The Pharma Innovation Journal 2018; 7(8): 543-550

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2018; 7(8): 543-550

www.thepharmajournal.com
Received: 15-06-2018
Accepted: 20-07-2018

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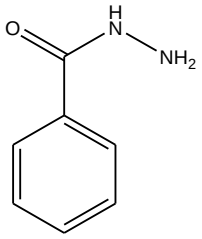
Benzohydrazides: As potential bio-active agents

Deepa Kumari and Himangini Bansal

Abstract
Benzohydrazides are have gained great importance due to their diverse biological properties including anti-bacterial, anti-fungal, anti-convulsant, anti-cancer and anti-tubercular activities. This review article is comprised of information regarding all distinct benzohydrazide derivatives which were synthesised by various authors.

Keywords: benzohydrazide, MIC, tautomerisation, etc

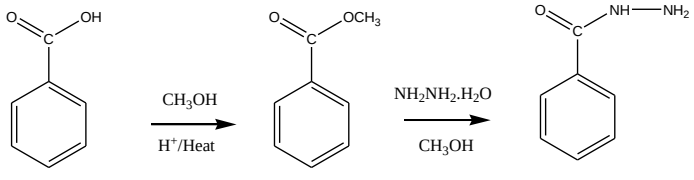
Introduction
Hydrazines and their derivatives constitute an important class of compounds that has found wide utility in organic synthesis, while hydrazines have traditionally been employed as reagents for the derivatization and characterization of carbonyl compounds [1-3]. Recently hydrazides-hydrazones have gained great important due to their diverse biological properties including anti-bacterial, anti-fungal, antiinflammatory, anti-malarial and anti-tubercular activities [4-9]. Benzohydrazide or Benzoic-hydrazide ($C_7H_8N_2O$) is a heterocyclic moiety with diverse actions. It can be taken as potential pharmacophore or as a lead compound. This review is all about the previously synthesised derivatives of benzohydrazide by various authors.



Benzohydrazide OR Benzoic-hydrazide.

Molecular weight = 136.154 g/mol, Melting point 115 °C.

General procedure for synthesis of Benzohydrazide
(a) Conventional Method: The mixture of Methyl benzoate (1.35 mL, 0.01mol) and hydrazine hydrate (0.58 mL, 0.012 mol) was taken in a flat bottomed flask and refluxed for 2 h [10, 11]. The reaction mixture was cooled at room temperature, white precipitate was obtained. It was filtered and washed thoroughly with water.
(b) Microwave Method: The mixture of methyl benzoate (1.35 mL, 0.01 mol) and hydrazine hydrate (0.583 mL, 0.012 mol) was taken in a 100 mL beaker and was refluxed at 350 W for 2 min, then 1 mL of ethanol was added and the reaction mixture was subjected to microwave irradiation for one more minute at 500 W [12-14]. The resulting white precipitate was washed thoroughly with water and dried. It was further recrystallized from ethanol.

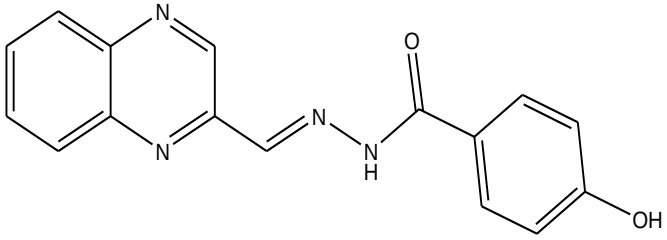


Benzoic acid — Methylbenzoate — Benzohydrazide

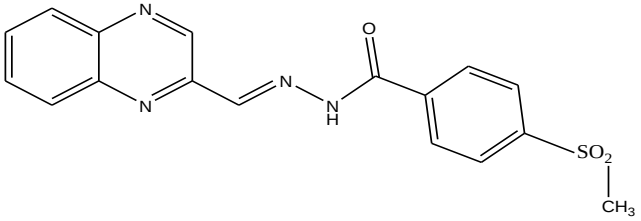
Biological profile of benzohydrazides

Anti-Bacterial Activity

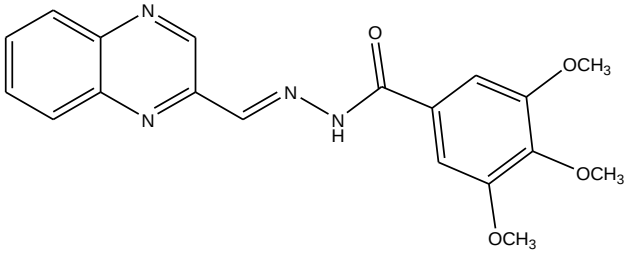
Synthesis of novel quinaxaline-benzohydrazides (6a-m) from condensation of quinoxaline-2-carboxaldehyde 4 with various benzohydrazides (5a-m) in ethanol at reflux temperature. All the derivatives were characterized by 1 H NMR, IR and mass spectroscopic analysis. The synthesized quinoxaline-benzohydrazides (6a-m) were screened for antibacterial activity. Most of the compounds shown significant antibacterial activity. Compounds 6c, 6d& 6h exhibited excellent activity as compared other synthesised compounds [15].



