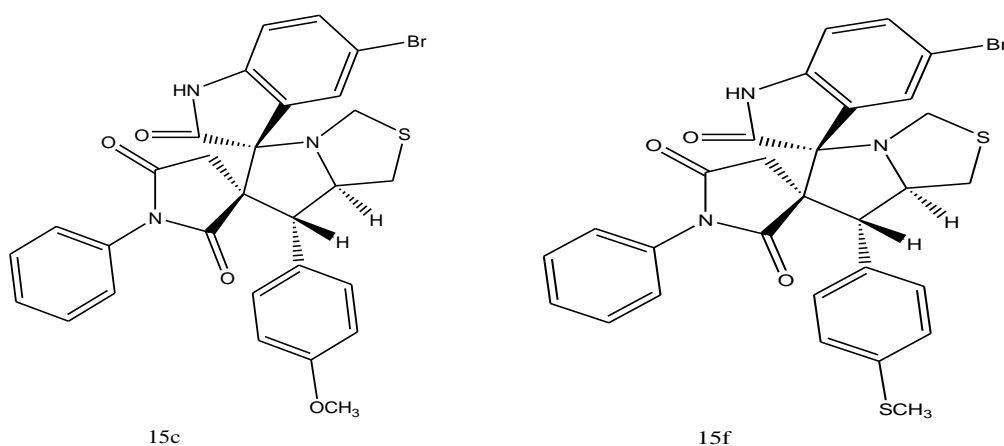
TarekAboul-Fadlet.al (2015)¹⁷ Showed promising activity against the wild-type strain with MIC values range between 10-0.156 $\mu\text{g}/\text{mL}$. The most active derivatives (D8) were further tested against a panel of six single resistant Mycobacterium tuberculosis strains. The results revealed interesting results regarding derivative D8 which showed enhanced activity against the Streptomycin resistant strain. Further investigations showed D8 to have equipotent activity to INH against rifampin-resistant strains as well as being 4 times more active than rifampin against the ofloxacin-resistant strains.



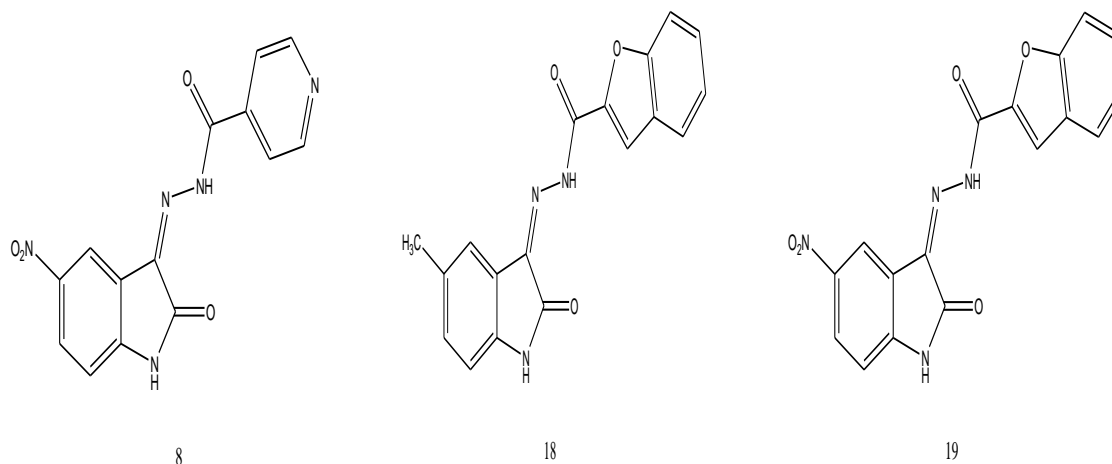
Davie Cappoen et.al (2014).¹⁸ A library of substituted 1,3-diaryltriazines based on the acting component of the anti-trypanosomal drug, diminazene aceturate was created and evaluated for its potential as anti-tubercular agents. Several compounds were identified with Sub-micro molar inhibitory concentration against M. Tuberculosis and other clinical relevant mycobacterial species such as mycobacterium bovis, mycobacterium ulcerans, mycobacterium avium and although the library of the compounds showed a considerable acute cytotoxicity, A genotoxicity could not be observed. Finally the triazene 14 was selected with the best biological properties ($\text{IC}_{50}=3.26\mu\text{M}$, $\text{NI}_{50}=24.22\mu\text{M}$, $\text{SI}=7.44$). The compound 14 showed the ability to inhibit the growth of intracellular replicating and multi-drug resistant M. Tuberculosis



