# A Review For Biological Activity On Hydrazide Hydrazones: A Promising Moiety

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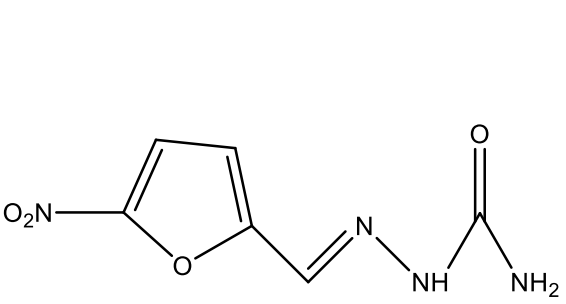
**Abstract:**
**Hydrazide-hydrazones derivatives are available in numerous bioactive atoms and show a wide variety of biological activities, like antibacterial, antitubercular, antifungal, anticancer, mitigating, anticonvulsant, antiviral and antiprotozoal activity. In this manner numerous researchers synthesised different hydrazide-hydrazones and assess them for their activity. This paper is centred on the overview of the literature finding of the last 15 years covering the research on antimicrobial, anticancer and anticonvulsant of hydrazide-hydrazones derivatives.**
**Keywords: Hydrazide-hydrazones, antibacterial, anticonvulsant, anticancer.**

## Introduction:

Hydrazide-hydrazones a carbonyl category with azomethine group (-NH-H=CH-) is very popular moiety in last two decade's for research because of its play a vital role in the research work as intermediate. This is the very interesting topic for the researcher due to their wide verity of promising biological activities including anti-microbial, anti-cancer[1-4], anti-conversant, anti-tubercular5-8, anti-inflammatory[9,10] analgesic activities[11-12]. The basic structure of hydrazones having two nitrogen (-$NNH_2$) and one carbon (C=O) atoms which make C=N bond by conjugation of a lone pair of electrons of nitrogen. They are showing both nucleophilic as well as electrophilic nature for activity. The general method for the synthesis of the hydrazones is the reaction of hydrazine with carbonyl compounds such as aldehydes or ketones in solvents like ethanol, methanol, butanol.

In this case some hydrazide-hydrazone components have been considered as drugs and have been used in clinics, such as furazolidone[13], Nifuroxazide,(D) an oral antibiotic; used in colitis and enteritis caused by bacteria or protozoan infections, treatment respectively, Nitrofurazone[14]in the treatment of skin infections due to skin grafts and nitrofurantoin[15] in urinary infections.

(Fig.1)

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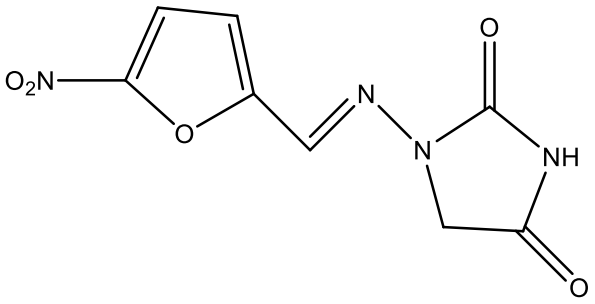
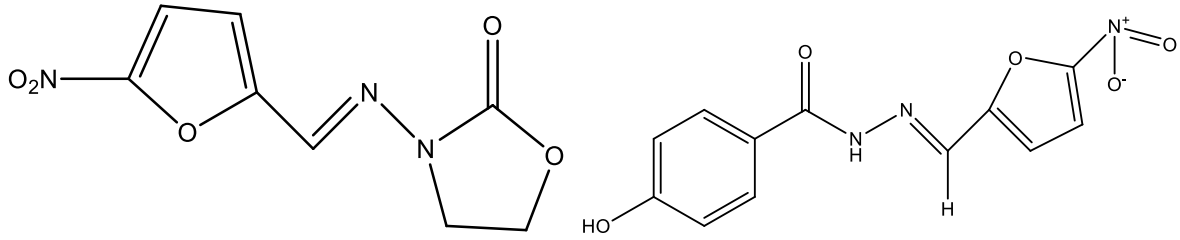



B



C D

**Fig. 1** Chemical structure of medicines containing hydrazide-hydrazone moiety: nitrofurazone (A), nitrofurantion (B) and furazolidone (C)

**Antibacterial Activity:** The multi- resistant bacterial strains property of bacteria increase the searching of effective and non-toxic agents for new researchers. Even some drug (mentioned previously) are used with compromised immune system of patients. So the scopes of hydrazide-hydrazones showed promising result with less side effects. In this series Łukasz Popiołek et al. in 2019 synthesised 19 new compounds of hydrazide-hydrazones of 5-nitrofuran-2-carboxylic acid. The condensation processed with various aliphatic and aromatic aldehydes gave these new series with antibacterial activity and then compare that with vitro antimicrobial assays. This research showed the substitution of alkyl chains showed higher activity against Gram-negative bacteria than hydrazones with aryl substituents. The substitutions also showed anti-fungal activity. Researcher found by structure-activity analysis that short alkyl chains are good for activity like compound no. 1,2,3,4 and 5.[16](Fig 2 and table 1)

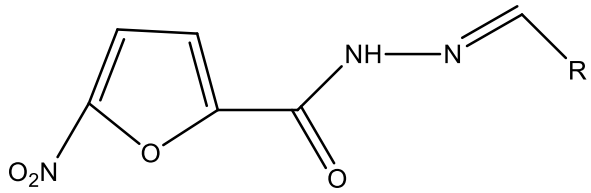
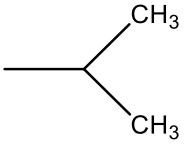
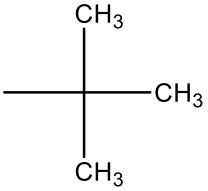
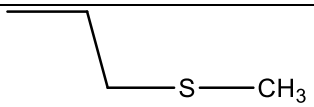


**Fig 2:** 5-nitrofuran-2-carboxylic acid hydrazide-hydrazones derivatives.

**Table no -1:** Derivatives of 5-nitrofuran-2-carboxylic acid hydrazide-hydrazones

| Compound no | R |
|---|---|
| 1 |  |
| 2 |  |
| 3 |  |
| 4 |  |
| 5 |  |
| 6 | 2-iodophenyl |

The compound 6 which contain 2-iodophenyl substituent, were showed highest minimal fungicidal concentrations against all reference Candida spp.

In 2019 an another scientist Van Hien Pham et al. have been synthesized hydrazide- hydrazones with 1-adamantane carbonyl moiety with various substituted benzaldehyde and acetophenones. The new synthesized compounds were tested for activities against some Gram-negative and Gram-positive bacteria, and the fungus Candida albicans. Compound 7,8,9,10 (Fig 3) showed potent activity for antibacterial against Gram-positive bacteria such as Enterococcus faecalis (ATCC13124), Staphylococcus aureus (ATCC25923), and Bacillus cereus (ATCC 13245).[17]

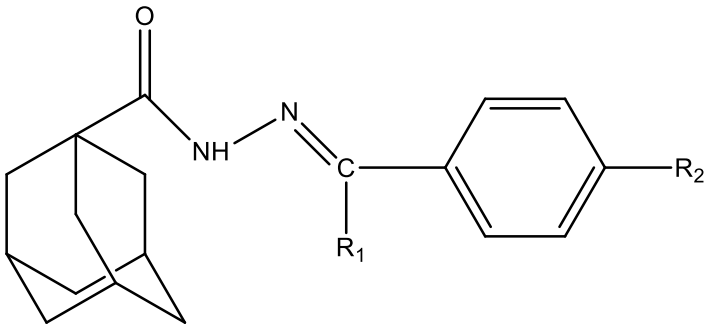



**Fig 3:** Hydrazide-hydrazones with 1-adamantane carbonyl

**Table no-2:** Results of Hydrazide-hydrazones with 1-adamantane carbonyl derivatives

| Comp. No | $R_1$ | $R_2$ | Minimum inhibitory concentration (MIC) in µM | | |
|---|---|---|---|---|---|
| | | | Enterococcus faecalis | Staphylococcus aureus | Bacillus cereus |
| 7 | H | -OH | 12.5 | 12.5 | 12.5 |
| 8 | H | $-NO_2$ | 25 | 25 | 25 |
| 9 | $CH_3$ | -OH | 12.5 | 25 | 25 |
| 10 | $CH_3$ | $-NO_2$ | 12.5 | 50 | 100 |
| STD: Streptomycine | | | 350 | 350 | 175 |

In 2018 one more scientist Samir Y Abbas and his team synthesized some quinoxaline N- propionic and O-propionic hydrazide derivatives as antibacterial agent for different bacterial strains. In that they found compound no 13 showed fourfold potency against bacterial strains for A. fumigatus (table no 2) and compound 12 and 11 showed two fould and equipotent activity for various strain against gentamycin as standard drug. The values of Minimum inhibitory concentration in µg/mL are summarized in Table no. 2. The study of quinoxaline N- propionic hydrazide derivative (fig 4) showed that Changing the substituent on pyrazole from phenyl to 4-chlorophenyl to 4- methylphenyl (11→12→13) had a moderate difference in the antimicrobial activity. The 3-p-tolyl-pyrazolyl is responsible for this in case of compound 13.[18]