6c

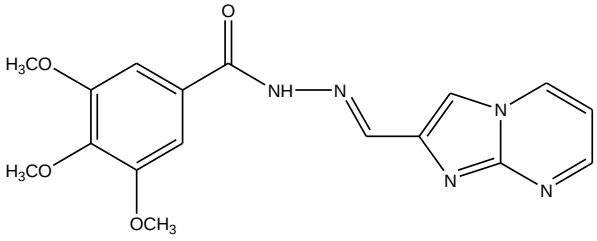


6d

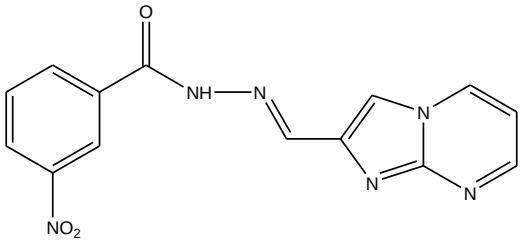


6h

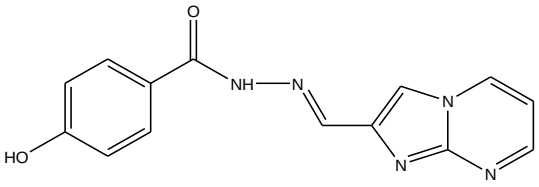
Synthesis of new imidazo [1, 2-a]pyrimidin-2-yl)methylene) benzohydrazides (5a-j) from 2-aminopyrimidine as starting material. All the synthsised compounds (5a–j) were screened for anti-bacterial activity. The Compounds 5c, 5d, 5g, 5i & 5j exhibited excellent activity as compared other synthesised compounds [16].



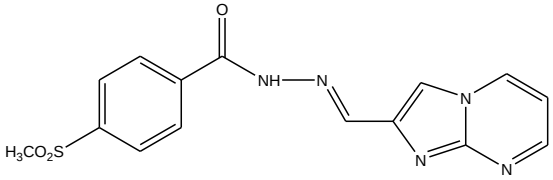
5c



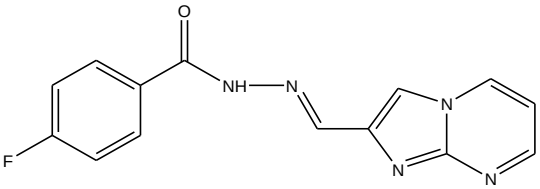
5d



5g



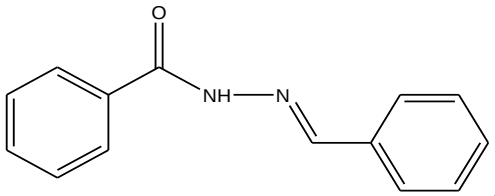
5i



5j

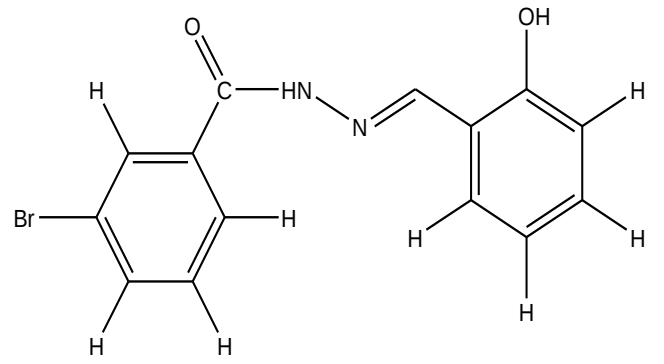
Anti-cancer activity

Synthesis of novel N1 [(Substituted Phenyl) Benzylidene] Benzohydrazides and were characterized by IR, 1H NMR, 13C NMR and mass spectra. The synthesized compounds (2a-2e) have been screened for their in-vitro cytotoxicity against human lung carcinoma cell lines (A-549) by MTT assay. All the compounds showed moderate to significant inhibitory activities. The synthesized compound (2a) analogueis having significant anti lung cancer activity [17].