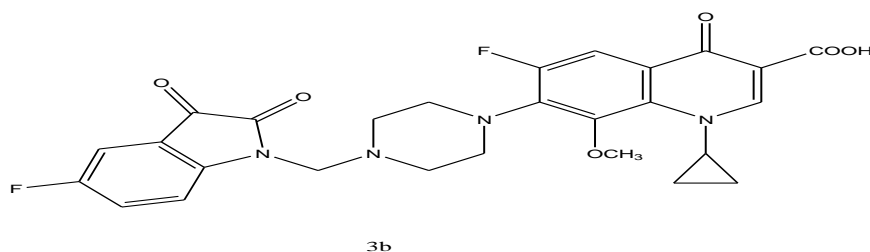
Saoussen Haddad et.al (2014)¹⁹ A novel anti-tubercular agents, a series of original dispiropyrrolothiazole derivatives have been synthesized by three-component 1,3-dipolar cycloaddition of (E)-3-arylidene-1-phenyl-pyrrolidine-2,5-diones, 1,3-thiazolane-4-carboxylic acid and cyclic diketones. The newly synthesized compounds were screened in vitro against Mycobacterium tuberculosis H37Rv and the most active compounds were tested for cytotoxicity studies. Some compounds exhibited significant activity, in particular dispiropyrrolothiazole derivatives 15c and 15f emerged as the most promising antitubercular agent



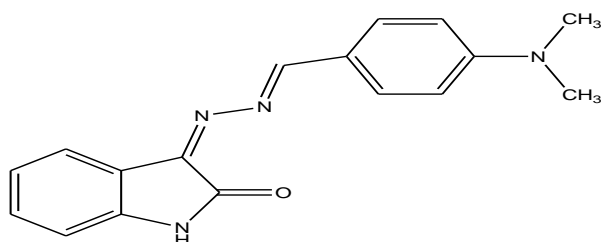
TarekAboul-Fadl et.al (2011)²⁰ A series of Schiff bases of indoline-2,3-dione were synthesized and investigated for their Mtbgyrase inhibitory activity. Promising inhibitory activity was demonstrated with some of these derivatives, which exhibited IC₅₀ values ranging from 50–157 μ M. The orientation and the ligand-receptor interactions of such molecules within the Mtb DNA gyrase. Among the tested compounds the terminal aromatic ring benzofuran showed the best activity. Promising new leads for developing a novel class of Mtbgyrase inhibitors were obtained from Schiff bases of indoline-2,3-dione



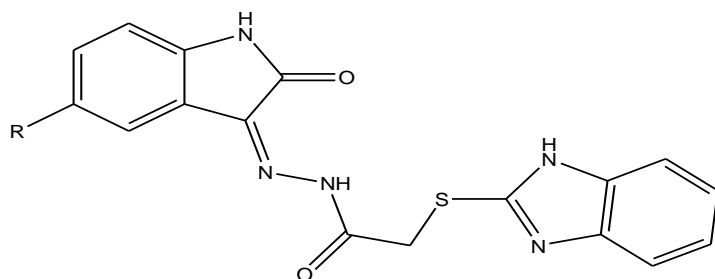
Lian-Shun feng et.al (2011)²¹ A Series of novel 8-OCH₃ Ciprofloxacin, methylene and ethylene isatin derivatives. With remarkable improvement in lipophilicity were synthesized in this study. These derivatives were evaluated for their invitro activity against some mycobacteria. All of the synthesized compound were less active then the parent 8OCH₃ Ciprofloxacin against mycobacterium smegmatis CMCC93202, but most of the methylene isatin derivatives were more active then 8-OCH₃, Ciprofloxacin, isoniazid, and rifampin against MTB H37Rv ATCC 27294, It was noted that compound 3b (MIC:0.074μM) was 2-13 fold more potent then the reference compound.