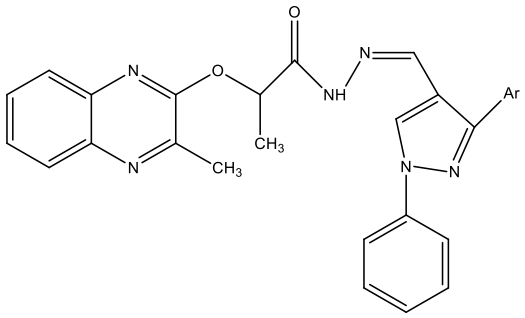
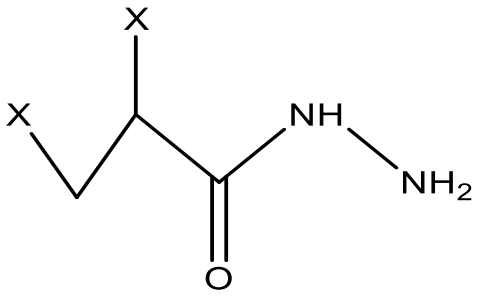



**Fig no. 4:** Propanoic acid derivative

**Table No. 3** Results of Propanoic acid derivative

| Comp. no | Ar | S.aureus | S.epidermidis | S.pyogenes | B. subtilis | E.faecalis |
|---|---|---|---|---|---|---|
| 11 | $C_6H_5$ | 29.9 | 27.6 | 28.5 | 34.8 | 23.8 |
| 12 | $C_6H_4Cl_4$ | 29.2 | 26.1 | 28.3 | 36.3 | 23.6 |
| 13 | $C_6H_4(CH_3)_4$ | 30.0 | 28.2 | 28.5 | 32.9 | 26.4 |
| Std: Gentamycin | | | | | | |

Łukasz Popiołek et al. in 2017 obtained a series of hydrazide hydrazones of 2,3-disubstituted propionic acid by the using ethyl ester and in second step hydrazide-hydrazones were obtained by condensation reaction of appropriate hydrazide with various aromatic and hetero-aromatic aldehydes (fig 5). And all the compounds tested for the antimicrobial activity against Gram positive like S. aureus S. epidermidis , B. subtilis, B. cereus, Micrococcus luteus and Gram-negative bacteria B. bronchiseptica, E. coli, Klebsiella pneumoniae, Proteus mirabilis, S. typhimurium, P. aeruginosa. But the 2-3- dibromo propionic acid were showed good activity against all in comparison of other derivative. These compound also tested for anti-fungal activity where fungi belonging to yeasts (Candida albicans ATCC 10231, Candida parapsilosis ATCC 22019). They are showed good to moderate activity.[19]

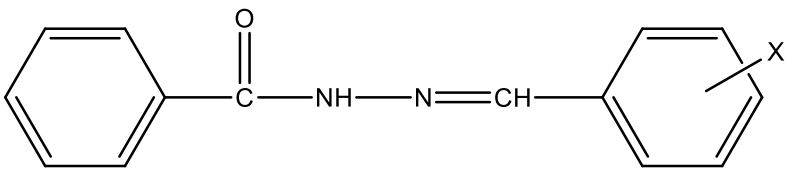



Compound 14

**Fig 5:** new hydrazide-hydrazones of 2,3-dihalogen (Br and Cl) substituted propionic acids as compound 14

The in vitro screening result of newly synthesized (E)-N'-1(substituted benzylidene) benzohydrazides moiety revealed that some of the compounds had significant antimicrobial activity by G. Thirunarayanan et. al in 2017. They synthesized ten newly benzohydrazide by the reaction of appropriate mixture of benzohydrazide and ortho, meta and para substituted benzaldehydes with sodiumhydroxide solution in ethanol as a solvent. The antibacterial activity measured by zone of inhibition in mm values and all the benzohydrazide derivatives have been showed satisfactory sensitivity against M. luteus bacterial strain except 2-chloro and 3-hydroxy substituents.[20]

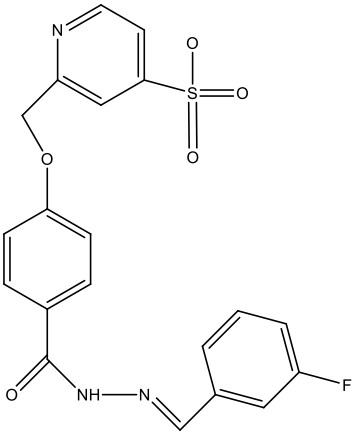
X= H, 3-Br, 2-Cl, 4-Cl, 4-F, 3-OH, 4-OH, 4-C $H_3$, 2-$NO_2$, 3-$NO_2$




Compound 15

**Fig 6:** benzohydrazide showing interesting activity against all used bacterial strains.

Dommati et al. in 2016 obtained novel 14 new benzohydrazide derivatives by using vanilline as starting material and evaluated them for in vitro antibacterial activity. The highest activity showed by compound 15 and 16 (fig 7)against two Gram-negative bacteria, (E.coil (ZOI=24, 22) and P. aeruginosa ZOI= 20,18) and Gram positive (S.aureus ZOI= 25, 20 and S.pyrogenes ZOI= 18, 16) bacterial strain by using control as Norfloxacin at 50µg/mL.[21]

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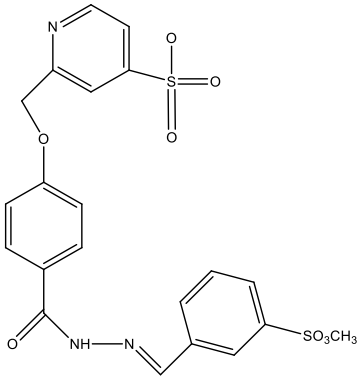


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**Fig 7:** benzohydrazide derivatives

Where as in 2016 Lukasz Popiolek and Anna Biernasiuk synthesized another series of hydrazide-hydrazones of phenylacetic and hydroxyacetic acid by the condensation reaction of 2-substituted acetic acid hydrazide with different aromatic aldehydes (fig 8). All synthesised compounds were screened for antimicrobial and anti-fungal activity by using the broth microdilution method. In this series they found one compound very strong activity against all tested reference Gram positive bacteria with B. subtilis, even 32 and 16 times more than standard drug cefuroxime and ampicillin respectively. Whereas the activity against B. cereus was 8 times higher than activity of cefuroxime for the same compound 18. [22]

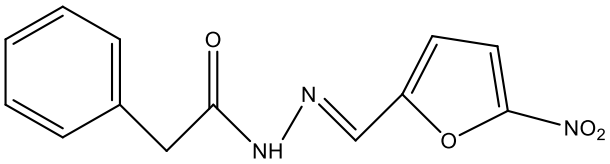



**Fig 8:** substituted acetic acid hydrazide Compound 18

In 2016 Madhusudan Raju et al. synthesized and evaluated antimicrobial activity for N-substituted-1-benzyl-1H-1,2,3triazole-carbohydrazide derivatives (fig 9). Four out of ten newly synthesized compounds showed significant antimicrobial activity against Gram positive bacteria (Staphylococcus aureus and Staphylococcus pyogenes) and Gram-negative bacteria (Escherichia coli and Pseudomonas aeruginosa). These four compounds embedded with hetrocyclic rings such as Quinaxaline (Compound 19), Quinoline (compound 20), Imiddazole (compound 20) and Pyridine ring (compound 21) (table 4) [23]

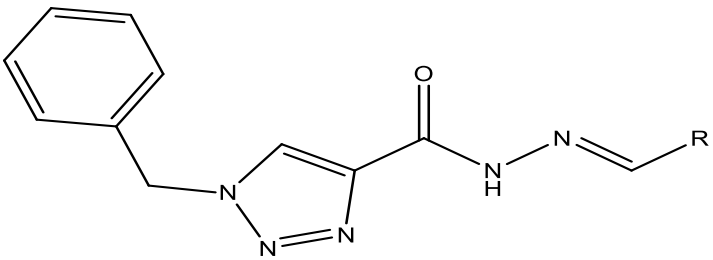
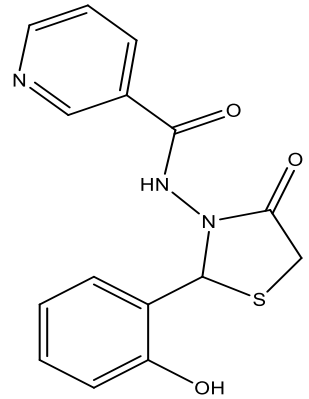



**Fig 9:** 1,2,3triazole-carbohydrazide derivatives

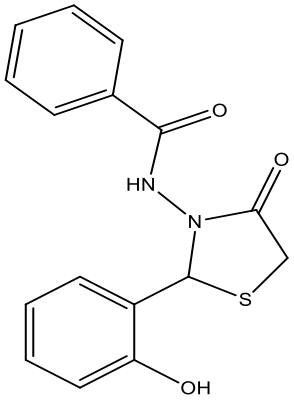
**Table no 4:** Results of 1,2,3triazole-carbohydrazide derivative

| No. of Comp | R | Zone of Inhibition (mm) | | | |
|---|---|---|---|---|---|
| | | S. aureus | S. pyogenes | E.coil | P. aeruginosa |
| 19 | Quinaxaline | 21 | 23 | 27 | 26 |
| 20 | Quinoline | 22 | 23 | 24 | 23 |
| 21 | Imiddazole | 23 | 22 | 26 | 25 |
| 22 | Pyridine | 22 | 21 | 25 | 26 |
| Std. | Ciprofloxacin (Conc. 250 µg/mL) | 28 | 27 | 22 | 22 |

