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ISSN: 2278-1862

Journal of Applicable Chemistry

2020, 9 (4): 514-530

(International Peer Reviewed Journal)

Review

Dimedone as the Source for Antimicrobial Agents; Synthesis and Anti-Microbial Property of Compounds Obtained Using Dimedone as the Precursor

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Accepted on 8th June, 2020

ABSTRACT

Dimedone, a cyclic 1,3-diketone having flanked dimethyl groups acts an excellent precursor for the synthesis of partially hydrogenated and fused heterocyclic compounds. It serves as an important precursor for the synthesis of compounds possessing anti-bacterial and anti-fungal activity. In the present review application of dimedone as a precursor for the synthesis of anti-microbial compounds is discussed.

High Lights:

- Dimedone acts as an excellent precursor for the synthesis of partially hydrogenated and fused heterocyclic compounds.
- It serves as an important precursor for the synthesis of compounds possessing anti-bacterial and anti-fungal activity.
- In the present review application of dimedone as a precursor for the synthesis of anti-microbial compounds is discussed. It is used for polyhydroacridine, tetrahydro benzopyran, polyhydroquinolines, etc synthesis.

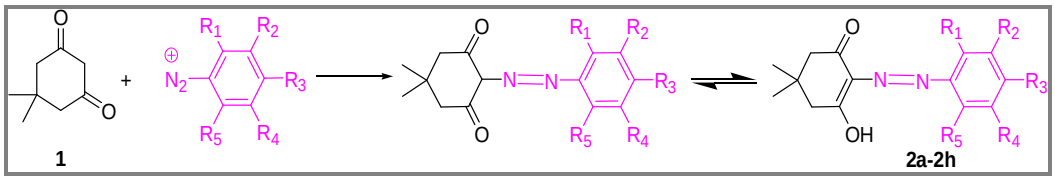
Keywords: Anti-microbial, 1,3-diketone, Pyrrolo[2,3-d]pyrimidines, Heterocyclic.

INTRODUCTION

5,5-dimethyl-1,3-cyclohexanedione(Dimedone) is an cyclic 1,3-diketone having flanked dimethyl groups. It is an excellent precursor for the synthesis of partially hydrogenated and fused heterocyclic compounds [**1**]. Dimedone is commonly used as synthetic reagent in various reactions such as in multi-component heterocyclization [**2, 3**], synthesis of complexes with trivalent metals [**4**], polyhydroacridine [**5**], tetrahydro benzopyran [**6, 7**], polyhydroquinolines [**8**], pyrrolo[2,3-d]pyrimidines [**9**], 1,4-dihydropyridines [**10**], 1,8-dioxo-octahydroxanthenes [**11, 12**], indenol[1,2-b]quinoline dione [**13**], xanthenes derivatives [**14**] and spiro compounds [**15**]. In organic chemistry

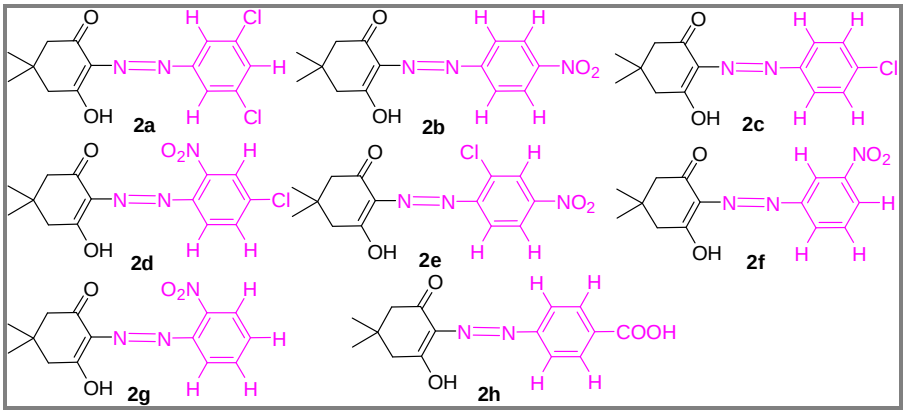
dimedone is also used for the determination of presence of aldehyde group in a compound. Over the years while working on total synthesis, structural modification of natural products [**16, 17**], development of methodologies for bioactive molecules, etc. our group also used dimedone as precursor in various synthetic processes [**18-29**]. In the present review application of dimedone as a precursor for the synthesis of anti-microbial compounds is discussed. Dimedone has been used for the synthesis of compounds possessing anti-bacterial and anti-fungal activity by various research groups.

Mbabazi Jolocam *et al.* in 2011: synthesized a series of compounds (**2a-2h**) from dimedone (5,5-dimethyl cyclohexan-1,3-dione, **1**) by coupling it with diazotizedaromatic amines (Scheme 1) [**30**]. Diazotization of the aromatic amines was performed in sodium acetate solution and hydrochloric acid with sodium nitrite solution at 0–5°C. The solution of the diazotized product was added to dimedone dissolved in ethanol under cold conditions (0-5°C). The reaction mixture was stirred overnight at ambient temperature to obtain the desired products (**2a-2h**) which were re-crystallized from ethanol.

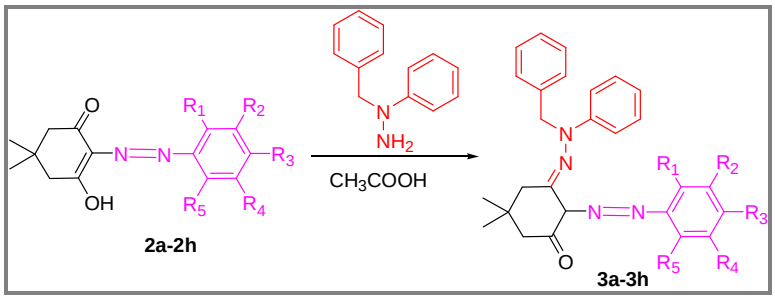


Scheme 1. Coupling of dimedone with diazotizedaromatic amines to deliver biologically active compounds.

Table 1. Biologically active compounds obtained by reaction of dimedone with diazotizedaromatic amines



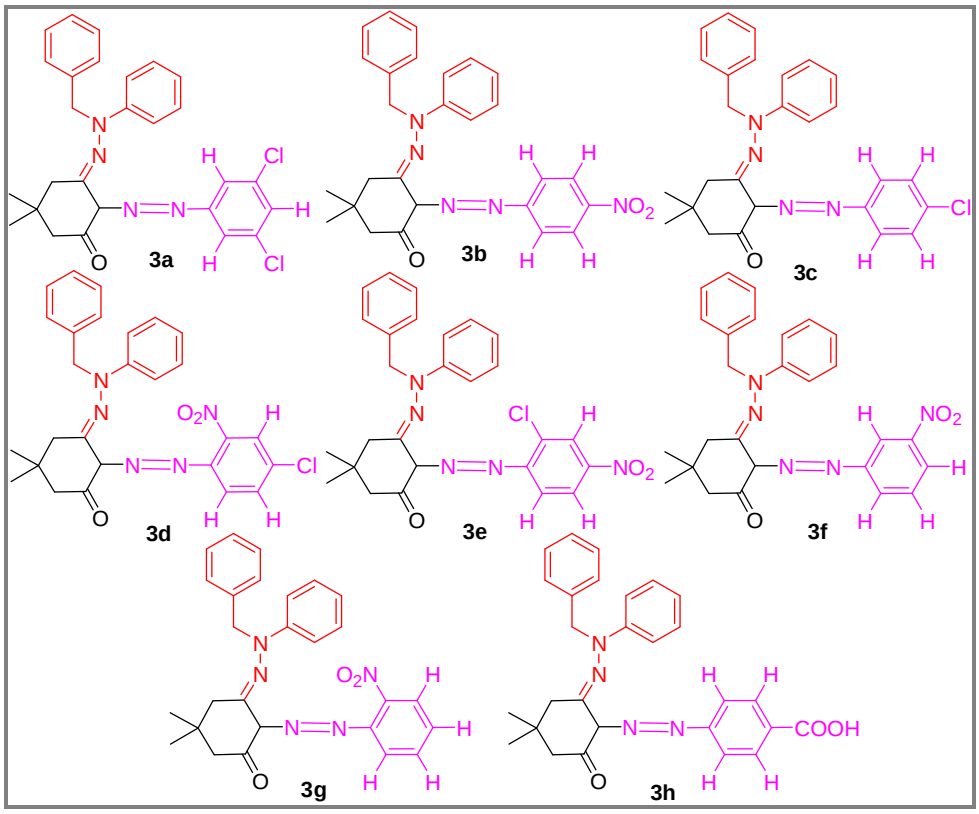
In order to synthesize another series of products (**3a-3h**) the compounds (**2a-2h**) were dissolved in a mixture of acetic acid and *N*-benzyl-*N*-phenyl hydrazine (Scheme 2). The resulting solution was refluxed for 3 - 4 hours, cooled, filtered and subsequently re-crystallised from methanol and water.