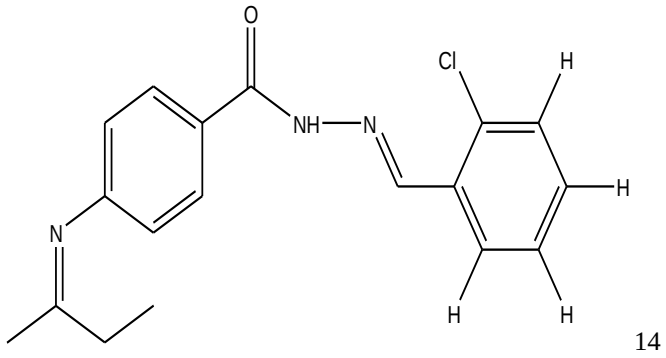
2a

Synthesis of 2/3-bromo-*N'*-(substituted benzylidene/3 phenylallylidene) benzohydrazides. The synthesised compounds (1-22) were evaluated for their *in vitro* anticancer potential against human colon(HCT 116) cancer cell line. The compound 4(IC_{50} = 1.88± 0.03 µM) was found to be the most potent anticancer agent [18].



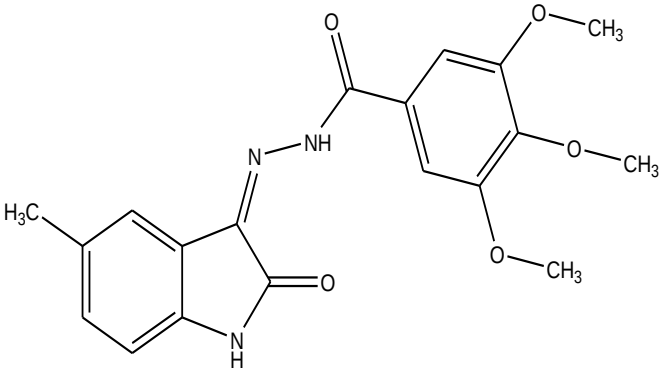
4

Synthesis of N′-(substituted)-4-(butan-2 lideneamino) benzohydrazides. The synthesised compounds were evaluated for their in vitro anticancer potential against human colorectal cancer cell line. The compound 14 (IC_{50}= 37.71µM) was found to be a most potent anticancer agent [19].



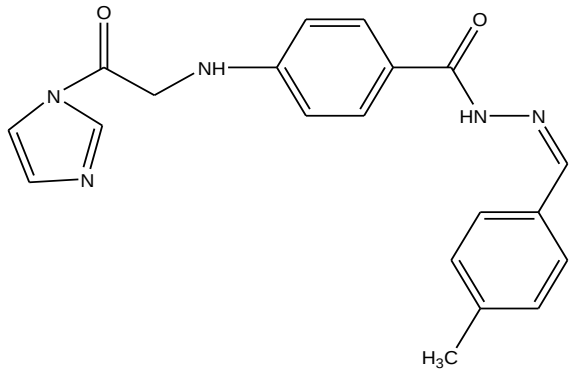
14

Synthesis of N'-[2-oxo1, 2 dihydro-3 H-indol-3-ylidene] benzohydrazides. The synthesised compounds (5a-5y) were evaluated for their cytotoxic activity on human cervix carcinoma grown on a plate (HeLa cells), T-cells and on another cancer cell line L1210 cells. These Benzohydrazide S show potent anti-cancer activities and are effective at much lower concentrations (nanomoles compared to micromoles) for most drugs. The compound 5t was found to be a most potent anticancer agent with an IC_{50} value of 660 nM [20].



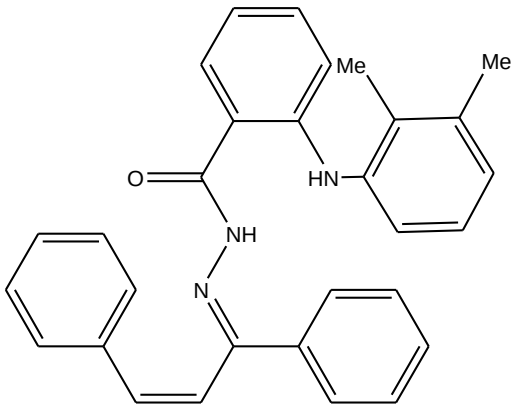
5t

Synthesis of N ’-substituted benzylidene/2-hydroxynaphthalen-1-ylmethylene/3-phenylallylidene/5-oxopentylidene- 4 - (2-oxo-2- (4H-1, 2, 4-triazol-4-yl) ethylamino) benzohydrazides. The synthesized compounds (1-17) were evaluated for their anticancer potentials against human colorectal cancer (HCT116) cancer cell line. The Compound 7 (IC_{50} = 14.90 µM) was found to be the most potent anticancer agent [21].