In 2014, Lukasz Popiolek synthesised 1,3-thiazolidin-4-one derivatives obtained from carboxylic acid hydrazides. These hydrazides were the resultant of equimolar solution of benzoic or nicotinic acid hydrazide with appropriate aromatic aldehydes. Where Corresponding N-substituted hydrazide derivatives in of 1,4- dioxane and mercaptoacetic acid gave 2,3-disubstituted-1,3-thiazolidin-4-one derivatives. All the synthesized compounds were subjected to in vitro antimicrobial assays. In which one of the Compound 23 showed maximum activity with MIC = 62.5-1000 µg/ml and MBC ≥ 1000 µg/ml for approximately all the strains. But Compound 24 showed mild activity to all investigated Staphylococci and S. Pneumoniae with MIC = 1000 µg/ml, Bacillus spp. (MIC 250-1000 µg/ml) and good bioactivity to M. luteus and Bordetella bronchiseptica (MIC = 62.5 µg/ml). [24]




Compound 16




Compound 17

Compound 23 Compound24

**Fig 10:** carboxylic acid hydrazides

In another researcher, Chandrasekhar et al. in 2013 synthesised fifteen new hydrazone derivatives. For this they used 2,5-Difluorobenzoic acid with systematic conversion by hydrazide and then by various benzaldehydes. All compounds were tested for E. coli, P. aeruginosa, S. aureus and S. pyogenes has revealed activities against the control drug Ampicillin. Compound 26, 29, 30 (fig 11)showed excellent activity(Table no.5) for E.coli and 25, 27 and 28 displayed good activity towards all the tested bacterial strains.[25]

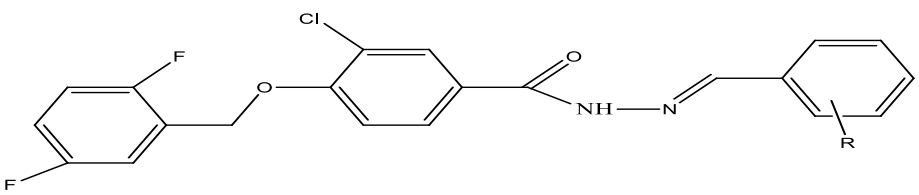



**Fig 11:** 2,5-Difluorobenzoic acid with different derivatives

**Table no. 5:** Results of in vitro antibacterial screening results of 2,5-Difluorobenzoic acid with different derivatives

| Compound | R | MIC (ug/ml) | | | |
|---|---|---|---|---|---|
| | | E.Coil | P.aeruginosa | S.Aureus | S.Pyogenes |
| 25 | 3,4,5-OMe | 22 | 20 | 21 | 19 |
| 26 | 4-$CF_3$ | 24 | 21 | 22 | 21 |
| 27 | 4-$OCF_3$ | 22 | 20 | 21 | 19 |
| 28 | 3-$CF_3$ | 19 | 18 | 20 | 18 |
| 29 | 2-$CF_3$ | 23 | 22 | 24 | 21 |
| 30 | 2,4-di-fluoro | 24 | 21 | 23 | 21 |
| Std | Ampicillin | 22 | 20 | 21 | 19 |

Among the nicotinic acid benzylidene hydrazide analogs by Rakesh Narang and his team in 2012 synthesized some compounds. In that compound 31, 32, 33, 34, 35 and 36 (fig 12) tested for in vitro antibacterial and antifungal activity . The tested Compounds showed most potent antimicrobial activity on the basis of the measurement of MIC against two Gram-positive S. aureus, B. subtitlis and one Gram-negative E.coli bacterial strains, when compared to Norfloxacin used as a control (MIC= 25- more then 25). (table no. 6)The QSAR study of theses compound indicated that the presence of chloro group, electron withdrawing group ($NO_2$), -OH gp in phenyl ring enhanced the activity.[26]

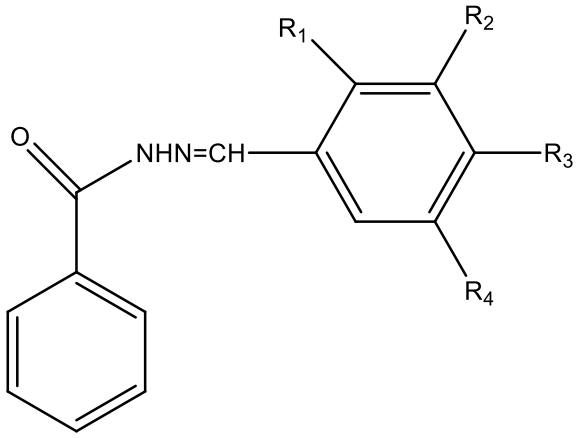



**Fig: 12** nicotinic acid benzylidene hydrazide

**Table 6:** nicotinic acid benzylidene hydrazide derivatives with antibacterial and antifungal activities.

| C. No. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | S.aureus | B.subtitlis | E.coil | C.albicans | A.niger |
|---|---|---|---|---|---|---|---|---|---|
| 31 | Cl | H | H | H | 1.33 | 1.94 | 1.33 | 1.33 | 1.94 |
| 32 | Br | H | H | H | 1.09 | 1.39 | 1.39 | 1.39 | 1.69 |
| 33 | $NO_2$ | H | H | H | 1.33 | 1.94 | 1.33 | 1.33 | 1.94 |
| 34 | $OCH_3$ | H | H | $OCH_3$ | 1.36 | 1.36 | 1.96 | 1.36 | 1.96 |
| 35 | H | $OCH_3$ | OH | H | 0.43 | 0.43 | 0.43 | 1.34 | 1.64 |
| 36 | H | $OC_2H_5$ | OH | H | 1.36 | 1.36 | 1.06 | 1.36 | 1.96 |
| Std | Norflxacin | | | | 1.12 | 1.29 | 1.54 | 1.56 | 0.43 |

Balasubramanian Narasimhan et al. in 2011 synthesised and evaluated antimicrobial activity, as well as performed QSAR studies of twenty new compounds of 3-ethoxy-4-hydroxybenzylidene/4-nitrobenzylidene hydrazided. Two of the new compounds (37 and 38) showed the antimicrobial activity higher than that of ciprofloxacin against S. aureus, B. sublitis, E. coli. The best antibacterial

activity was displayed (fig 13: compound 37 and 38,) by the increase in chain length of acid portion with presence of electron withdrawing group $NO_2$. [27]

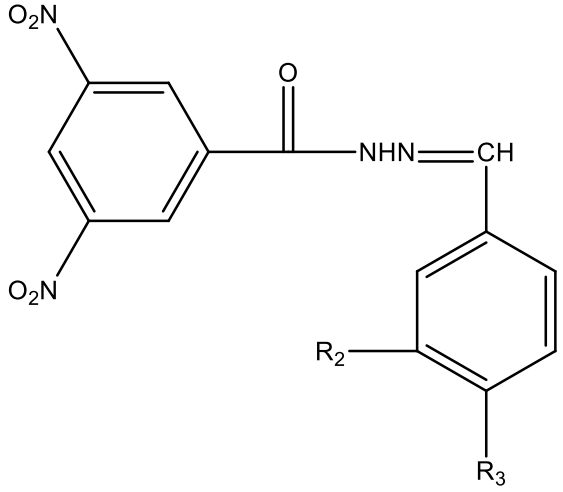



**Fig 13:** new compounds of 3-ethoxy-4-hydroxybenzylidene/4-nitrobenzylidene hydrazided for compound 37: $R_2$: OEt $R_3$: OH and compound 38: $R_2$ : H $R_3$: $NO_2$

In the series of searching of good anti-bacterial agent in 2011 an scientist team Sibel Suzena et al. have been synthesised some indole hydraozone derivatives with 1-Methylindole-3-carboxaldehyde and appropriate hydrazine by condensation process. All were inspected for antimicrobial activity for six different bacterial strains by using the two-fold serial dilution technique. Two derivatives of them (fig 14: Compound 39 and 40) showed good activity (ref. Table 4) and the study of activity of compounds indicates that it increased with the introduction of halogen atoms into the phenyl ring. Even mono halogenated derivatives having less activity in comparison of dihaloginated compounds specifically ortho-halogenated compounds were found more active than the others(table no 7).[28]

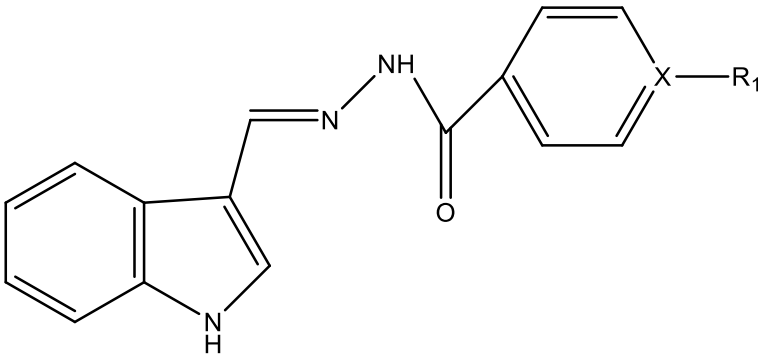



**Fig 14:** Indole Hydrazones derivatives

**Table 7:** Results of antibacterial activity of Indole Hydrazones derivatives.

| Comp | $R_1$ | X | *S. aureus* | MRSA standard | MRSA isolate | *E. coli* | *B. subtilis* | *C. albicans* |
|---|---|---|---|---|---|---|---|---|
| 39 | - | N | 100 | 100 | 50 | 50 | 50 | 12.5 |
| 40 | $OCH_3$ | C | 100 | 50 | 100 | 50 | 100 | 6.25 |
| Ampicillin as reference | | | 1.56 | 12.5 | Not tested | Not tested. | 50 | Not tested. |