Scheme 2. Coupling of dimedone with diazotized aromatic amines to deliver biologically active compounds.

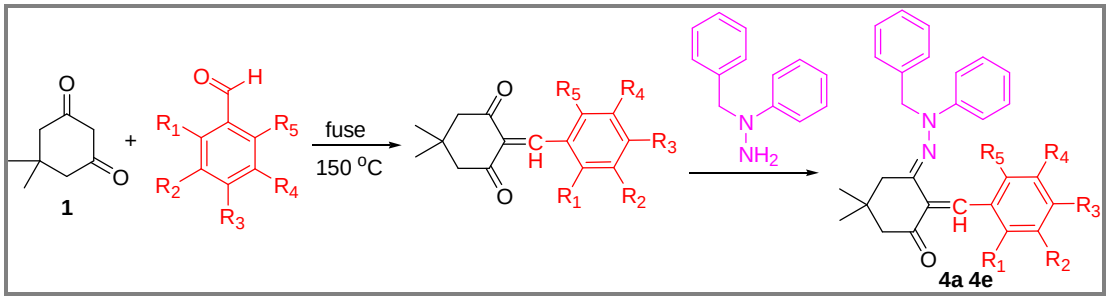
Table 2. The compoundsformed by the reaction of **2a-2h** with acetic acid

and *N*-benzyl-*N*-phenyl hydrazine



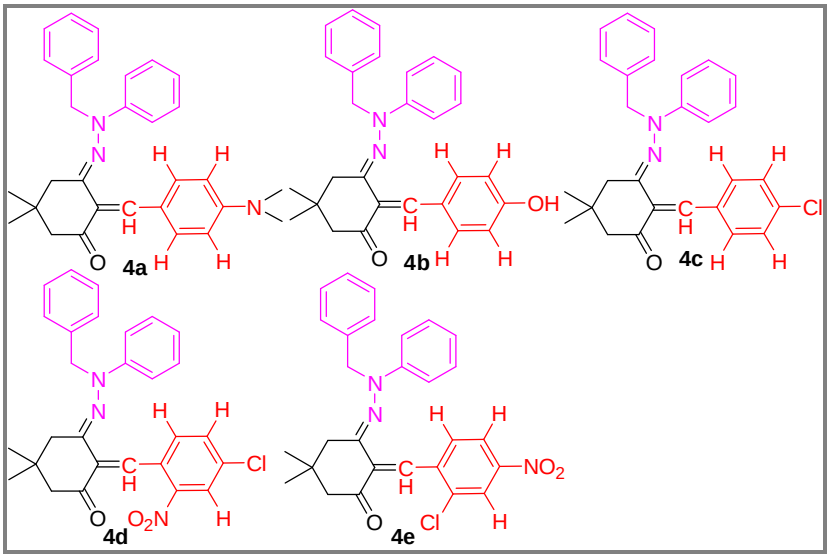
Investigation of the antimicrobial activity revealed good activity of two compounds (**3a** and **3c**) containing chlorine atom on the arylazo- group against gram-negative *Bacilli* (*Aerobacterium klebsiella, Bacillus Arizona, Bacillus proteus, Bacillus pseudomonas, Escherichia coli, Salmonella paratyphi*A, *Salmonella paratyphi*B, *Salmonella paratyphi*C, *Shigella flexneri and Shigella sonnei*). However, the compounds were found to be inactive against gram positive *Cocci* (*Staphylococcus aureus, Staphylococcus epidermis* and *Sarcinalutea*) and *Bacilli* (*Bacillus permal* and *Bacillus subtilis*) at 100 μg mL^{-1} concentration. Three compounds (**3b**, **3f** and **3g**) bearing $–NO_2$substituent at *para*, *meta*- and *ortho*-position of the arylazo-groupwere found to be inactive against gram-positive *Cocci* and *Bacilli* and gram-negative *Bacilli*. Compound (**3d**) was highly active against (*Aerobacterium Klebsiella* and *Bacillus Arizona*) and moderately active against (*Bacillus proteus, Bacillus pseudomonas, Escherichia coli, Salmonella paratyphi*A, *Salmonella paratyphi*B, *Salmonella paratyphi*C, *Shigella flexneri* and *Shigella sonnei*) strains of gram-negative *Bacilli*. Compound (**3e**) exhibited moderate activity against gram-negative *Bacilli* and *Staphylococcus aureus* and *Staphylococcus epidermis* strains of gram-positive *Cocci*. On the contrary, compound (**3e**) was inactive against *Sarcina lutea* strain of gram-positive *Cocci* as well as *Bacillus permal*and *Bacillus subtilis* strains of gram-positive *Bacilli*. Screening of the compounds (**3h**) possessing carboxyl group on the arylazo moiety revealed no activity against gram-positive *Cocci* and *Bacilli*. However, the activity of compound (**3h**) varied from moderately active (*Aerobacterium klebsiella, Bacillus Arizona, Bacillus proteus, Bacillus pseudomonas, Escherichia coli* and *Salmonella paratyphi*A) to highly activity (*Salmonella paratyphi*B, *Salmonella paratyphi*C, *Shigella flexneri and Shigella sonnei*) against gram-negative *Bacilli*.

Mbabazi Jolocam *et al.* in 2011 (Second compound series): Mbabazi Jolocam *et al.* in 2011 synthesized five compounds for evaluation of antimicrobial activity using dimedone as the starting material [**31**]. In this case dimedone was coupled with aromatic aldehydes at 150°C. The products obtained were refluxed with N–benzyl-N-phenylhydrazine in acetic acid for 3 to 4 hours (Scheme 3).



Scheme 3. Synthesis of antimicrobial compounds using dimedone, aromatic aldehydes and N-benzyl-N-phenyl hydrazine.

Table 3. Compounds synthesized using dimedone, aromatic aldehydes and N-benzyl-N-phenyl hydrazine

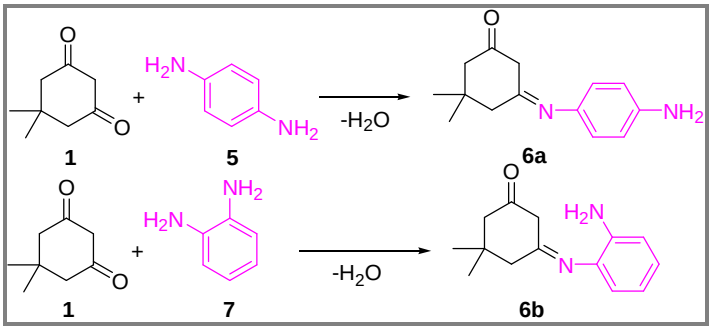


The synthesized compounds (**4a**-**4e**) were screened against gram-positive *Cocci* and *Bacilli* as well as gram-negative *Bacilli* and exhibited activity ranging from inactive to highly active. Two compounds **4a** and **4b** containing substituted amino (-N(CH_3)$_2$) and hydroxyl (-OH) groups, respectively were found to be inactive against all the strains of tested micro-organisms at a concentration of 100 µg mL^{-2}. Compounds **4c** and **4e** exhibited high antimicrobial activity against all the test micro-organisms. Compound **4d** showed high antimicrobial activity against *Sarcina lutea*, *Bacillus permal*, *Bacillus arizona*, *Bacillus proteus*, *Bacillus pseudomonas*, *Escherichia coli*, *Salmonella paratypi*B and *Salmonella paratypi*C. It however exhibited moderate biological activity towards *Staphylococcus aureus*, *Staphylococcus epidermis*, *Bacillus subtilis*, *Aerobacterium klebsiella*, *Salmonella paratypi*A, *Shigella flexneri* and *Shigella sonnei*.