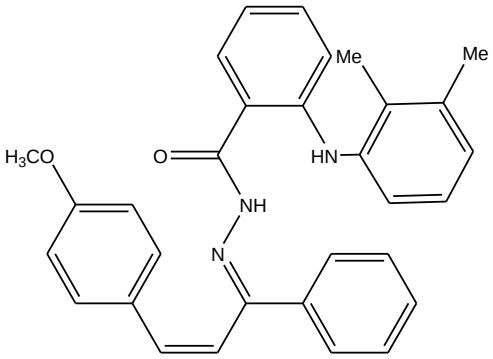


7

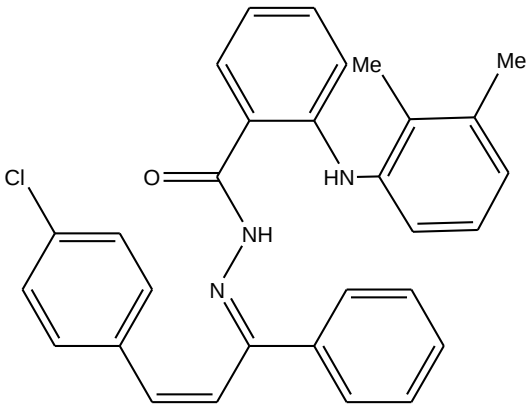
Synthesis of Nonsteroidal Anti-inflammatory Drug-based N-Allylidene Benzohydrazides. The synthesized compounds (3a-3e) were evaluated for their anticancer potentials against human colon cancer (HCT 15) cell line. The Compound 3b, 3c, 3d (IC_{50}= 13-15µg/ml) were found to be the most potent anticancer agent [22].



3b

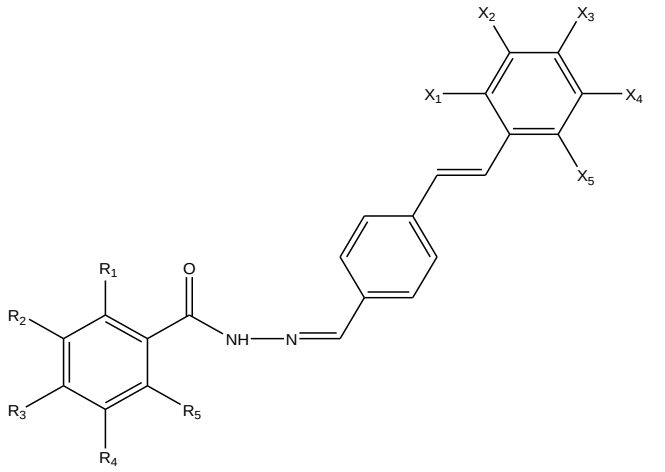


3c



3d

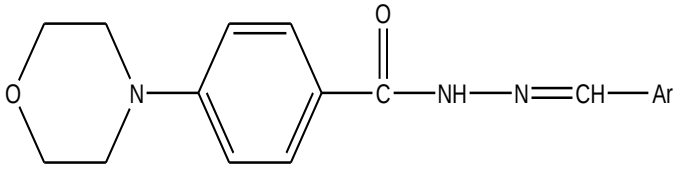
Synthesis of N'-(4-((substituted imino) methyl) benzylidene)-substituted benzohydrazides. The synthesised compounds (1-48) were evaluated for their anticancer potential. Compound 20 was found to be the most effective anticancer agent against both HCT116 and MCF7 cancer cell lines, with IC_{50} values of 19 and 18 µg/cm3, respectively [23].