Cristina Moldovan et al in 2011 have been synthesized new aroyl-hydrazones by condensing some derivatives of 4-[2-(4-methyl-2-phenyl-thiazole-5-yl)-2-oxo-ethoxy]-benzaldehyde and 2, 3 or 4-(2-arylthiazol-4-yl-methoxy)-benzaldehyde, respectively with isonicotinoyl hydrazide, in 50% acetic

acid by reflux . Newly synthesised compounds were screened for antimicrobial activity by using in vitro disk diffusion method. The various Gram-negative bacteria showed poor to moderate antibacterial activity, where compound 35(fig 15) being the only displayed Gram-positive bacterial growth inhibition (12-15 mm diameter of growth inhibition zone).[29]

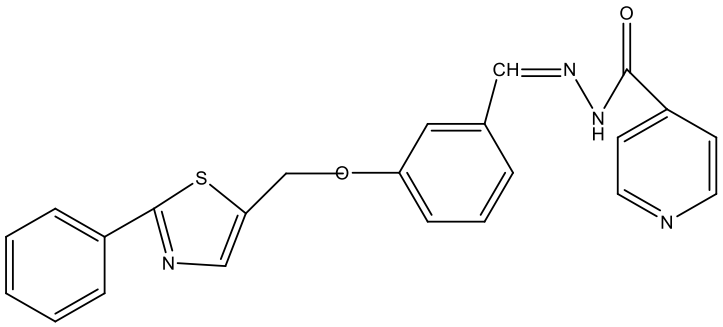



**Fig 15:** Aroyl-hydrazones derivative for compound 41

In another researcher in 2011, Golla Narayana Swamy et al. reported newly N'-arylidene-3-(4-chlorophenylsulfonyl) propanehydrazides derivatives. For this they reacted Benzaldehyde with 3-[(4-chlorophenyl)sulfonyl]propane hydrazide. All were tested for antibacterial and antifungal activity against two gram-positive bacteria B. subtilis and S. aureus and two gram-negative bacteria E. *coli* and S. *typhi* by using cup plate method. The compounds 43, 44 (fig 16 and table 8)showed prominent activity against gram positive bacteria. Compounds 42, 45 showed significant activity against gram negative bacteria.(Ref: Table-5). The study suggested that, the methoxy (ortho and meta both)or choloro group at phenyl ring showed mild to moderate activity in synthesised compounds of series of new hydrazones. [30]

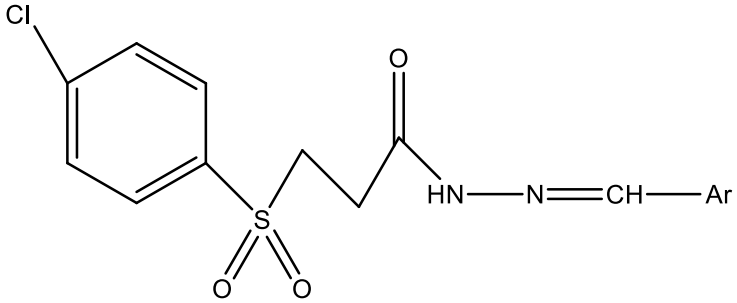
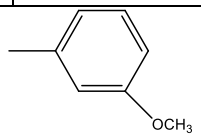
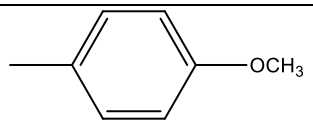
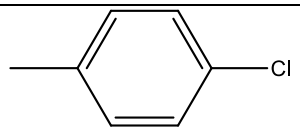
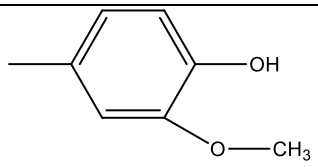



**Fig 15:** N'-arylidene-3-(4-chlorophenylsulfonyl) propanehydrazides derivatives

**Table-8:** N'-arylidene-3-[(4-chlorophenyl)sulfonyl]propanehydrazide derivative with antimicrobial activity in mm.

| Comp | R | B.subtilis | S.aureus | E.coli | Salmonella Typhi |
|---|---|---|---|---|---|
| 42 |  | 17 | 13 | 19 | 19 |
| 43 |  | 19 | 21 | 10 | 10 |
| 44 |  | 18 | 20 | 12 | 18 |

| | | | | | |
|---|---|---|---|---|---|
| 45 |  | 19 | 16 | 21 | 19 |
| STD | Ampicillin sodium | 24 | 22 | 20 | 21 |

Aakash Deep in 2010, reported biphenyl-4-carboxylic acid hydrazide-hydrazone derivatives. The reaction between biphenyl-4-carboxylic acid and methanol in the presence of sulfuric acid yielded corresponding methyl ester of biphenyl-4- carboxylic acid, which on reaction with hydrazine hydrate afforded the corresponding hydrazides (fig 17)in appreciable yield. Seven of the new compounds showed the in-vitro antimicrobial activity (table 9)higher than that of Ciprofloxacin against B. subtilis, E coli, P. aeruginosa by using two fold dilution method.[31]

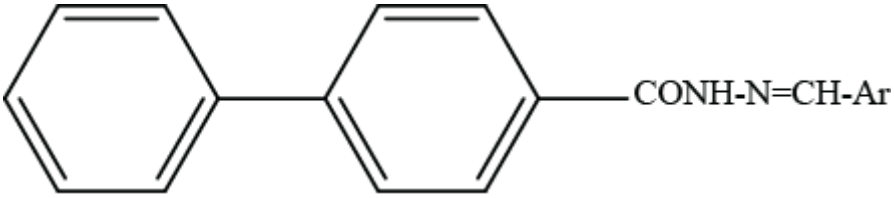



**Fig 16:** biphenyl-4-carboxylic acid hydrazide-hydrazone derivatives.

**Table-9:** Minimum inhibitory concentration (µg mL) of biphenyl-4-carboxylic acid hydrazide-hydrazone derivatives.

| Comp | Ar | E.coli | P.aeruginosa | S.aureus | B.subtilis |
|---|---|---|---|---|---|
| 46 | 2-$NO_2C_6H_4$ | 2.50 | 2.5 | 1.25 | 2.50 |
| 47 | 2-$ClC_6H_4$ | 0.31 | 1.25 | 0.62 | 0.31 |
| 48 | 3-$ClC_6H_4$ | 1.25 | 2.5 | 1.25 | 1.25 |
| 49 | 4-$ClC_6H_4$ | 1.25 | 2.5 | 1.25 | 2.50 |
| 50 | 3-$OCH_3C_6H_4$ | 1.25 | 0.62 | 0.62 | 2.50 |
| 51 | 4-$OCH_3C_6H_4$ | 2.50 | 1.25 | 2.50 | 1.25 |
| 52 | 3-$BrC_6H_4$ | 1.25 | 0.63 | 1.25 | 0.62 |
| Ciprofloxacin | | 0.01 | 0.25 | 0.15 | 0.12 |

In another research, Yusuf Özkay et al. in 2010 synthesised novel hydrazide hydrazones as a result of ester of 4-(1H-benzimidazole-2-yl)benzoic acid with hydrazine hydrate. The obtained compound were evaluated antibacterial activity as well as SAR studies of twelve benzimidazole-hydrazones. Five of synthesized compounds (Fig 18: 53, 54, 55, 56, 57) showed the most potent activity towards P.vulgaris and P. aeruginosa with MIC 50µg/mL against chloramphenicol. The activity of these compounds against S. typhimurium bacterial strain was significant with MIC value 6.25µg/mL. They suggested that electron withdrawing groups are lesser active against standard whereas the electron donating groups such as choloro, bromo and methyl substituted are showed higher activity.[32]

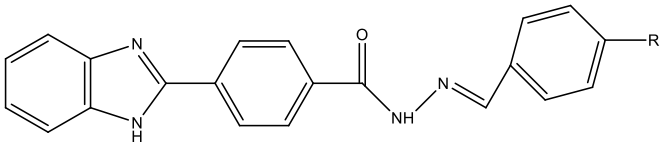



**Fig-18** Novel benzimidazole-hydrazone obtained from 4-(1H-benzimidazole-2-yl)benzoic acid. Where R= -OH (53); -Cl (54); -Br (55); -F (56); -$CH_3$ (57).