Manawwer Alam *et al.* in 2014: Manawwer Alam *et al.* reported the synthesis and evaluation of antimicrobial activity of 5-[(2-aminophenyl)imino]-3,3-dimethylcyclohexanone **6a** and 5-[(4-aminophenyl)imino]-3,3-dimethyl cyclohexanone **6b** [**32**]. The compounds **6a** and **6b** were prepared by refluxing dimedone and *o/p*-phenylene diamine **5**/**7**in ethanol at 40 and 50°C, respectively for 4 h. The reaction mixture was cooled at room temperature then washed with water and methanol to remove any unreacted material from the product (Scheme 4).

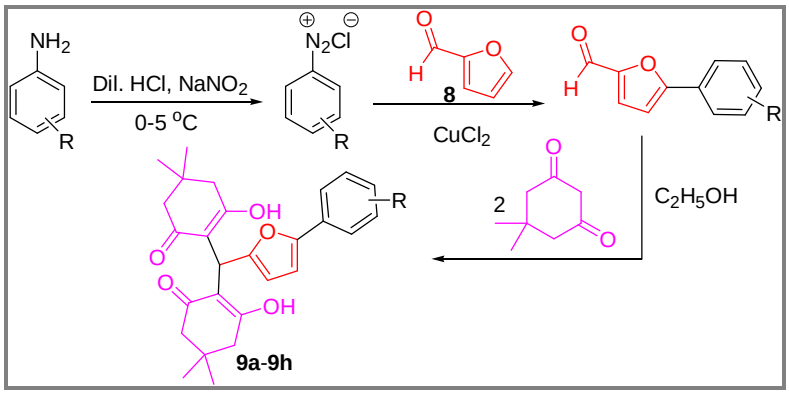
Antibacterial activity of the synthesized compounds **6a** and **6b** was analysed against the following bacterial strains: gram-positive, *Staphylococcus aureus* (ATCC 25923, 29213), *Bacillus subtilis* (ATCC 6633), *Staphylococcus epidermidis* and gram-negative, *Escherichia coli* (ATCC 25922),

Pseudomonas aeruginosa (ATCC 27853,) *Shigella, Salmonella*. In order to determine the antifungal activities of synthesized compound **6a** and **6b**, *C. albicans* (ATCC90028, 66027), *C. tropicalis* (ATCC 66029) and *C. parapsilosis* (ATCC 22019).The result showed that compound **6b** exhibited more antimicrobial activity except one bacterial strain (*Staphylococcus aureus*) compared to **6b**.



Scheme 4. Synthesis of aromatic Schiff's Bases from dimedone and diamine.

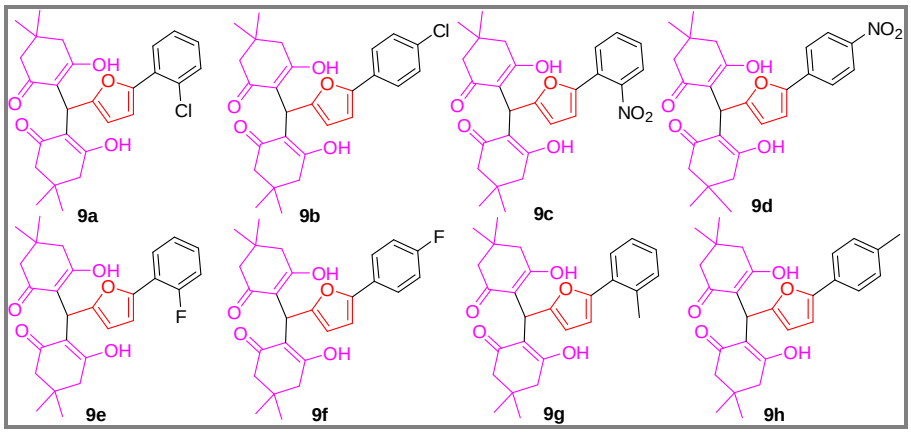
Mukhtar A. Wani *et al.* in 2016: Mukhtar A.Wani *et al*. synthesized bisdimedone derivatives using reported method of Horning and Honing [**33**]. The substituted aromatic amines after diazotization with $NaNO_2$ and HCl were treated with freshly distilled furfural aldehyde **8** and aqueous cupric chloride for 8 h to obtain 5-[(substituted-phenyl)]-furan-2-carbaldehyde. The product 5-[(substituted-phenyl)]-furan-2-carbaldehyde obtained was reacted with dimedone in ethanol over heating for 25 minutes to afford the bisdimedone compound (Scheme 5).The products obtained (**9a-9h**; Table 4) were evaluated for antimicrobial activity against *S. aureus*, *E. coli*, *P. mirabilis*, *P. aeruginosa* and *K. pneumonia* bacterial strains as well as *A. flavus*, *A. fumigatus*, *A. niger* and *C. albicans* fungal strains. Among the 8 synthesized compounds 2-(2-chloro-phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)-methylfuranand 2-(4-flor-phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)methylfuran showed good activity against *Proteus mirabilis* and *Klebsiella pneumonia*. The compounds 2-(4-chloro-phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)-methylfuran and 2-(2-chloro-phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)-methylfuran showed prominent activity against *Staphylococcus aureus*. The synthesised bisdimedone derivatives also showed fungicide activity.

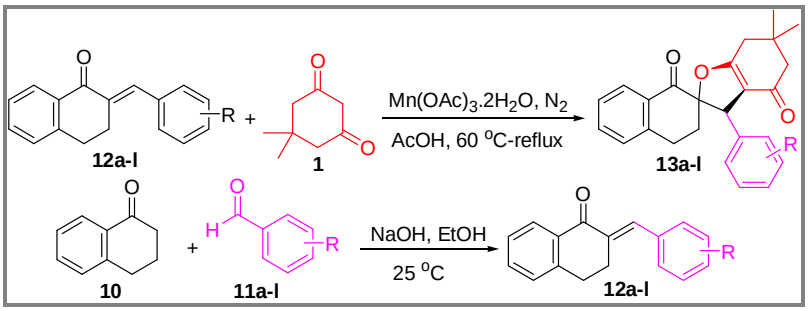


Scheme 5. Synthesis of furfural substituted bisdimedone derivatives.

Mustafa Ceylan *et al.* in 2016: The spirobenzofuran derivatives (**13a-l**), 6,6-dimethyl-3-aryl-3′,4′,6,7-tetrahydro-1′*H*,3*H*-spiro[benzofuran-2,2′-naphthalene]-1′,4(5*H*)-dione were obtained by $Mn(OAc)_3$-mediated addition of dimedone (**1**) to chalcone-like compounds **12a–l** [**34**]. The starting Chalcone-like compounds **12a–l** were synthesized in basic medium by the addition of different benzaldehyde derivatives (**11a–l**) to 1,2,3,4-tetrahydro-1-napthalone (**10**).

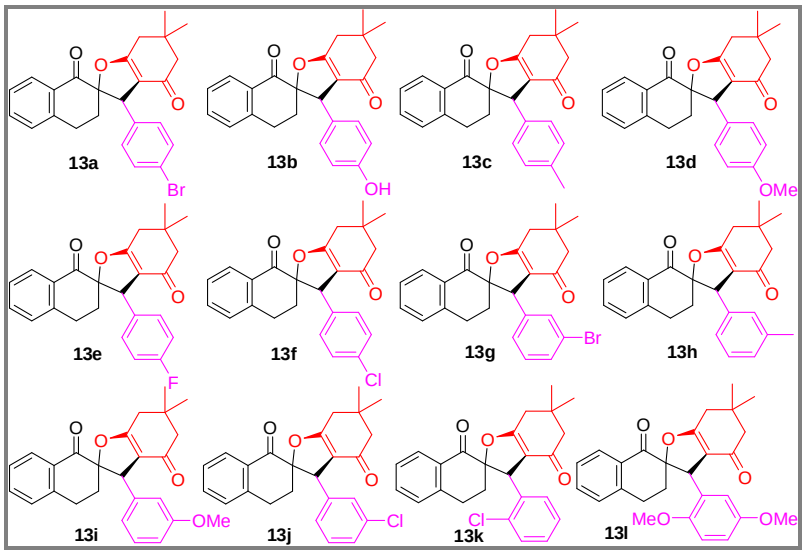
Table 4. Furfural substituted bisdimedone derivatives





Scheme 6. Synthesis of spirobenzofuran derivatives.