20

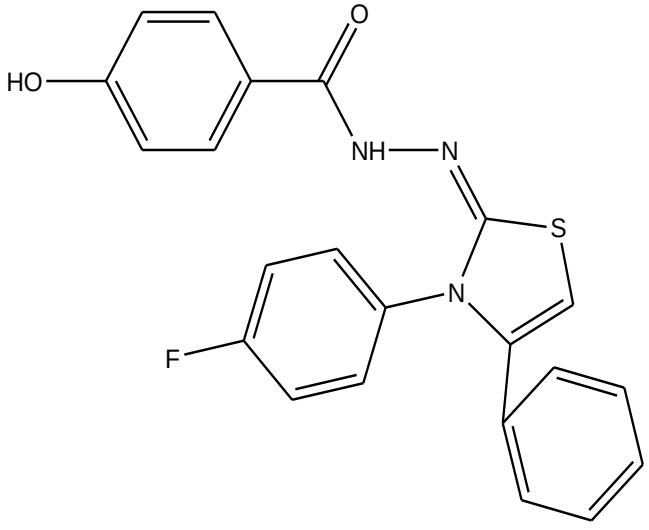
Anti-mycobacterial activity

Synthesis of Novel 4-(morpholin-4-yl)-N '-(arylidene) benzohydrazides. The synthesized compounds (5a-5j) were evaluated for their antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv and compound 5c & 5d were found to be the most potent antimycobacterial agent [24].

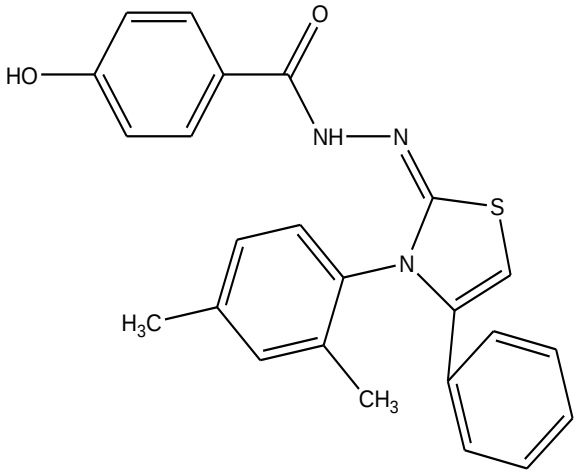


5

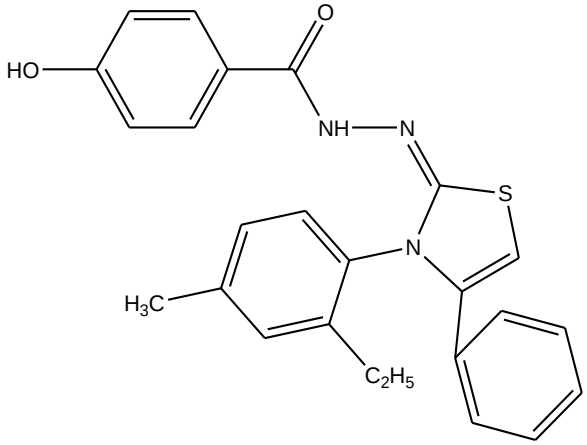
Synthesis of new p- hydroxybenzohydrazide. The synthesized compounds (4.a-4.h) were assayed *in vitro* for their antimycobacterial activity against *M. tuberculosis* H37Rv.Compounds that (4.a), (4.d) and (4.g) were found as potent inhibitor of H37RV [25].



4a



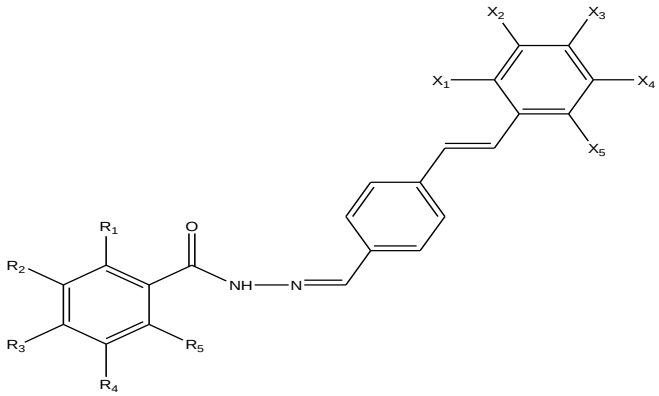
4d



4g

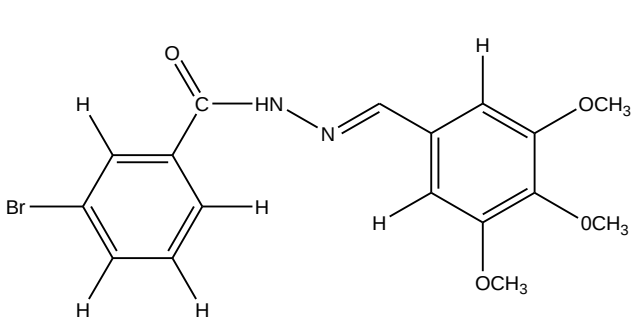
Anti-viral activity

Synthesis of N'-(4-((substituted imino) methyl) benzylidene)-substituted benzohydrazides. The synthesised compounds (1-48) were evaluated for their antiviral activity against HIV-2 strain ROD. Compound 29 (IC_{50} C 1 µg/cm3) was more potent than the standard drug nevirapine (IC_{50} C 4 µg/cm3) and that 39 (IC_{50} C 4 µg/cm3) was equipotent [26].