Ahmet Ozdemir et al. synthesized in 2009, a series of imidazole arylidene- hydrazide (imidazo [1,2-a]pyrazine-2-carboxylic acid arylidene-hydrazides) derivatives containing hydrazide-hydraozone moiety (fig 19 and table 10)and evaluated them for antibacterial activity against a panel of bacterial strains. All the synthesised compounds showed greater antibacterial activity against P. vulgaris than other tested bacteria. All synthesised compounds showed their moderate activity against (MIC=50µg/mL) S. aureus, E. faecalis, E. coli, S. thyphimurium, P. aeruginosa, Klebsiella spp. with Chloramphenicol as a reference drug.[33]

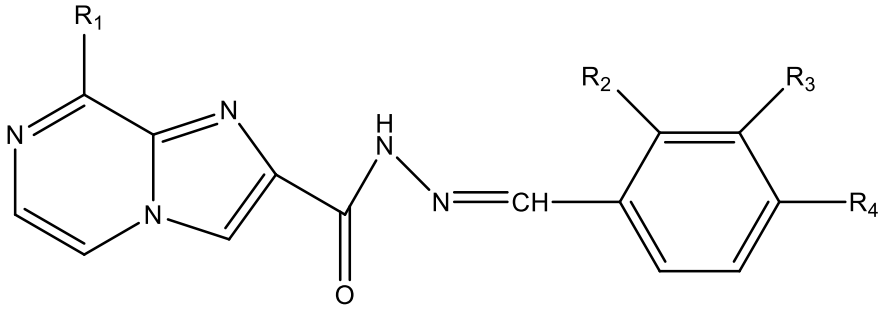



**Fig 18:** imidazole arylidene- hydrazide derivatives

**Table-10:** imidazole arylidene- hydrazide

| Compound | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| 58 | H | H | H | H |
| 59 | H | H | H | Cl |
| 60 | H | H | H | $CH_3$ |
| 61 | H | H | H | $OCH_3$ |
| 62 | H | H | H | $NO_2$ |
| 63 | H | Cl | H | H |
| 64 | H | $CH_3$ | H | H |
| 65 | H | H | Cl | H |
| 66 | H | H | $CH_3$ | H |
| 67 | H | H | H | $N(CH_3)_2$ |
| 68 | $NHCH_3$ | H | H | H |
| 69 | $NHCH_3$ | H | H | Cl |
| 70 | $NHCH_3$ | H | H | $OCH_3$ |
| 71 | $NHCH_3$ | Cl | H | H |

Balasubramanian Narasimhan et al. in 2009, synthesised Benzoic acid hydrazide derivatives and tested for anti in vitro antimicrobial activity by tube dilution method. In case of Staphylococcus aureus, compounds 73 and 74 (fig 20) were found to be most active other stain Bacillus subtilis, Escherichia coli, the QSAR studies showed that electron withdrawing substituents on the benzoic acid moiety, like NO2, S. aureus, on the benzylidene moiety both electron withdrawing (compound 73) and electron donating (compound 74) groups favoured the antibacterial activity. The contrary result observed with the compound containing electron withdrawing group.[34]

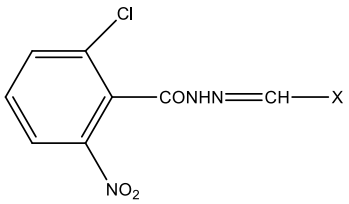



**Fig-20:** New Benzoic acid hydrazide derivatives X= 1-methyl -3-nitrobenzene (Compound 73) and X= 1,2 dimethoxy-4-methylbenzene for compound 74.

N.G. Kandile et al. in 2009, synthesized Pyridazines derivatives and evaluated for in vitro antimicrobial activities against Staphylococcus aureus and Streptococcus faecalis and Escherichia coli and Pseudomonas aeruginosa bacteria by using agar diffusion method at a concentration 20 mg/mL. The MIC values against these bacterial strains were in range of 10-26 mm/mg, which can be assessed as very strong antibacterial activity. It is worth to underline that the highest value of MIC was presented by compound 75 (fig 21) against all strains using DMSO as the solvent.[35]

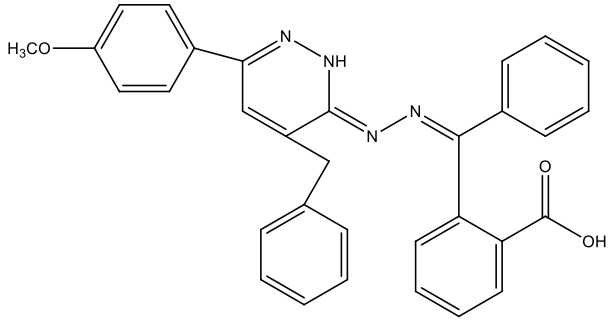



**Fig 21:** Pyridazines Hydrazide derivatives

Kamel A. Metwally et al. in 2006, have been synthesized some 2-arylquinoline-4-carboxylic acid hydrazide–hydrazones. For synthesis of these they used Pfitzinger reaction. The substituted isatins by the sequence of reactions with methylketones in aqueous ethanol with isatine gave 2-arylquinoline-4-carboxylic acid, and further derivative of this by using acid hydrazides (fig 22). They were tested for antimicrobial S. aureus and E.coli, with standard drugs ampicilline by using twofold series dilution method. Compounds 76,77,78,79 and 80 (table 5) shows potent activity. The study of activity showed that nitro group in 7Arylidene side chain, and introduction of chloro group at C-6 of the quinolone ring are promising changes in this derivatives.[36]

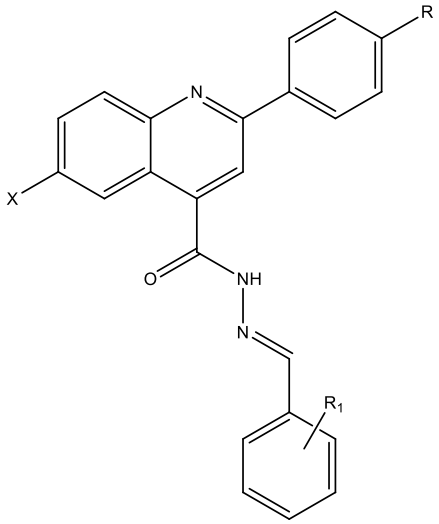



**Fig-22:** 2-arylquinoline-4-carboxylic acid hydrazide–hydrazones.

**Table no 11 :** Derivatives of 2-arylquinoline-4-carboxylic acid hydrazide–hydrazones.

| Comp. No | X | $R_1$ | R |
|---|---|---|---|
| 76 | - | $C_6H_4$-$NO_2$ (o) | Br |
| 77 | Cl | $C_6H_4$-$NO_2$ (o) | Br |
| 78 | Cl | $C_6H_4$-$NO_2$ (p) | Br |
| 79 | Cl | $C_6H_4$-$NO_2$ (o) | Br |
| 80 | Cl | $C_6H_4$-$NO_2$ (p) | $OCH_3$ |

Certain Novel quinoxalines (2-[4-(Ethoxycarbonyl)anilino]-3-methyl quinoxaline) derivative synthesized by Omneya M. et al. in 2004 were tested against four bacterial strains and one fungal strain. The measurement zones of growth of inhibition for the obtained compounds were mild to moderate to those of tetracycline and nystatin used as control. In the case of compound 81, (fig 23) it showed broad spectrum activity for all strains.[37]

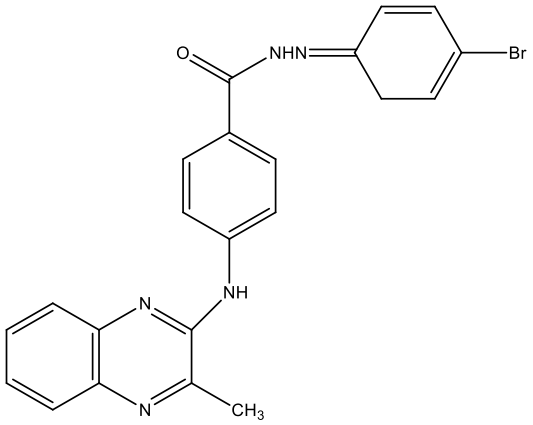



**Fig 23:** Novel quinoxalines (2-[4-(Ethoxycarbonyl)anilino]-3-methyl quinoxaline) derivative as compound 81

**Anticancer Activity:** Malignant growth being the subsequent driving reason for death around the world, various tests have been proceeding to create compounds having minor or no results; and hydrazide hydrazones were accounted for to display negligible or mild side effects. From last few years, hydrazone-hydrazide fund to possess anticancer[38-41] drug too.