Table 5. Library of spirobenzofuran derivatives synthesized. (Change numbering 13a-l)

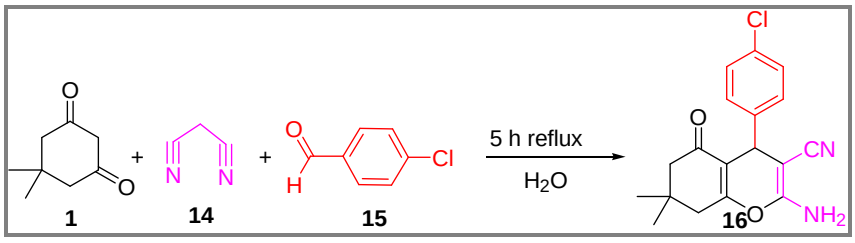


The synthesized compounds (**13a–l**) were tested for their antibacterial activity against six different types of human pathogenic bacterial strains. The microorganisms used were*Staphylococcus aureus* (ATCC®29213), *Bacillus subtilis* (ATCC®6633) which are Grampositive bacteria and *Escherichia coli* (AU tıp), *Pseudomonas aeruginosa* (ATCC®9027), *Proteus vulgaris* (KUEN 1329), which are Gram-negative bacteria, and *Candida albicans* (ATCC®1213) which are Gram-positive fungi. In these tests, sulbactam/cefoperazone (SCF) were used as standard, and dimethyl sulfoxide (DMSO) was used as negative control.

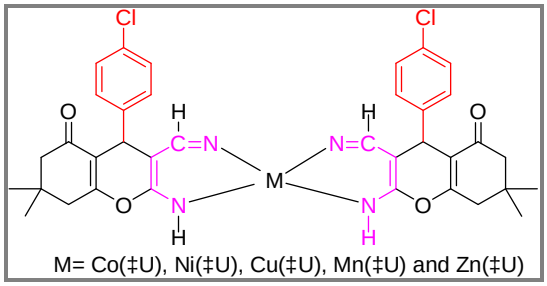
Most of the compounds **13a–l** displayed moderate to good activity against 6 bacterial strains. The most active compound was **13l** (containing 2 methoxy groups) against *S. aureus* with 16 mm of inhibition zone. Compounds (**13j, 13k**, and **13l**) show good activity against *B. subtilis* with 15 mm of inhibition zone. Also, compound **13d** (containing methoxy group) exhibited the highest activity against *E. coli* with 16 mm of inhibition zone. Moreover, Compounds (**13d, 13f**, and **13l**) demonstrated good activity against *P. aeruginosa* with 15 mm of inhibition zone. Compound **13k** (containing chlorine atom) showed remarkable activity against *P. vulgaris* with 15 mm of inhibition zone. *C. albicans* was inhibited well by six of the compounds, 4-methyl (**13c**, 15 mm), 4-methoxy (**13d**, 15 mm), 4-fluorine (**13e**, 15 mm), 4-chlorine (**13f**, 14 mm), 3-methyl (**13h**, 14 mm), and2, 5-dimethoxy (**13l**, 15 mm). Among the compounds, compounds containing methoxy group (**13d** and **13l**) were more active than the others.

In this paper, spirobenzofuran derivatives, 6,6-dimethyl-3-aryl-3′,4′,6,7-tetrahydro-1′*H*,3*H*-spiro[benzofuran-2,2′-naphthalene]-1′,4(5*H*)dione, **13a–l** were synthesized using Mn(OAc)3-mediated-oxidative free radical additions between tetralone-based chalcone-like compounds **12a–l** and dimedone (**1**), and their antibacterial activities were screened against human pathogen Gram-positive and Gram-negative bacteria. Especially, compounds **13d** and **13l** (containing methoxy group) exhibited good antibacterial activity as compared with SCF.

Hoda Pasdar *et al.* in 2017: A novel series of complexes of the type [M ($C_{18}H_{17}N_2O_2Cl)_2$], where M= Co(II), Ni(II), Cu(II), Zn(II) and Mn(II) and $C_{18}H_{17}N_2O_2Cl$ correspond to the bidentate ligands, were synthesized, and characterized by UV-Vis, FTIR and Mass spectroscopies [35]. The bidentate ligand was synthesized in a typical one-pot, three-component condensation of malononitrile**14**, 4-chlorobenzaldehyde **15** and dimedone **1**in the present of alum as catalyst (Scheme 7). The synthesized ligand **16** and its metal complexes **17** were screened for *in vitro* antibacterial activity against Gram-negative (*Escherichia coli)* and Gram-positive (*Staphylococcus aurous)* bacterial strains. The most antibacterial activity of the synthesized compounds belongs to cobalt and copper complexes. The minimal inhibitory concentrations (MICs) against *E.Coli* and *S.aureus* were 16 and 32 µg mL^{-1}, respectively. The results of these studies showed that the metal complexes have more antibacterial activities as compared with the non-complexes ligand. The complexes were prepared by the reaction of ligand with metal salts in the molar ratio 2:1 in refluxing conditions. The complexes of Co (II), Ni (II), Cu (II), Mn (II) and Zn (II) are stable at room temperature.

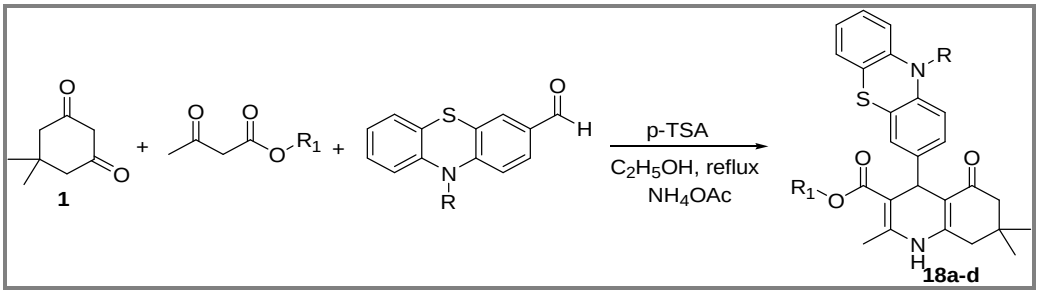


Scheme 7. Synthesis of bidentate ligand.



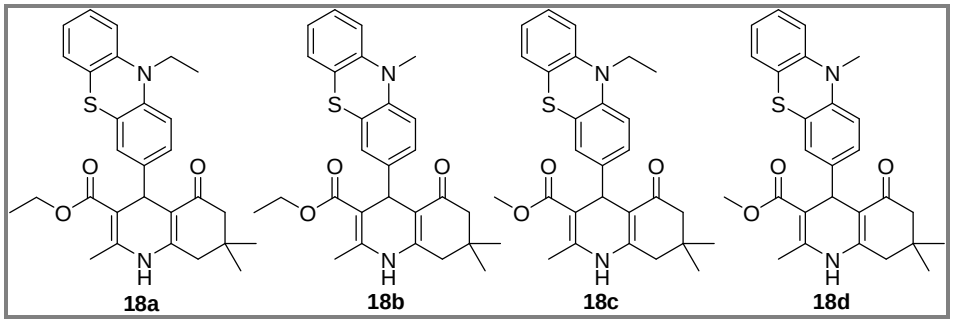
Scheme 7a: Proposed structure of Metal complexes,

Synthesis of *d*1,4 -Dihydropyridine derivatives containing phenothiazine moiety: The compounds **18(a-d)** were synthesized by treatment of one equivalent of 10-alkyl-3-formylphenothiazine, one equivalent of dimedone and ammonium acetate with one equivalent of ethylacetoacetate in presence of *p*-TSA (10 mol %) under reflux and ultrasonic irradiation giving the hexahydroquinoline-3-carboxylate **18(a-d)** (Scheme 8)**.**



Scheme 8. Synthesis of hexahydroquinoline-3-carboxylate derivatives.