Anti-microbial activity

Synythesis of 2/3-bromo-N'-(substituted benzylidene/3-phenylallylidene) benzohydrazides. The synthesised compounds (1-22) were evaluated for their *in vitro* antimicrobial potential against five micro-organisms. The compounds 3, 15 and 18 ($pMIC_{am}$ = 1.62 µM/ml) were found to be most potent anti-microbial agents [27].



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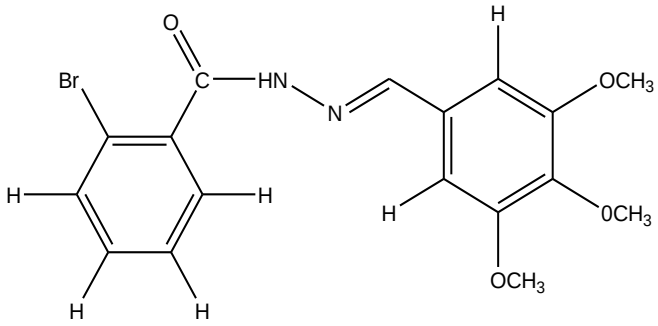
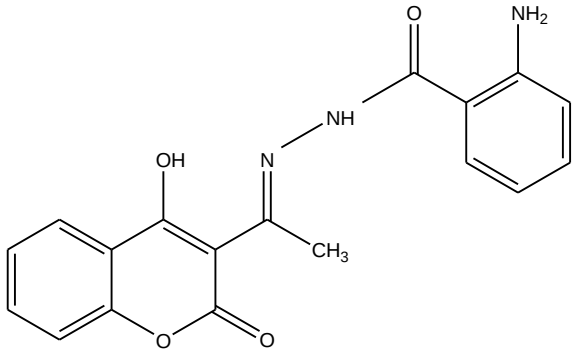


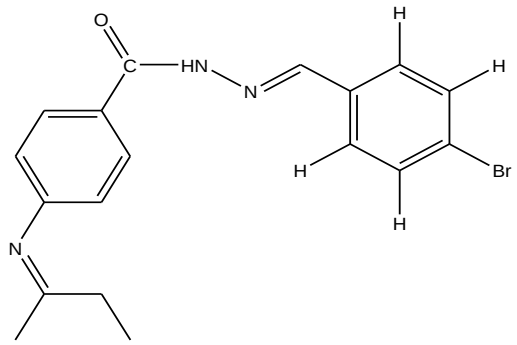
18

Synthesis of 2-substituted-N'-(1-(4-hydroxycumarinyl) ethylidene) benzohydrazides by condensation of 2substituted benzohydrazide with 3-acetyl-4-hydroxycumarine. The synthesised compounds (4a-4f) were evaluated against antimicrobial agent. Compound 4f was found to be a most potent antimicrobial agent [28].



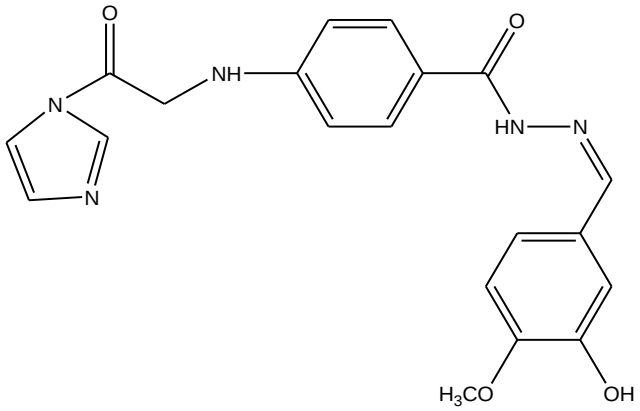
4f

Synthesis of N′-(substituted)-4-(butan-2-lideneamino) benzohydrazides. The synthesised compounds (1-21) were evaluated against *in vitro* antimicrobial potential. The compound 6 ($pMIC_{ca}$ = 2.07 µM/ml) was found to be a most potent anti-fungal agent [29].