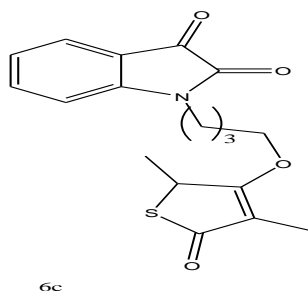
Sangamesh A. Patil et. al (2011)²² reported the synthesis, biological evaluation Co (II), Ni (II),and Mn (II) metal complexes of novel isatinschiff base ligand, the complexes show activity against mycobacterium tuberculosis strain H37Rv.



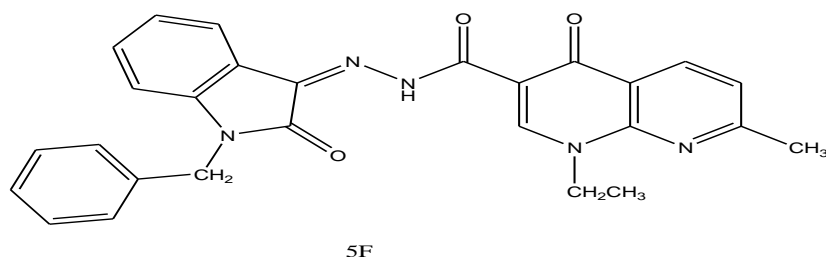
Sandeep K. Gupta et.al (2011)²³ reported the synthesis some thiobenzimidazolyl derivatives, most of them reported good antitubercular activity against mycobacterium tuberculosis



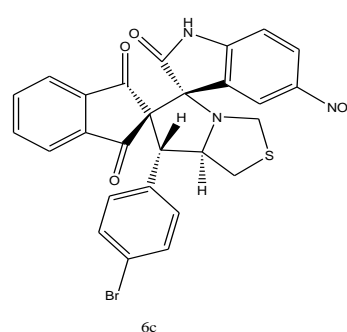
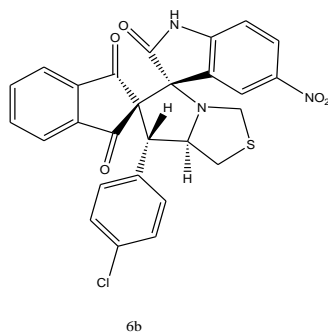
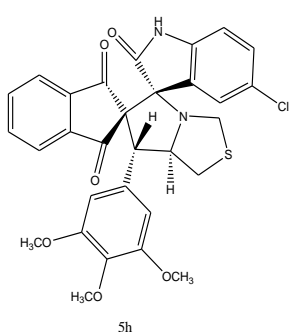
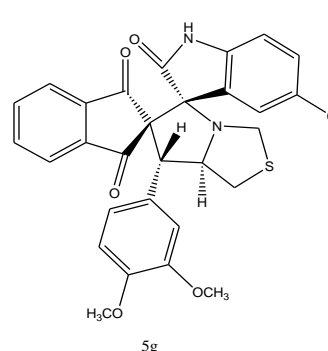
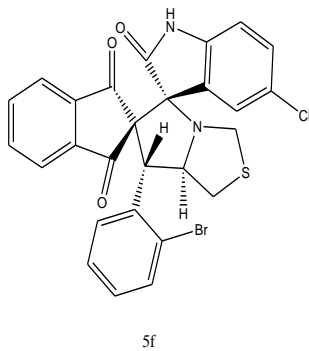
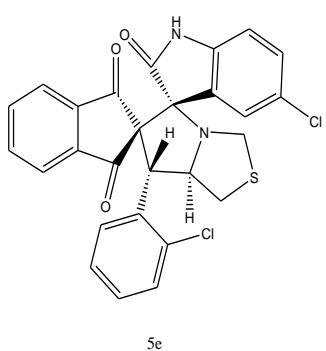
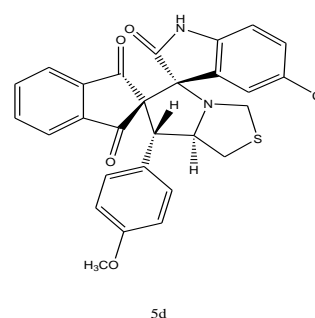
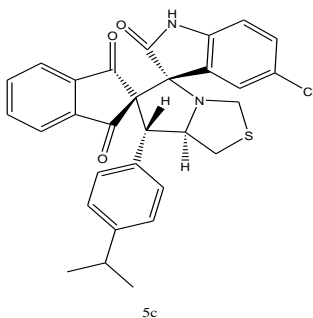
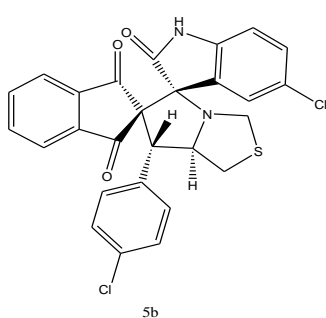
Renate.H.Hans.et.al (2011)²⁴The novel series of thiolactone-isatin hybrid of tetracyclic analogs. The compounds tested in the LORA Assay the unsubstituted intermediates (6c) appears to the most promising activity with an MIC 28.8 μ M. It is comparable to the standard drug moxifloxacin MIC 31.1 μ M. The tetracycles devoid antitubercular activity where as the advanced intermediate displayed growth inhibitory activity against H₃₇RV Strain of mycobacterium tuberculosis as revealed by BACTEC, MABA and LORA assay.