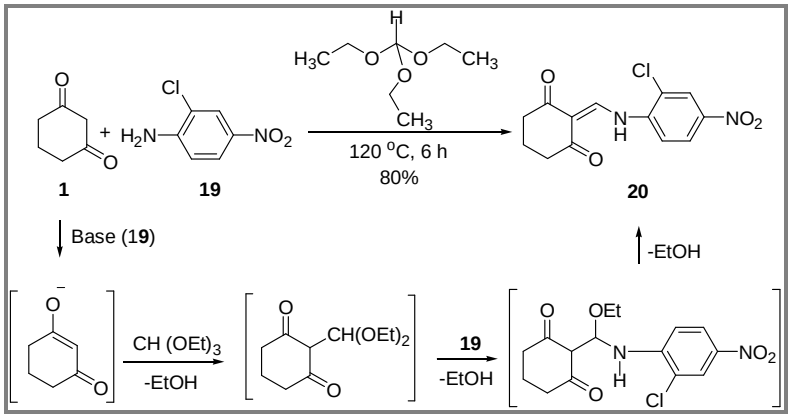
Table 6. Fourhexahydroquinoline-3-carboxylate derivatives synthesized



The compounds **18(a-d)** were screened for antibacterial activity against three "Gram +ve" bacterial strains, *S. aureus* (MTCC 3381), *P. aeruginosa* (MTCC 2295) and *B. cereus* (MTCC 8372) and two "Gram -ve" bacterial strains, *E. coli* (MTCC 1302), *K. pneumonia* (MTCC 3384) at 25, 50 µg mL^{-2} concentration by agar well diffusion method using Muller Hinton agar as the medium. Compounds **18a** and **18b** showed good activity against *S. aureus, P. aeruginosa, E. coli and K. pneumonia* and moderate activity against *B. cereus* while compound **18b** exhibited significant activity against *B. cereus*. Compound **18d** showed moderate activity against *S. aureus, P. aeruginosa, E. coli, K. pneumonia* while compounds **7c** exhibited significant activity against *S. aureus, P. aeruginosa, E. coli, K. pneumonia* and *B. cereus.* Compound **18d** showed moderate activity against *B. cereus* (Table 6).

Muzafar Ahmad Rather *et al.* in 2017: This study utilised whole cell based phenotypic screening of thousands of diverse small molecules against Mycobacterium tuberculosis H37Rv (M. tuberculosis) and identified the cyclohexane-1,3-dionebased structures **21** and **22**(Table 7) as hits [**28, 29**]. The selected hit molecules were used for further synthesis and a library of 37 compounds under four families was synthesized for lead generation. Evaluation of the library against *M. tuberculosis* lead to the identification of three lead antituberculosis agents (**53**, **54** and **57;** Table 10). The most potential compound, 2-(((2-hydroxyphenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (**54**) showed an MIC of 2.5 µg mL^{-1}, which falls in the range of MICs values found for the known antituberculosis drugs ethambutol, streptomycin and levofloxacin. Additionally, this compound proved to be non-toxic (<20% inhibition at 50 µM concentration) against four human cell lines. Like first line antituberculosis drugs (isoniazid, rifampicin and pyrazinamide) this compound lacks activity against general Gram positive and Gram negative bacteria and even against *M. smegmatis*; thereby reflecting its highly specific antituberculosis activity.

The synthesis was started from commercially availablecyclohexan-1,3-dione **1** and substituted anilines**19**. Condensation of cyclohexan-1,3-dione with substituted anilines in presence of triethylorthformate at 120^{o}C resulted the formation of aniline-dione conjugate in decent yield (Scheme 9). Mechanistic investigation of this reaction makes us to believe that this reaction might be happening initially with condensation of cyclohexan-1,3-dione with triethylorthformate and aniline is acting as a base. Subsequent condensation with aniline and elimination of ethanol leads to the formation of product quite uneventfully.



Scheme 9. Synthesis of niclosamide analogues and plausible reaction mechanism.

Table 7. Two hit molecules synthesized

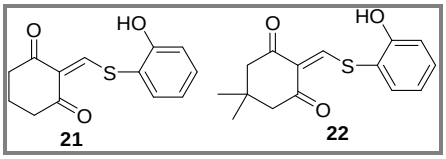


Table 8. Five more synthesized compounds

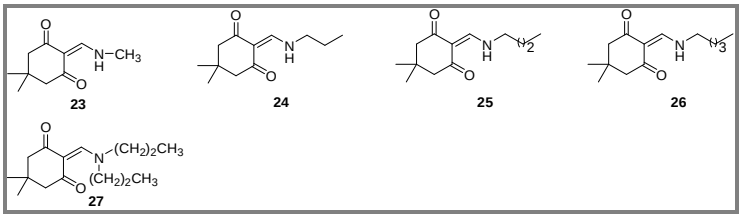
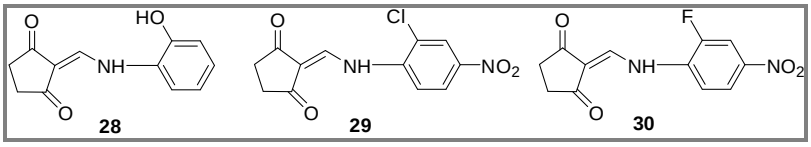
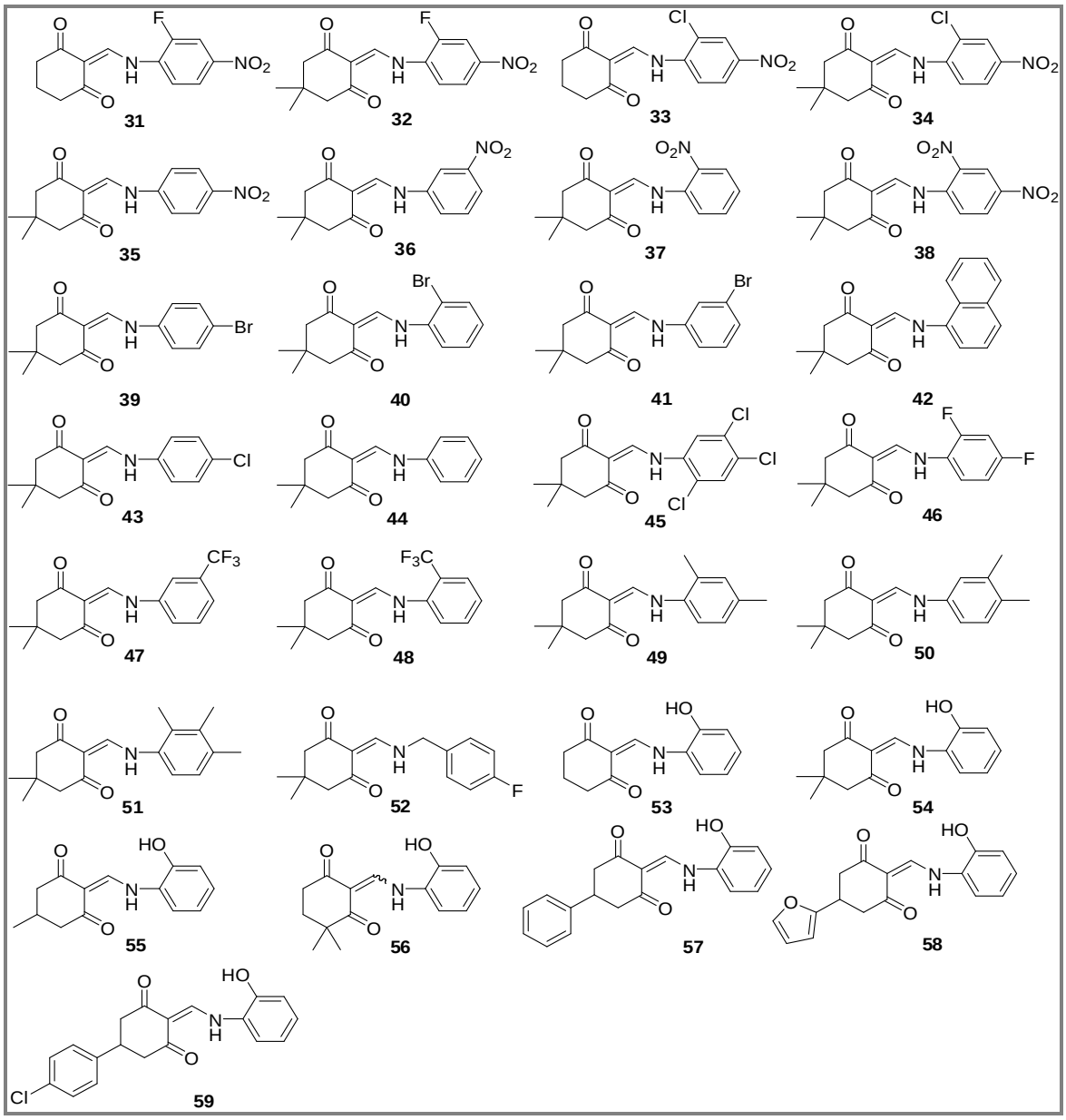