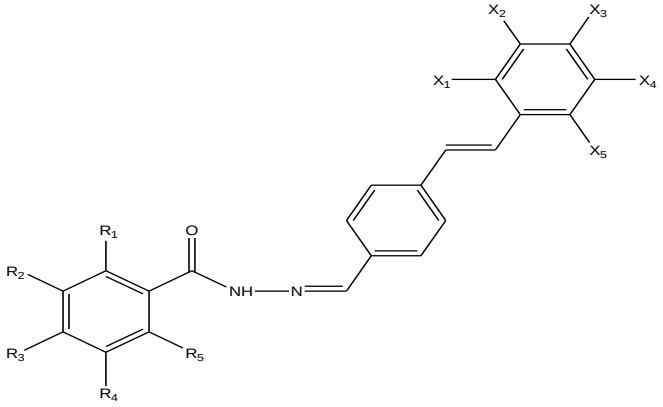
6

Synthesis of N’-substituted benzylidene/2-hydroxynaphthalen-1-ylmethylene/3-phenylallylidene/5-oxopentylidene-4-(2-oxo-2-(4H-1, 2, 4-triazol-4-yl) ethylamino) benzohydrazides. The synthesized compounds (1-17) were evaluated for their anti-microbial potentials & all compounds were found to be more potent against *A. niger* than other bacterial and fungal strains tested. Compound 14 (pMICan = 2.10 µM/ml) having antifungal activity comparable to the standard drug fluconazole was found to be the most potent antifungal agent [30].



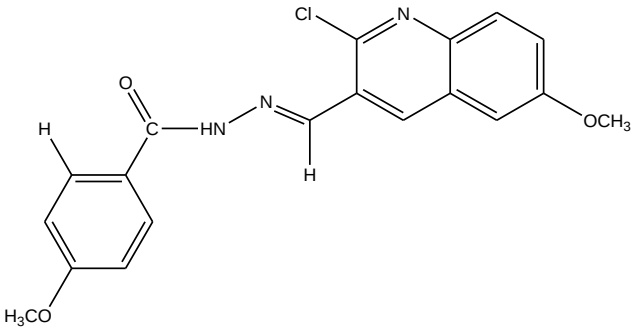
14

Synthesis of N'-(4-((substituted imino) methyl) benzylidene)-substituted benzohydrazides. The synthesised compounds (1-48) were evaluated for their antimicrobial potential. The compound N’-[4-[(4-chlorophenylimino) methyl] benzylidene] -3-nitrobenzohydrazide (25) and N’-[4-[(2-chlorophenylimino) methyl] benzylidene]-4-nitrobenzohydrazide (27) (pMICam = 1.51) were the most potent antimicrobial agents [31].

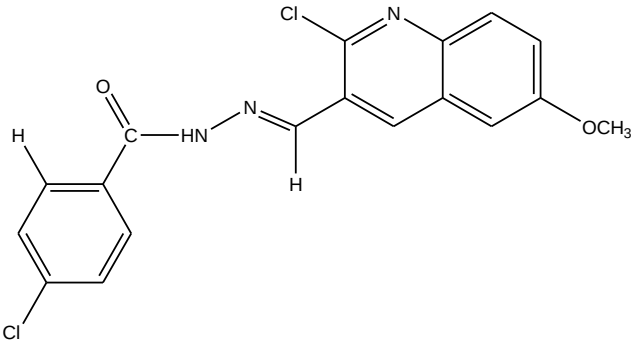


Anti –bacterial activity

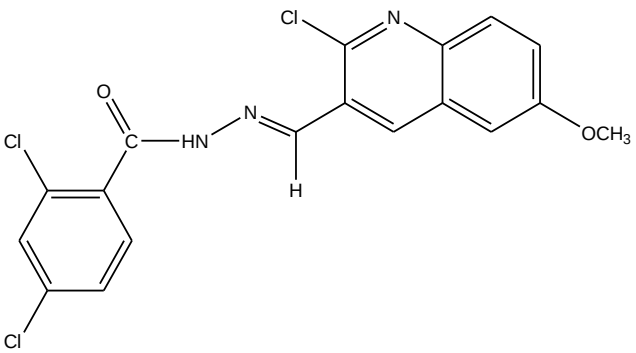
Synthesis of N′ -[(2-chloro-6-methoxyquinolin-3-yl) methylidene]-substituted benzohydrazide by the treatment of 2-chloro-6-methoxy-3-quinolinecarbaldehyde with the substituted benzohydrazides. The structures of the synthesized compounds have been characterized by using IR and 1H NMR spectroscopy. These compounds were screened for their antibacterial as well as antifungal activity. Compounds show greater antibacterial activity as compare to antifungal activity. However, among the series of 5a- 5e synthesised compounds5c,5d & 5e were most active [32].