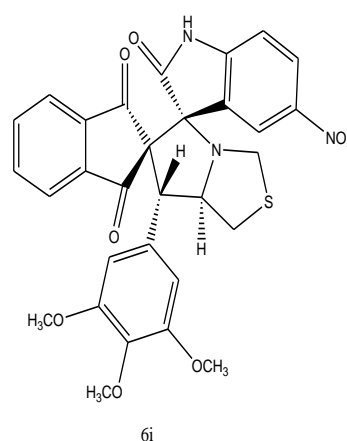
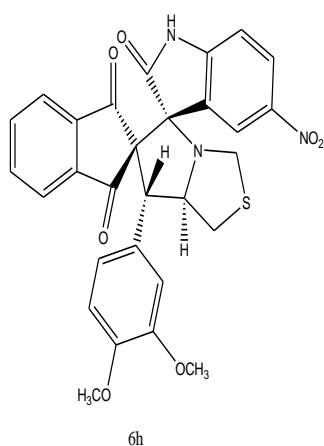
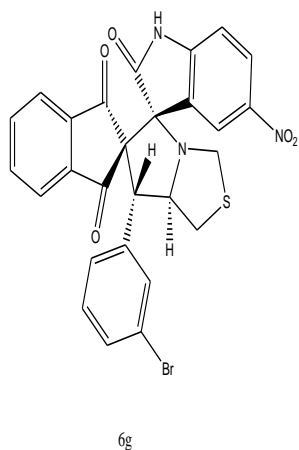
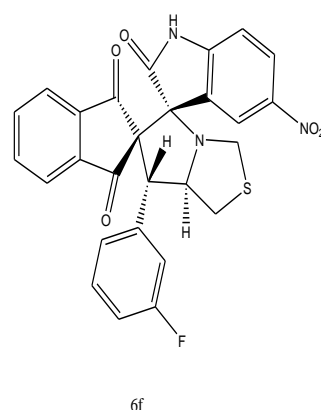
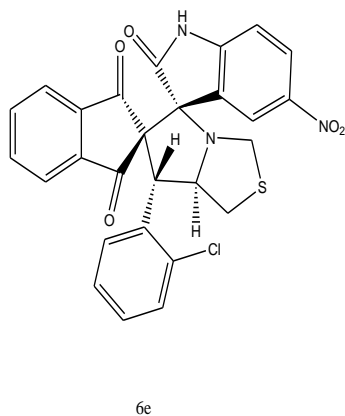
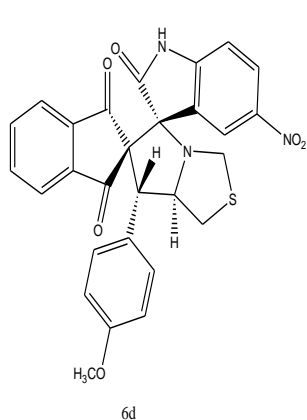