Table 9. Three more compounds synthesized



Initial screening and synthesis of the active compounds: All compounds were assessed for their potential to inhibit M. tuberculosis H37Rv growth in Middlebrook 7H9 broth with supplements as previously described. The minimal inhibitory concentrations (at which no visible growth was observed MICs) of the standard antituberculosis drugs rifampicin, isoniazid, ethambutol, streptomycin and levofloxacin are 0.078, 0.313, 1.56, 1.25 and 2.5 μg mL^{-1}, respectively. These results are in good agreement with the literature. Our initial phenotypic screening of small synthetic molecules identified two compounds (**21** and **22**) as potential antituberculosis hits. Though these compounds exhibited some activity against M. tuberculosis, this activity was not significant enough to proceed with them

Table 10. The library of synthesized compounds



for further antituberculosis drug discovery as their MIC values ranged between 40–80 μg mL^{-1}, which was significantly higher than the standard drugs. However, this anti-TB activity was a clue to the synthesis of a diverse library of molecules using this scaffold in order to find better lead structures for further study.

Initially, we synthesized few 2-alkyl-aminomethylenecyclohexane-1,3-dione-based compounds (family A, Table 7) via the condensation reaction of 1,3-cylohexadiones with various aliphatic amines in the presence of triethylorthoformate (Scheme 7). It is notably that all these compounds were obtained in excellent yield and their structures were confirmed using various spectroscopic techniques. When these compounds were evaluated against M. tuberculosis, it was observed that this synthetic approach totally diminished the activity of the parent compounds and the MIC values increased and were found to be >80 μg mL^{-1} (highest experimental concentration). Therefore, a new synthesis was designed to produce 2-phenylaminomethylene-cyclopentane-1,3-dione-based compounds from 1,3-cylopentadione and substituted-anilines (family B, Table 1, entries 6–8) in the

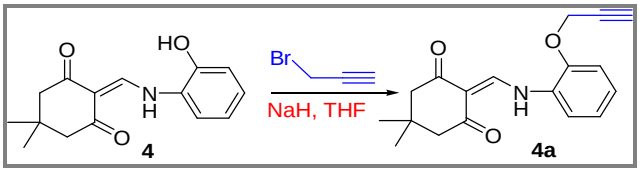
presence of triethylorthoformate. Like family A, the compounds of family-B were also screened against M. tuberculosis and this approach also led to a loss of activity (MIC >80 μg mL^{-1}). These synthetic approaches indicated that the 1,3-cylohexanedione moiety in the parental structures was critical for activity and therefore, in the next synthetic strategy this was preserved like in the parental compounds 5 and 6. Variations were made only on the right-hand portion of the scaffold with various substituted anilines in order to produce a series of 2-phenylaminomethylene-cyclohexane-1,3-diones (family C, Table 1, entries 9–34). When this family was screened against M. tuberculosis, it was observed that most of the compounds also had no activity (MIC >80 μg mL^{-1}), however, some of the compounds from this family exhibited some enhanced activity, specifically two compounds, 2-(((2-hydroxyphenyl)amino)methylene)-cyclohexane-1,3-dione (37) and 2-(((2-hydroxyphenyl)amino) methylene)-5,5-dimethylcyclohexane-1,3-dione (39), which showed excellent activity with MIC values of 5–10 and 2.5 μg mL^{-1}, respectively. Indeed, the MIC of 39 was found in the MIC range found for the standard antituberculosis drugs ethambutol, levofloxacin and streptomycin. It is worth mentioning that these results demonstrate about a 32-fold activity enhancement of the parent compounds due to the above structure activity guided synthesis. Further, by these observations, it is clear that by changing the substituent at the C-5 position of the 1,3-cyclohexanedione ring changes its MIC values considerably. Based on this fact, we next sought to synthesize 5-aryl-2- phenyl aminomethylene-cyclohexane-1,3-dione-based compounds (family D, Table 1, entries 35–37). It was observed that this structure activity guided synthesis also resulted in an improvement of the antituberculosis activity when compared to parent compounds 5 and 6, especially one of the compounds, 2-(((2-hydroxyphenyl)amino)methylene)-5-phenylcyclohexane-1,3-dione (41), which exhibited a significant MIC value of 5–10 μg mL^{-1} (Table 1).

Structural activity relationship (SAR) revealed that: (a) the presence of 1,3-cylohexadione motif and o-hydroxyl aryl ring in the scaffold are crucial for anti-TB activity (compounds 5, 6, 37–43). By replacing the 1,3-cylohexadione motif with 1,3-cyclopentadione, a drastic reduction in activity was observed (compound 12); (b) the presence of 5,5-gem-dimethyl substitution at C-5 in the 1,3-cylohexadione moiety seems to be optimal for significant MIC values (compound 39). Compounds with no substitution at the C-5 position (37) or bearing other substituents (compounds 38, 41–43) are comparatively less active than compound 39. By changing the position of the gem-dimethyl group to the C-4 position in the 1,3-cylohexadione motif also substantially diminishes the anti-TB potential (40); (c) it was interesting to note that the compounds containing a S-linkage (5, 6) exhibit lower activity than the compounds containing a –NH– linkage (37 and 39) even if the other framework was preserved. This was possibly due to the hydrogen bonding between –NH– and one of the carbonyl groups in the 1,3-dione moiety that imparts rigidity in the structure; (d) finally, it was also observed that the compounds containing analiphatic moiety are not active (compounds 7–11), while as those containing an aromatic motif with appropriate substitution are generally active (compounds 33–39). Among these compounds, the compound containing a 5,5-gem-dimethyl substitution on the 1,2-cyclohexanedione moiety connected through a –NH– linkage to the o-hydroxyl-aryl moiety (compound 39) was the most active compound found in this study. Compounds containing C-5 aryl substitution (compound 41) also look promising for future exploration. Based on this study and keeping in consideration the significant MIC value of compound 39 (2.5 μg mL^{-1}), it was further studied towards the advancement of tuberculosis drug discovery.

The present study describes the synthesis and evaluation of a library of 2-phenylamino methylenecyclohexane-1,3-diones against M. tuberculosis. This study identified "2-(((2-hydroxy phenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione" as a potential lead molecule whose MIC matches those of the standard anti-TB drugs ethambutol, levofloxacin and streptomycin. Further, its activity is highly selective against M. tuberculosis when compared to other microbes and it proved to be non-toxic to human cell lines. The structure–activity relationship data is also presented for future study. To the best of our knowledge, this study has introduced a new chemical entity with potential that is worth exploring as a future drug candidate for TB.