It is worth to mention that according to the most recent article published by Rafat M. Mohareb et al. (2019) had synthesised a lots of compound in series of hydrazide–hydrazone derivatives bearing 5H-chromen-5-one. All the newly synthesized compounds were evaluated for three different cell line of human named as HCT116 (colon carcinoma cell), MGC803 (gastric carcinoma cell), and Huh7 (hepatoma carcinoma cell) by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5- diphenyltetrazolium bromide) method. In that 5-Fluorouracil was used as positive control drug.[42]

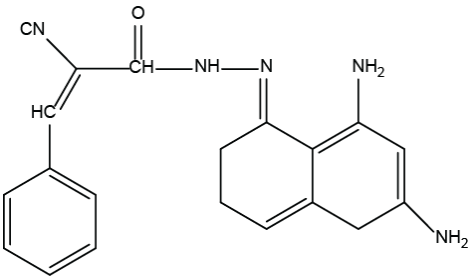



**Fig 24:** hydrazide–hydrazone derivatives bearing 5H-chromen-5-one

Among the series of 20 pyridinium-hydrazone derivative were synthesised by Alptüzün et al. in 2018. In that they were used 4 –chloropyridine with hydrazine monohydrate starting reactant which resulted as 4 –hydrazinylpyridine. This 4 –hydrazinylpyridine gave their derivatives with the reaction of various aromatic aldehydes. In last step of this reaction with substituted alkyl halide team found their pyridinium-hydrazone derivative (fig25: compounds 82,83,84,85 and 86) and evaluated them for three different cancer cell line with one non- cancer cell line (Table 12)by three different methods. The researcher found that compound a special series of derivative was having high activity because of the butylene chain.[43]

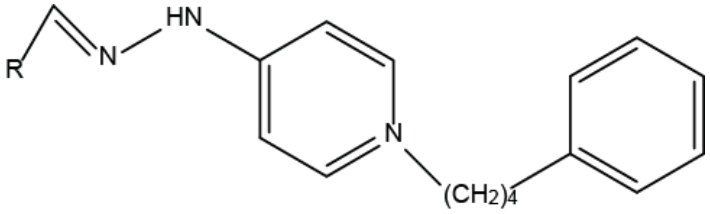



**Fig 23:** Pyridinium-hydrazone derivative

**Table no 12:** IC 50 for pyridinium-hydrazone derivative

| Comp | R | $IC_{50}$ ± SD (µM) | | | |
|---|---|---|---|---|---|
| | | U2OS | MCF-7 | PC3 | HEK293 |
| 82 | Phenyl | 4.7 ± 0.05 | 5.75± .24 | 8.54±.30 | 7.98±.31 |
| 83 | p-nitrophenyl | 5.21±.25 | 5.59±.37 | 6.71±.16 | 9.60±.19 |
| 84 | p-hydroxyphenyl | 3.47±.73 | 3.27±.38 | 7.86±.37 | 8.05.77 |
| 85 | Naphthalene-1-yl | 4.64±.05 | 6.44±.66 | 6.10±.23 | 8.92±.20 |
| 86 | Anthracene-9-yl | 3.33±.10 | 3.57±.33 | 3.91±.11 | 4.57±.14 |
| Std | doxorubicin | 1.89±.28 | 1.99±.10 | 2.88±.19 | 1.10±.07 |

Jaya shree et al. in 2016 tested newly synthesised Pefloxacin hydrazone for in vitro against the human prostate cancer cell line (PcC-3) for Pefloxacin hydrazone. These Pefloxacin hydrazone were prepared by microwave irradiation of Pefloxacin acid hydrazide with various aldehydes. The percentage of cell death was measured for each compound at various concentrations along with $IC_{50}$ (half-maximal inhibitory concentration) values. Compound 90 and 89 have shown excellent cytotoxicity compared to doxorubicin. Similarly, 87, 88 have shown very good anticancer activity compared to the reference compound Rifampicin and Isoniazid. (Fig 26 and table no:13).These synthesised compounds were showed versatile activity like antibacterial, anti-fungal and Antimycobacterial activity.[44]

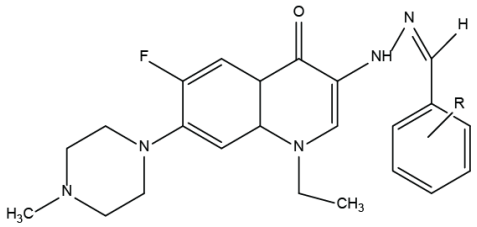
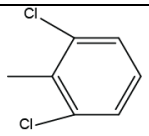
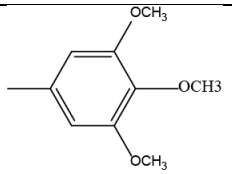
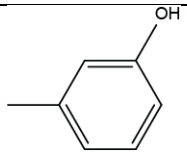
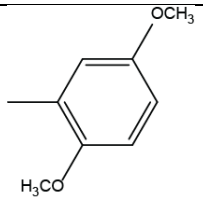



**Fig 26:** Pefloxacin derivatives

**Table No 13:** Anticancer activity of pefloxacin derivatives against human prostate Pc-3 cancer cell lines

| Comp no | R | $IC_{50}$ (µ/mL) |
|---|---|---|
| 87 |  | 4.9 |
| 88 |  | 8.5 |

| | | |
|---|---|---|
| 89 |  | 3.0 |
| 90 |  | 3.4 |
| Std | Doxorubicin | 5.0 |

A new thiazolidine-5-ylidenes compounds prepared from reaction of thioureas with either dimethyl acetylenedicarboxylate (DMAD) or diethyl acetylenedicarboxylate (DEAD) under microwave irradiation by Mahmoodi et al. in 2016. In the cytotoxicity assay by using MKN-45cell line these compounds showed potential toxicity like compound 91 (fig 27) showed high toxicity with IC 50 = 8.7± 0.04) in the reference of standard drug.[45]

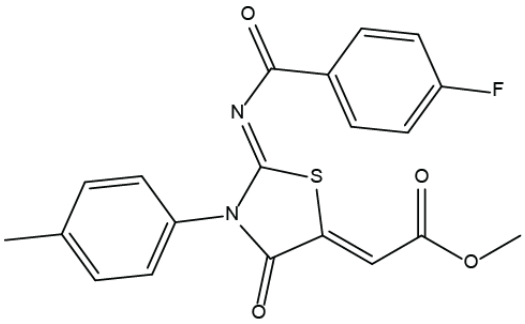
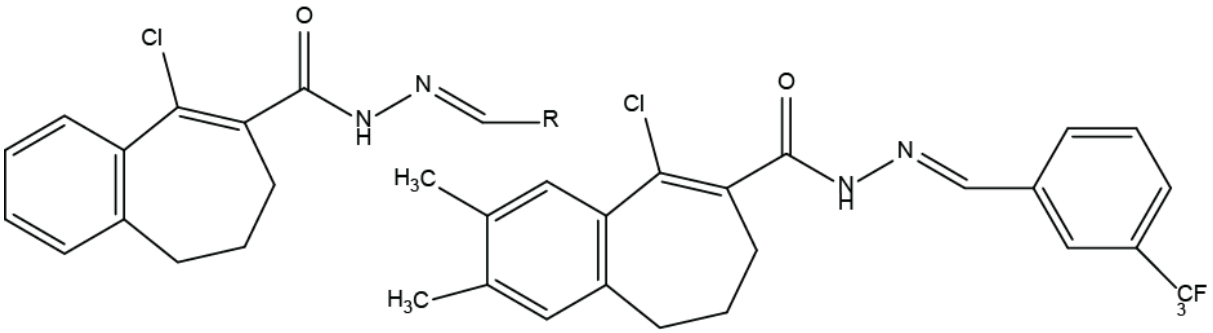


**Fig 27:** Thiazolidine-5-ylidenes derivative.

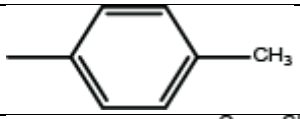
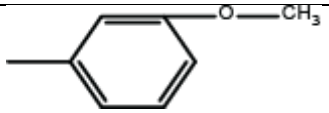
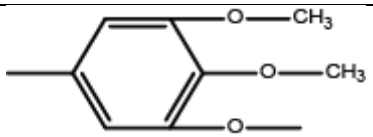
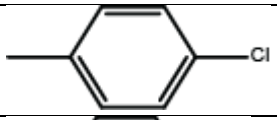
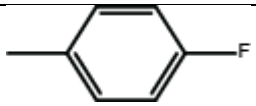
Nagarapu Lingaiah et al. in 2014 synthesised two different series of novel analogues of benzosuberones tethered with hydrazone–hydrazides by different aldehydes with substituted hydrazides, The all synthesised compounds were evaluated for four different types of human cell line {HeLa (cervical), MIAPACA (pancreatic), MDA-MB-231 (breast) and IMR32 (neuroblastoma)} for GI50 at different concentrations. The compounds 5a, 5b, 5d, 5e, and 5f (fig: 26 and table 14) exhibited promising anti-proliferative activity for all cell line except HeLa (cervical. Whereas only one compound (97) (fig 27) showed good activity from another series. The SAR studies showed that Presence of substituent (p-Me, m-OCH3, o, m, p-tri OCH3, p-Cl, p-F and m-CF3) on tail side group was associated with a significant increase in the growth inhibitory effect against human cancer cell lines.[46]



Compound 97

**Fig 26 and 27:** Benzosuberones tethered with hydrazone–hydrazides derivatives

**Table no 14:** Results for benzosuberones tethered with hydrazone–hydrazides derivatives

| Comp no | R | HaLa | MIAPACA | MDA | IMB |
|---|---|---|---|---|---|
| 92 |  | 2.3±.9 | <0.01 | 0.2±.01 | 0.14±.03 |
| 93 |  | 15.6±.4 | <0.01 | 0.3±.06 | <0.01 |
| 94 |  | 8.2±.5 | 1.4±.09 | <0.01 | <0.01 |
| 95 |  | 2.3±.9 | <0.01 | 0.26±.9 | 0.14±.03 |
| 96 |  | 1.3±.08 | <0.01 | 0.41±.01 | 0.27±.01 |