Tarek-Aboul-Fadl et.al (2010)²⁵The anti-TB drugs with enhanced activity against MDR strain. In the recent years Schiff's bases of 1H-indole-2,3-diones are reported to exhibit anti-TB activity. It was investigated against four Mycobacterium strain, Mycobacterium intercellulari, Mycobacterium Xenopi, Mycobacterium Smegmatis & Mycobacterium Cheleneo. Modest anti-TB activity was observed within the investigated compounds however, compound 5f revealed potent anti-TB activity with MIC 0.625 μ g/ml which is 20 times greater than the reference drug isoniazid INH (MIC=12.5 μ g/ml)

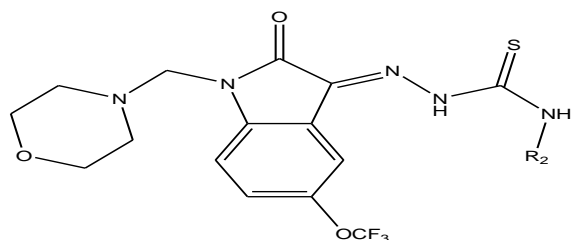


Shanmugavel Uma Maheswari et.al (2010)²⁶A Facile 1,3-dipolar cycloaddition of azomethineylide generated insitu from the reaction of 1,3-thiazolane 4-carboxylic acid and isatin to 2-arylidene 1,3-indanediones furnished novel dispiro-oxindolylpyrrolothiazoles regio and stereo selectivity in moderate to good yield (60-92%) Invitro anti-tubercular screening of 27 compounds against mycobacterium tuberculosis H₃₇Rv (MTB) disclosed that spiro [5.3^I]-5^I-nitrooxindolespiro [6.3^{II}]-1H-indene-1^{II},3^{II} [2H]-dione -7 [4-bromophenyl] tetrahydro -1H Pyrrolo [1,2-c][1,3] thiazole has the maximum potency with a minimum inhibitory concentration [MIC] of 1.4μM. Against MTB, being 3.4 and 5.4times more potent then ciprofloxacin and ethambutol respectively.





OzlenGuzel et.al (2008)²⁷ New series of 5-trifluoromethoxy 1-morpholinomethyl-1H-indole 2,3-dione-3-thiosemicarbazones 5e. The synthesized compounds were evaluated for in vitro antituberculosis activity against mycobacterium tuberculosis H37Rv.



CONCLUSION:-

Isatin scaffolds are bioactive substances it has inspired medicinal chemist to development many pharmacophore moieties and to synthesize new potential anti-TB agents. TB is one of the major life

threatening infectious disease in world wide. Isatinanalogs are elucidated are more potent then the reference drugs.