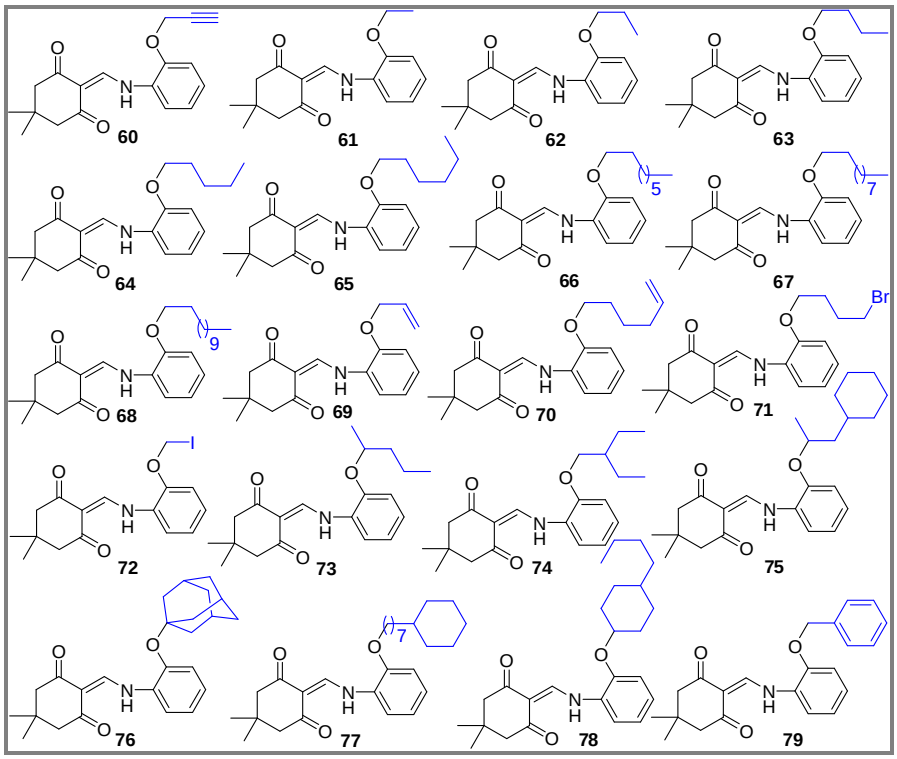
Ali MohdLone *et al.* in 2018: The study was designed with an aim to synthesize a series of 2-(((2-ether)amino)methylene)-dimedone derivatives and evaluate the synthesized compounds for anti microbial activity [**23, 24**]. Compound library was synthesized by reaction with alkyl, alkenyl, alkynyl and alicyclic bromo-compounds (Scheme 10).

The compounds were evaluated for their antibacterial activity against Gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*, *Clostridium sporogenes*) and Gram-negative bacteria (*Pseudomonas aeruginosa*, *Escherichia coli*). The activity of these compounds was also evaluated against fungi (*Aspergillus fumigatus*, *Penicillium chrysogenum*, *Fusarium oxysporum*, *Candida albicans*) and molds (*A. niger* and *A. oryzae*). Broth microdilution method and CLSI guidelines with minor modification were used for the determination of anti-bacterial and antifungal activity, respectively. Although four compounds (**4i**, **4j**, **4k** and **4l**) showed good antibacterial activity but compound **4k** was found to be most active chemotype in the series. Compound **4k** was found to be active against *S. aureus*, *B. cereus* and *B. subtilis* bacterial strains at one dilution lower compared to the control ciprofloxacin. Antibacterial activity of compound **4k** was comparable to ciprofloxacin against *S. pyogenes* and *M. luteus*. The compound **4d**, **4e** and **4s**showed good antifungal and antimold activity compared to other chemotypes. However, in comparison to fluconazole both the compounds showed lower activity. The results merit the antimicrobial promise of the 2-(((2-ether) amino) methylene)-dimedone analogs (Table 11).

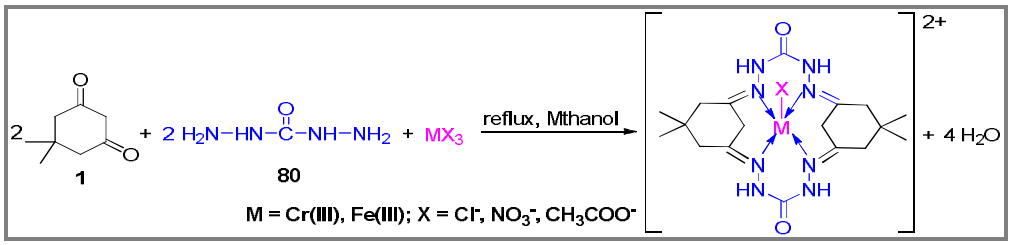


Scheme 10. Synthesis of 2-(((2-hydroxyphenyl)amino)methylene)-dimedone propargyl ether.

Table 11. Library of synthesized compounds.

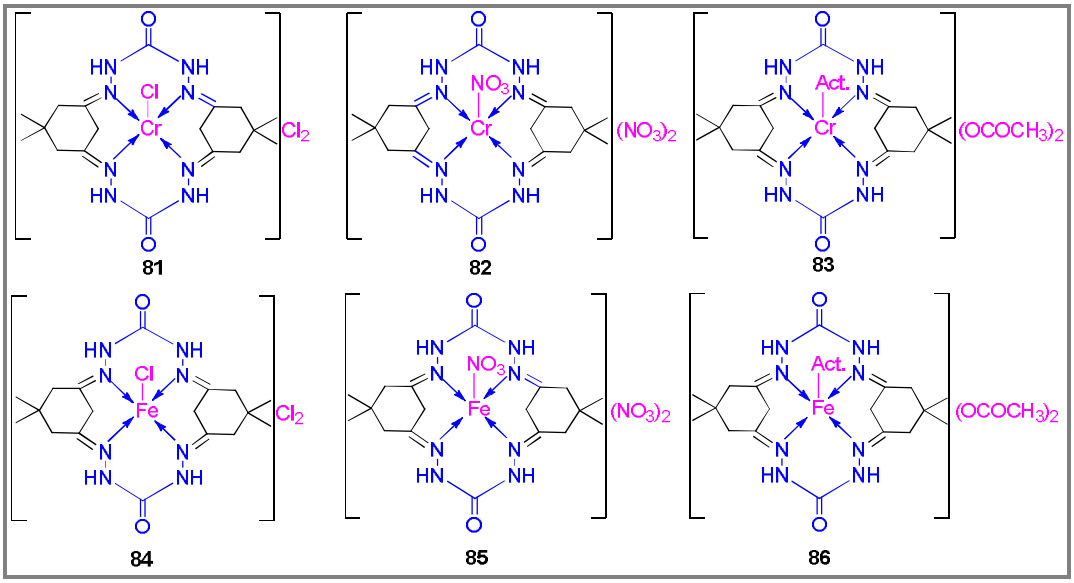


D.P. Singh *et al.* in 2014: D.P. Singh *et al.* in 2014 synthesized six complexes by the template condensation reaction between dimedone and carbohydrazide in methanol solvent (Scheme 11). The complexes obtained were having general formula $[M(TML)X]X_2$; where TML is a tetradentate macrocyclic ligand; M = Cr(III), Fe(III); X = Cl^-, NO_3^- and CH_3COO^- (Table 12) [36].



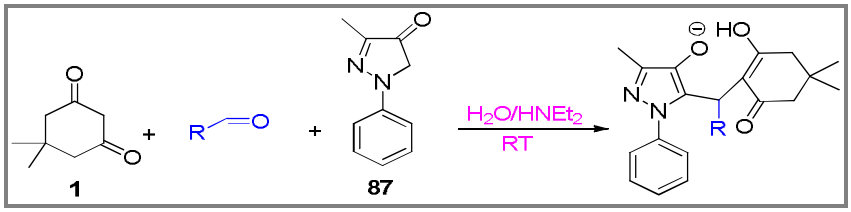
Scheme 11. Synthesis of macrocyclic complexes derived from dimedone and carbohydrazide with trivalent metal salts.