Pawel staczel et al. in 2013 used the general strategy for the construction of the central imidazole ring is based on condensation of the corresponding α- hydroxyiminoketones with methylideneamines. The hydrazones derivatives obtained from 3-oxido-1H-imidazole-4-carbohydrazides. These compounds were detected for Cytotoxicity assay by using MTT reduction assay for Mouse fibroblast cells L929 (ATTC, mouse fibroblasts) or human tumor cells HeLa (ATTC human epithelial cells). Among the synthesized derivatives (Table 14), it is worth to mention tow compounds 97 and 98 (fig 30)which showed weak cytotoxic effect on both tested cell lines. Where the toxicity of compound 99 was more than four-fold higher for L929 line($LC_{50}$=38 mg/mL) and three-fold higher for HeLa cells($LC_{50}$ = 111 mg/mL).[47]

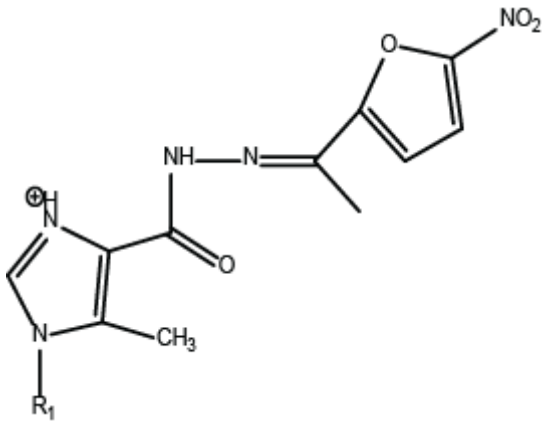


**Fig 28:** hydrazones derived from 3-oxido-1H-imidazole-4-carbohydrazides

**Table no 15:** hydrazones derived from 3-oxido-1H-imidazole-4-carbohydrazides with results for cytotoxicity

| Comp no | $R_1$ | L929 ($LC_{50}$µg/mL) | Hela ($LC_{50}$µg/mL) |
|---|---|---|---|
| 97 | Benzyl | 277 | >300 |
| 98 | Methyl | 168 | >300 |
| 99 | Cyclohexyl | 38 | 111 |

Dalip Kumar and Kavita Shah's team in 2012 synthesised Novel bis(indolyl)hydrazide–hydrazones in three steps from indol as starting material. All synthesised compounds were screened for their in vitro

cytotoxicity against six human cancer cell lines: prostate (PC3, DU145 and LnCaP), breast (MCF7 and MDA-MB-231) and pancreatic (PaCa2). Most of the compounds have shown significant to moderate cancer cell growth inhibition (IC50 < 10 lM) (table 15)And the result was evaluated with SAR studies of Indole. The substituents like N1-(4-chlorobenzyl), bromo and fluoro on indole ring are crucial for cytotoxicity even bromo substitution showed good activity (Fig 29) for compounds 100 and 101.[48]

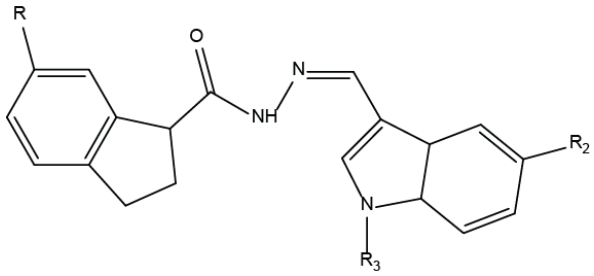
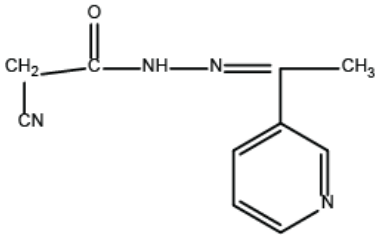



**Fig 29:** Novel bis(indolyl)hydrazide–hydrazones

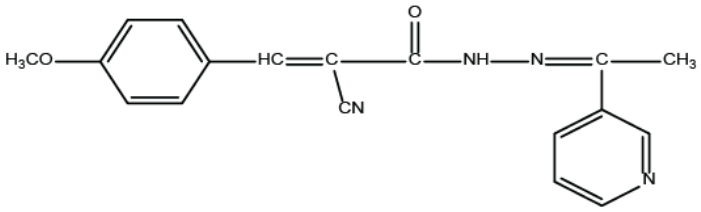
**Table no 16:** Novel bis (indolyl)hydrazide–hydrazones with six different human cell line

| Comp | R | R2 | R3 | LnCaP | MCF7 | MAD-MB | DU145 | PaCa2 | PC3 |
|---|---|---|---|---|---|---|---|---|---|
| 100 | H | Br | 4-ClC6H5CH2 | 3.7 | 3.2 | 1.0 | 3.6 | 8.7 | 12.4 |
| 101 | Br | OCH3 | 4-OCH3C6H4CH2 | >100 | 3.1 | 61.2 | 84.4 | 44.5 | 28.0 |
| Std | Doxorubicin | | | 5.23 | 11.67 | 3.07 | 15.65 | 18.23 | 62.26 |

In 2011, Rafat M. Mohareb and his team worked on the reaction of cyanoacetyl hydrazine with 3-acetylpyridine in 1,4-dioxane to form the hydrazide-hydrazone derivative (compound 102).The latter was reacted with different hetrocyclic to give coumarin, pyridine, thiazole and thiophene derivatives. The effect of synthesized compounds on the in vitro growth of three human tumor cell lines representing different tumor types, namely, breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and CNS cancer (SF-268) was evaluated. The results indicated that compound 102 (fig 32) showed the highest inhibitory effect against all the three tumor cell lines. In addition compound 103 (fig 30) showed the best inhibitory effect against CNS cancer (SF-268), while some more compounds showed high inhibitory effects against non-small cell lung cancer (NCI-H460) and breast adenocarcinoma (MCF-7), respectively.[49]




Compound 102




Compound 103

**Fig 32:** Hetrocyclic hydrazide-hydrazone derivative

Güniz Küçükgüzel et al. in 2010 prepared some newly 4 –aminobenzoic acid hydrazides by using Ethyl 4-aminobenzoate with hydrazine hydrate. Which on further reaction with aldehyde gave 4-Amino-N'-[(4-fluoro/4-(trifluoromethyl) phenyl)methylene] benzohydrazide. All the synthesized compounds were screened for anti-tubercular, antiviral and anticancer potency. For evaluation of anticancer and cytotoxicity they used MTS method. In that Compounds 104, 105, and 106 (fig 33 and table no 16) caused 10-20% cytotoxic effect at the highest concentration on 4th day of the incubation period for A 549 and L 929 cell lines.[50]

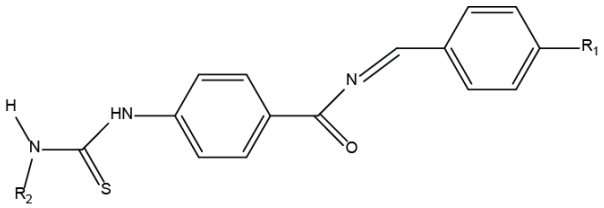



**Fig: 33-**aminobenzohydrazide hydrazones

**Table no 16:** 4-aminobenzohydrazide hydrazones

| Comp | R | R2 |
|---|---|---|
| 104 | -F | -C6H5 |
| 105 | -CF3 | -C6H5 |
| 106 | -CF3 | -C6H4F |

**Anticonvulsant activity:** Epilepsy is one of the main ten positioned problem in the World. It is a common neurological disorder characterized by excessive temporary neuronal discharge resulting in unpredictable recurrence of unprovoked seizures. After the discovery of phenytoin[47], it become a most favourable drug for this disorder. Albeit a few new anticonvulsant are as of now in clinical use, a few sorts of seizure are as yet not satisfactorily treated with current treatment. Current medications treatment is joined by various result including laziness, ataxia, gastrointerstinal disturbances, gingival hyperplasia, hirsutism and megaloblastic anaemia.[48,49] These realities gives the field of anticonvulsant drugs disclosure high priority.