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REFERENCES:-

1. www.isatinwikipedia.com
2. www.who.com
3. www.tuberclosispathophysiology.com
4. SivanandhanKarunanidhi, BalakumarChandrasekaran, Novel thiomorpholine tethered isatinhydrazones as potential inhibitors of resistant Mycobacterium tuberculosis Bioorganic Chemistry 115 (2021) 105133
5. Zainab M. Elsayed, Wagdy M. Eldehna, Development of novel isatin–nicotinohydrazide hybrids with potent activity against susceptible/ resistant Mycobacterium tuberculosis and bronchitis causing–bacteria Journal of Enzyme Inhibition and Medicinal Chemistry 2021, VOL. 36, NO. 1, 384–393
6. Yaohuan Zhang, Ruo Wang, Tesen Zhang, Weitao Yan, Yihong Chen, Yanping Zhang, Muyang ZhouBenzofuran-isatin-hydroxylimine/thiosemicarbazide hybrids: Design, synthesis and in vitro anti-mycobacterial activity evaluationChinese Chemical Letters(2018) doi.org/10.1016/j.ccl.2018.11.032
7. Yan Xu^a, JianguoGuan^{a,*}, ZhiXu^b, ShijieZhao^b Design, Synthesis and in vitro anti-mycobacterial activities of homonuclear and heteronuclearbis-isatin derivatives Fitoterapia 127 (2018) 383-386
8. Feng Gao, Hua Yang, Tianyu Lu, Zijian Chen, Long Ma, ZhiXu, Paul Schaffer, Guangming LuDesign, synthesis and anti-mycobacterial activity evaluation of benzofuran-isatin hybridsEuropean Journal of Medicinal Chemistry(2018)
9. Xinjia Yan, ZaoshengLv, Jing Wen, Shijia Zhao, ZhiXuSynthesis and in vitro evaluation of novel substituted isatin-propylene-1H-1,2,3triazole-4-methylene-moxifloxacin hybrids for their anti-mycobacterial activitiesEuropean Journal of Medicinal Chemistry2017S0223-5234(17)30993-5
10. Leyla Yurttaş^{1,*}, Merve Ertaş², MeralYılmaz Cankılıç³, ŞerefDemirayak²Synthesis and Antimycobacterial Activity Evaluation of Isatin-derived 3- [(4- aryl - 2- thiazolyl)]hydrazone]-1H- indol- 2, 3- dionesActa Pharm. Sci.Vol 55 No: 1. 2017
11. U. Usha Rani^{1*}, P. Sivappa Naidu¹, G. Sukanya¹, P. Sri Datha¹, S. Pramod Kumar¹, Venkata Rao Vutla^{2*}Synthesis and Biological Evaluation of Isatin incorporated Quinoxalines as Anti-Tubercular AgentsInt. J. Pharm. Sci. Rev. Res., 47(2), November - December 2017; Article No. 13, Pages: 67-70