Table 12. Library of synthesized compounds



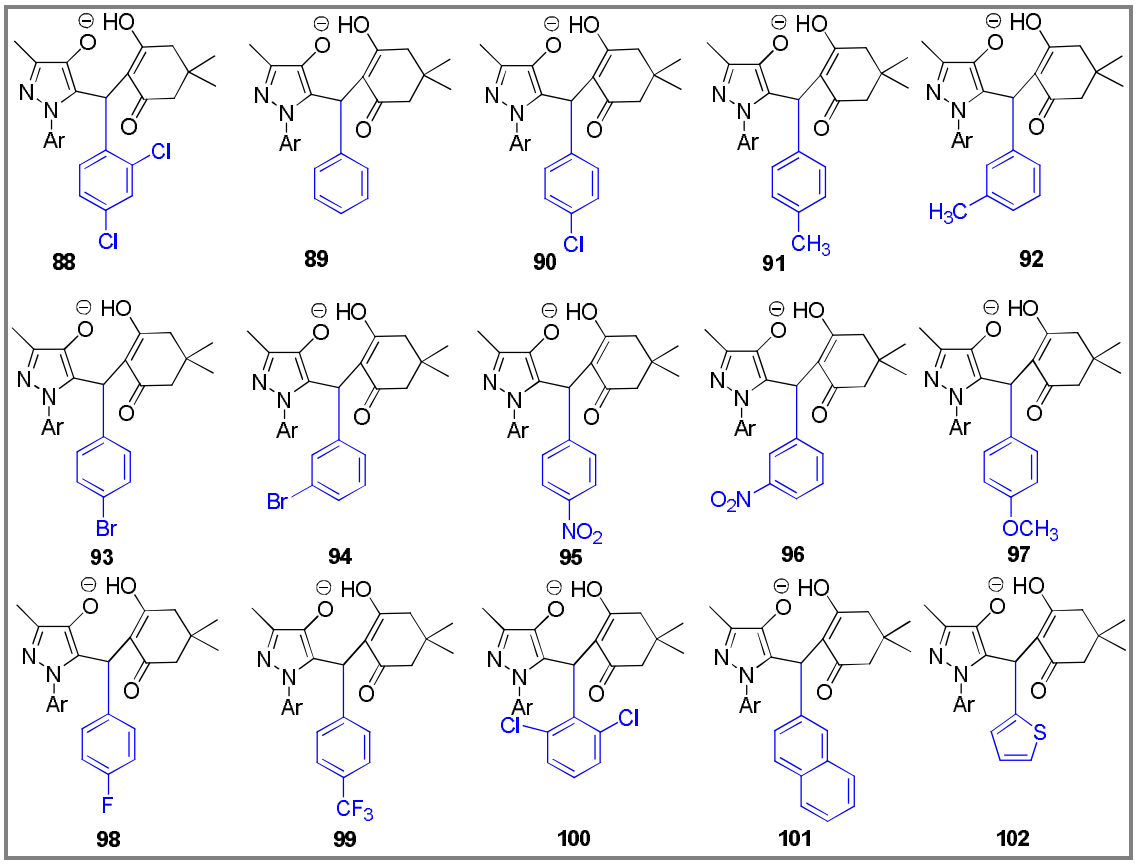
The synthesized macrocyclic complexes were screened for antibacterial activity against Gram-positive and Gramnegative bacteria *in vitro*. In this study macrodilution tube method was used for determination of Minimum Inhibitory Concentration (MIC) of the synthesized complexes against various bacterial strains. The antibacterial activity of the synthesized complexes was compared with the standard antibiotics, linezolid and cefaclor. The MIC of linezolid against B. cereus, S. aureus, E. coli and S. typhi was measured as 4.0, 4.0, 16.0 and 32.0µg mL^{-1}, respectively, while as that of cefaclor as 8.0, 2.0, 8.0, 16.0 µg mL^{-1} against B. cereus, S. aureus, E. coli and S. typhi, respectively. Among the synthesized complexes **82**, **85** and **86** exhibited good antibacterial activity against both Gram (+) and Gram (-) bacteria with zone of inhibition in the range 26.0 to 26.6 mm. Complex **83** showed MIC of 32.0µg mL^{-1} against S. typhi which is equal to the MIC shown by the standard antibiotic linezolid for the same bacterial strain. Complex **86** showed MIC of 16.0 µg mL^{-1} against S. typhi which is equal to the MIC shown by the standard antibiotic cefaclor for the same bacterial strain. The complexes **82** and **86** showed MIC of 16.0 µg mL^{-1} against E. coli which is equal to the MIC shown by the standard antibiotic linezolid for the same bacterial strain. Complexes **83** and **85** showed MIC of 8.0 µg mL^{-1} against E. coli which is equal to the MIC shown by the standard antibiotic cefaclor for the same bacterial strain. Complex **86** showed MIC of 4.0 µg mL^{-1} against S. aureus, which is equal to the MIC shown by the standard antibiotic linezolid for the same bacterial strain. Complex **81** showed MIC of 8.0 µg mL^{-1} against B. cereus, which is equal to the MIC shown by the standard antibiotic cefaclor for the same bacterial strain.

Assem Barakat *et al.* in 2018: Assem Barakat *et al.* in 2018 synthesized pyrazole-dimedone derivatives (Scheme 12) via one pot Knoevenagel condensation Michael addition of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one, 1,3-dicarbonyl compound (dimedone) and various aldehydes in the aqueous diethyl amine (Table 13) [37]. This one pot three component reaction delivered the hybrid compounds **88**–**102** in very good yields.



Scheme 12. Synthesis ofpyrazole-dimedone derivatives.

Table 13. Library of pyrazole-dimedone derivatives synthesized



The antibacterial activity of the novel pyrazole-dimedone compounds were evaluated against gram positive bacteria including *E. faecalis* ATCC29212, S. aureus ATCC 29213, and B. subtilis ATCC 10400. Ciprofoxacin was used as standard drug. The results revealed that all pyrazole-dimedone compounds were active against the tested strains including S. aureus, *E. faecalis*, and B. subtilis. Pyrazole-dimedone **98** was the most active compound against B. subtilis with MIC value of 8.0 µg L^{-1}. Compounds **92** and **99** having 3-methyl and 4-trifuromethyl substituents on the phenyl ring respectively exhibited good activity against S. aureus with MIC value of 16.0 µg L^{-1}. Compounds **88-91**, **93**, **94**, **96**, **98** and **100**–**102** showed relatively lower activity against S. aureus with MIC value of 32.0 µg L^{-1}. Compounds **95** and **97** having 4-nitro and 4-methoxy substituents on the phenyl ring were the least active derivatives against S. aureus with MIC values of 64.0 µg L^{-1}. Compound **89** bearing unsubstituted phenyl ring exhibited good activity against *E. faecalis* with MIC values of 16.0

µg L^{-1}. Compounds **88**, **90**-**92**, **94**, **95** and **97**–**102** showed lower activity against *E. faecalis* with MIC value of 32.0 µg L^{-1}. Compounds 93 and 96 having 4-bromo and 3-nitro substituents on the phenyl ring respectively were shown as the least active derivatives against *E. faecalis* with MIC value of 64.0 µg L^{-1}. Substituted pyrazole-dimedone **89** without substituent on the phenyl ring and **102** having thiophene ring exhibited good activity against B. subtilis with MIC value of 16.0 µg L^{-1}. Compounds **88**, **90**, **91**, **93**–**97** and **99**–**102** showed lower activity against *B. subtilis* with MIC value of 32.0 µg L^{-1}. Compound **92** having 3-methyl substituent on the phenyl ring was shown to be the least active against B. subtilis with MIC value of 64.0 µg L^{-1}.

The newly synthesized pyrazole-dimedone derivatives were evaluated for their antifungal activity against fungi *C. albicans* (ATCC 2091) by the diffusion agar and serial dilution method (BSAC, 2015). Fluconazole was used as standard antifungal agent. Results revealed that all pyrazole-dimedone compounds 88-**102** were active against the tested-strains *C. albicans* ATCC 2091. Pyrazole-dimedone **102** bearing thiophene was the most active compounds from this series against *C. albicans* ATCC 2091 with MIC value of 4.0 µg L^{-1}. Compounds **90**, **91**, **95**, **98** and **100** possessed good activity against C. albicans with MIC values of 16.0 µg L^{-1}. Compounds **88**, **89**, **92**–**94**, and **96**, **97**, **94** and **101** were the least active among this series as antifungal agent with MIC values of 32.0 µg L^{-1}.

APPLICATION

- Dimedone acts as an excellent precursor for the synthesis of partially hydrogenated and fused heterocyclic compounds.
- It serves as an important precursor for the synthesis of compounds possessing anti-bacterial and anti-fungal activity.
- In the present review application of dimedone as a precursor for the synthesis of anti-microbial compounds is discussed.
- It is used for polyhydroacridine, tetrahydrobenzopyran, polyhydroquinolines, etc synthesis.

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