In the series of searching for effective and less side effects drug in 2015 Nadeem Siddiqui and Ruhi Ali have been synthesised a pharmacophore-based model series of 20 new derivatives of of N-(substituted-2-oxo-4-phenylazetidin-1-yl)-2-((6- substitutedbenzo[d]thiazol-2-yl)amino)acetamide derivatives. All the synthesised compounds were evaluated for anticonvulsant activity using the maximal electroshock seizure (MES) test and the subcutaneous pentylenetetrazole test in albino mice. An acute neurotoxicity study on the synthesized molecules was also carried out using the rotarod test. Only two compound were showed promising activity results of these tests revealed that two compounds, 107 and 108 (fig 34) showed promising activity with ED values of 15.4 and 18.6 mg/kg and protective indices of 20.7 and 34.9 in the MES test, respectively,(Table no.17) which are found to be approximately fourfold higher than those of the standard drugs phenytoin (6.9) and carbamazepine (8.1). The general structure activity relationship of these compounds showed that electron-withdrawing groups at benzothiazole nucleus increases the activity and unsubstitution and lipophillic electron-withdrawing groups on distal aryl ring result in higher activity in comparison with substitution with electron-releasing groups.[54]

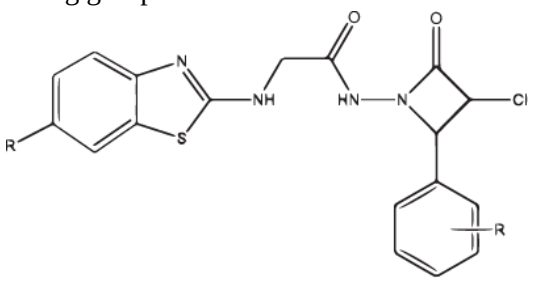
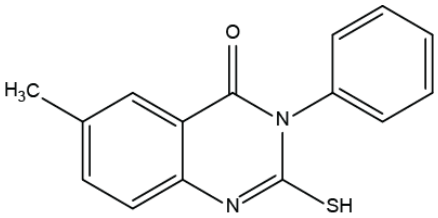



**Fig 34:** New Benzo[d]thiazol-2-yl-aminoacetamides derivatives (compound 108)

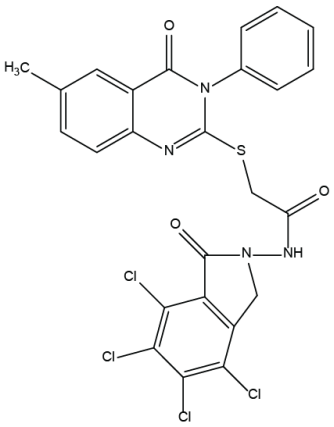
**Table No 18:** Results of New Benzo[d]thiazol-2-yl-aminoacetamides derivatives for anticonvulsant with neurotoxicity

| Comp no | R | R' | MES | | ScPTZ | | Neurotoxicity screen | |
|---|---|---|---|---|---|---|---|---|
| | | | 0.5 h | 4h | 0.5 h | 4 h | 0.5 h | 4 h |
| 107 | F | H | 30 | 100 | 100 | 100 | - | - |
| 108 | F | 2-Cl | 30 | 30 | 30 | 100 | - | - |

Hussein Ei-Subbagh in 2013 were designed and synthesized a new series of quinazoline analogs. All synthesised compounds were evaluated for their anticonvulsant activity. Compounds 109, 110, showed 70–100 % protection against PTZ-induced seizures acting as GABAA receptor agonists. Compound N-(3,4,5,6-tetrachlorophthalimido)-2-[(3-phenyl-4-oxo-6-methyl-3H-quinazolin2-yl)-thio]acetamide (fig 35: compound 110) representing the moderate active compounds. Those compounds possess the ability to prevent the spread of seizure discharge throughout neuronal tissues and to raise seizure threshold. The Structure activity relationship of the quinazolines proved that the electron donating 6-CH3 function contribute to the anticonvulsant activity rather than the electron-withdrawing 6-NO2 group.[55]



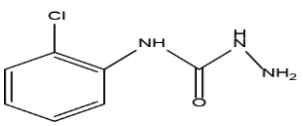

Compound 109



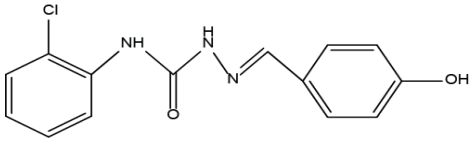

Compound 110

**Fig 35:** quinqzoline derivative for anticonvulsant activity

Ahsan et al. in 2013 were synthesised synthesized a series of seventeen new 2-(substituted benzylidene/ethylidene)-N-(substituted phenyl)hydrazine carboxamide analogues. All the compounds were tested for anticonvulsant activity. 2-(4-Hydroxybenzylidene)-N-(2-chlorophenyl)hydrazinecarboxamide (fig 36:112) was found to be the most active compound of the series showing protection at 4.0 h at a dose of 100 mg/kg against maximal electroshock seizure test and 50 % (2/4, 0.25, 1–2 h) and 100 % (4/4, 0.5 h) protection in 6 Hz psychomotor seizure test without showing any neurotoxicity. N-(2-chlorophenyl)hydrazine carboxamide (111) showed 100 % (4/4, 0.25–2 h) and 66.6 % (2/3, 4 h) protection in 6 Hz psychomotor seizure test.[56]




Compound 111




Compound 112

**Fig 36:** new 2-(substituted benzylidene/ethylidene)-N-(substituted phenyl)hydrazine carboxamide analogues

In 2012, Mohammad Shaquiquzzaman et al. synthesised fourteen new 2-(2-{substituted benzylidene} hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrileas. Which were evaluated for evaluated for their anticonvulsant effect in both MES and scPTZ method. They were also tested for their side effects i.e. neurotoxicity effect by rotarod test and CNS depression effect by Porsolt's swim pool test. In all these test the compounds 4 and 9 (fig 37 and table no 18) showed very potent activity in comparison of other compounds. This activity indicate that the p-substituted bromo and m-substituted nitro groups leads this.[57]

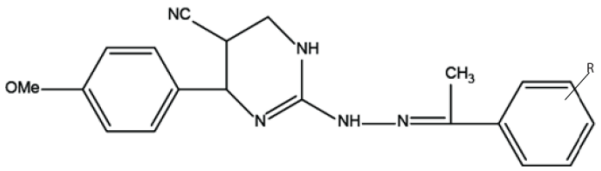



**Fig 37:** 2-(2-{substituted benzylidene} hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrileas.

**Table no 19:** Result of 2-(2-{substituted benzylidene} hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrileas.

| Comp no | R' | MES | | ScPTZ | | Neurotoxicity screen | |
|---|---|---|---|---|---|---|---|
| | | 0.5 h | 4h | 0.5 h | 4 h | 0.5 h | 4 h |
| 113 | 4-Br | 30 | 100 | 100 | 100 | - | 300 |
| 114 | 3-NO2 | 30 | 100 | 30 | 100 | 100 | 300 |
| Std | Phenytoin | 30 | 30 | - | - | - | - |

Laxmi Tripathi, in 2011, worked on N-(substituted) pyridine-4-carbohydrazide. These were resultant product of 4-substituted benzaldehydes with pyridine-4-carbohydrazide or Isatin. 4-substituted benzaldehydes were prepared by refluxing various substituted phenol with 4-fluorobenzaldehyde. The newly synthesized compounds were subjected to anticonvulsant screening by the anticonvulsant drug development (ADD) program protocol. This ADD include two method of testing convulsant (maximal electroshock (MES) and subcutaneous metrazole (scMET) using doses of 30, 100 and 300 mg/kg at two different time intervals). Neurotoxicity was observed by minimal motor impairment which was measured by the rotorod test. Compound 6(fig 38 and table no 19) was the most active one in this series at a dose of 100 mg/kg. Compound 3 and 10 also showed promising activity.[58]

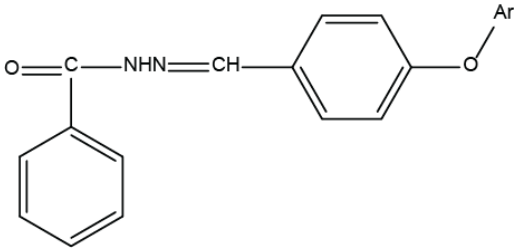
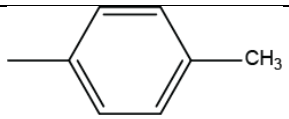
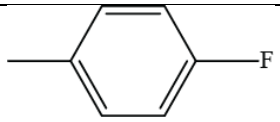
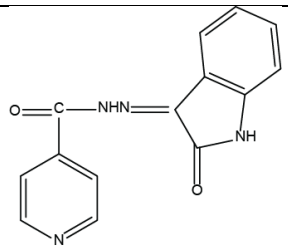



**Fig 38:** N-(substituted) pyridine-4-carbohydrazide

**Table no 19:** Most active N-(substituted) pyridine-4-carbohydrazide derivative with result

| Comp no | R' | MES | | | ScPTZ | | | Neurotoxicity screen | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0.5 h | 2h | 4h | 0.5 h | 2h | 4h | 0.5 h | 4 h |
| 115 |  | - | - | 300 | - | - | - | - | - |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 116 |  | - | 100 | 300 | - | - | - | - | - |
| 117 |  | - | - | - | - | - | - | - | - |
| Std | Phenytoin | 30 | 30 | 30 | - | - | - | - | - |

**Conclusion:**

In conclusion, this paper gives an overview of the anti-bacterial, anticancer and anticonvulsant properties of hydrazide-hydrazones derivatives. As presented in this study hydrazide-hydrazone moiety may be found and incorporated in various bioactive molecules. Thus this paper appears to be important for further development of hydrazide- hydrazones as promising moiety.

Conflict of Access: The author declare that has no competing interests.

**Abbreviation:**

S. aureus: Staphylococcus aureus
S. epidermidis: Staphylococcus epidermidis
B. subtilis: Bacillus subtilis
B. cereus: Baciilus cereus
M. luteus: Micrococcus luteus
B. bronchiseptica: Bacillus bronchiseptica
E.coil: Escherichia coli
E. faecalis: Enterococcus faecalis,
K. pneumonia: Klebsiella pneumoniae
K. spp: Klebsiella spp.
P. mirabilis: Proteus mirabilis
S. typhimurium: Salmonella typhimurium
P. aeruginosa: Pseudomonas areuginosa
P.vulgaris: Proteus vulgaris,
S.typhi: Salmonella typhi

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