12. Ruslan Gr. Redkin*, Evgeniya I. Syumka, Leonid A. Shemchuk, Valentin P. Chernykh Synthesis and antimicrobial activity of Bis-Derivatives of 3a', 6a' Dihydro-2'H-Spiro[Indole-3,1'-Pyrrolo[3,4-c]Pyrrole]-2,4',6'(1H, 3'H, 5'H)-Trione *Journal of Applied Pharmaceutical Science* Vol. 7 (06), pp. 069-078, June, **2017**
13. ZhiXu^a, ShuZhang^b, XufengSong^c, Min Qiang^a, ZaoshangLv^{a*} Design, Synthesis and invitro anti-mycobacterial evaluation of gatifloxacin-1H-1,2,3-triazole isatin hybrid *Bioorganic & Medicinal Chemistry Letters* **27** (2017) 3643-3646
14. Xianghua Xia, Qianhua Zhang, Lichun Zhao, Yuanqiang Hu Azide-alkyne cycloaddition towards 1H-1,2,3-triazole-tethered gatifloxacin and isatin conjugates: Design, synthesis and in vitro anti-mycobacterial evaluation *European Journal of Medicinal Chemistry* **2017** S0223-5234(17)30428-2
15. ChouroukMhiri, SarraBoudriga, MoheddineAskri, Michael Knorr, DharmarajanSriram, PerumalYogeeswari, Frédéric Nana, Christopher Golz, CarstenStrohmann Design of novel dispirooxindolopyrrolidine and dispirooxindolopyrrolothiazole derivatives as potential antitubercular agents *Bioorganic & Medicinal Chemistry Letters* (2015) S0960-894X(15)00773-8
16. Wagdy M. Eldehna^{1*}, Mohamed Fares¹, Marwa M. Abdel-Aziz² and Hatem A. Abdel-Aziz^{3,4,*} Design, Synthesis and Antitubercular Activity of Certain Nicotinic Acid Hydrazides *Molecules* (2015), 20, 8800-8815
17. TarekAboul-Fadl*, Mohammed K. Abdel-Hamid*, ¥ and Adel F. Youssef Schiff bases of indoline-2,3-dione (isatin) derivatives as efficient agents against resistant strains of Mycobacterium tuberculosis *Der PharmaChemica*, (2015) 7(8):217-225
18. Davie Cappoen^a, Jure Vajs^b, Cynthia Uythethofkan^a, Andrej Virag^b, Vanessa Methys^c, Marijan Kocevar^b, Luc Verschaeve^{d,e}, Martin Gazvod^b, Slovenko Polanc^b, Kris Huygen^{a,*}, Janez Kosmrlj^{b,*} Anti-mycobacterial activity of 1,3-diaryltriazenes *European Journal Of Medicinal Chemistry* **77** (2014) 193-203
19. Saoussen Haddad, a, b Sarra Boudriga, a François Porzio, b Armand Soldera, b Moheddine Askri, a, * Dharmarajan Sriram, c Perumal Yogeeswari, c Michael Knorr, d Yoann Rousselin, e Marek M. Kubickie Synthesis of novel dispiropyrrolothiazoles by three component 1,3-dipolar cycloaddition and evaluation of their antimycobacterial activity *RSC Advances* (2012) DOI: 10.1039/C4RA11940A
20. Tarek Aboul-Fadl^{1,*}, Hatem A. Abdel-Aziz¹, Mohammed K. Abdel-Hamid², Tilal Elsaman¹, Jane Thanassi³ and Michael J. Pucci³ Schiff Bases of Indoline-2,3-dione: Potential Novel Inhibitors of Mycobacterium Tuberculosis (Mtb) DNA Gyrase *Molecules* **2011**, 16, 7864-7879
21. Lian-Shun Feng^a, Ming-Liang Liu^{a*}, ShuZhang^b, Yun-Chai^a, Bo Wang^a, Yi-Bin-Zhang^a, Kailv^a, Yun Guan^a, Hui-Yuan Gur^a, Chun-Ling Xiao^{a***} Synthesis and invitro antimycobacterial activity of 8-OCH₃ Ciprofloxacin methylene and ethylene isatin derivatives *European Journal Of Medicinal Chemistry* **46** (2011) 341-348
22. Sangamesh AP, Manjunatha M, Udaykumar VK, Prema SB. Synthesis, spectral characterization and biological evaluation Co(II), Ni(II), Cu(II) and Mn(II) metal complexes of novel Isatin Schiff base ligand. *Der PharmaChemica* **2011**; 3: 97-108
23. Sandeep KG, Shyam SP. Synthesis and evaluation of antitubercular activity of some thiobenzimidazolyl derivatives. *Der PharmaChemica* **2011**; 3: 274-279.

24. Renate.H.Hans^a, Ian J.F.Wild^b,PaulD.VanHelden^b, BaojieWan^c, Scott G.Franzblau^c, Jiri Gut^d, Philip J.Rosenthal^d, Kelly Chibale^{e,f*} Novel Thiolactone-isatin hybrids as potential antimalarial and antitubercular agents *Bioorganic & Medicinal Chemistry Letters*21 (2011) 2055-2058
25. TarekAboul-fadl*, FayzahA.S.Bin-Jubair, OmimaAboul-Wafa Schiff bases of indoline-2,3-dione (Isatin) derivatives and Nalidixic acid carbohydrazide, Synthesis, anti-tubercular activity and pharmacophoric model building *European Journal of Medicinal Chemistry* 45 (2010) 4578-4586
26. Shanmugavel Uma Maheshwari^a, KamorajBalamurugan^a, Subbuperuma^{a*}, PerumalYogeeswari^b, DharmarajanSriram^b A facile 1,3-dipolar cycloaddition of azomethineylides to 2-arylidines 1,3-indanediones: Synthesis of dispiro-oxindoylpyrrolothiazoles and their anti mycobacterial evaluation *Bioorganic & Medicinal Chemistry Letters*20 (2010) 7278-7282
27. Ozlen G, Nilgun K, Aydin S. Synthesis and antituberculosis activity of 5methyl/trifluoromethoxy-1H-indole-2,3-dione 3-thiosemicarbazone derivatives.*Bioorg Med Chem*2008; 16: 8976–8987.