5c

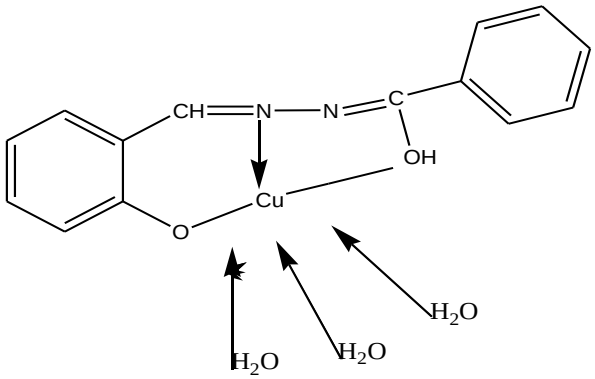


5d



5e

A. Padmaja *et al*. conducted a study on Structural Aspects and Biological Activity of (E)-N'[2-Hydroxybenzylidene] benzohydrazide and its Metal Complexes. The spectroanalytical studies of VO(II), Mn(II),Co(II),Ni(II) and Cu(II) complexes with the title compound (E)-N'-[2-Hydroxybenzylidene] benzohydrazide, as wellas antifungal and antibacterial activity of Cu(II)-HBBH complex were carried out. The complexes were characterizedby elemental analysis, IR, NMR, mass, ESR and TGA & DTA. The mode of bonding in these complexes has been suggested on the basis of analytical and spectroscopic data. The ligand coordinates to the central metal ion through oxygen of enolic form of carboxyhydrazone, phenolic oxygen and azomethine nitrogen atoms in VO(II), Mn(II), and Cu(II) complexes through the dissociation of two protons. While in Co(II) and Ni(II) complexes the dissociation of only phenolic proton is observed and hence the donor sites are oxygen of phenolic group, amide carbonyl oxygen and imine nitrogen. The Cu(II) complex exhibits lethal effect on gram negative bacteria *Escherichia coli* and fungal strain *Candida albicans.* It has also been observed that concentration of compounds play a vital role in the degree of inhibition [33].

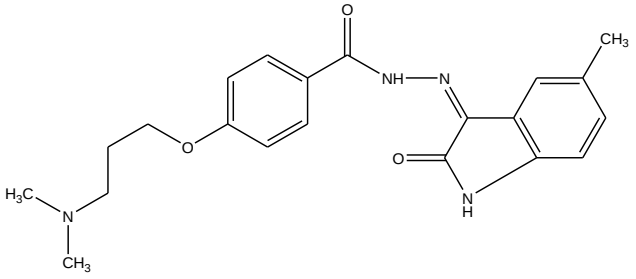


x. H_2O

Tentative structure of Cu (II)-HBBH Complex.

Anti-convulsant activity

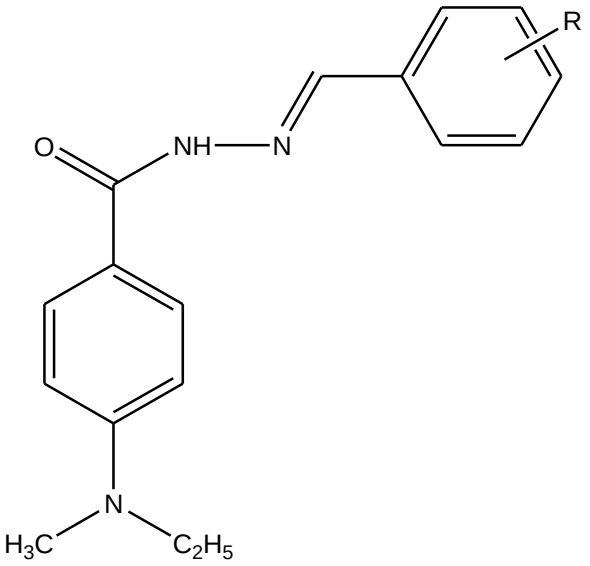
Synthesis of novel NN-dialkylaminoalkoxy-2-oxoindole-3-ylidene benzohydrazide derivatives. Among the synthesised (VIIa-VIIj) compounds, VIIb (R-CH3) has protected more than 80% of the mice against MES and PTZ induced convulsions. Compounds having electron donating groups at C-5 of isatin nucleus seemed to be necessary in providing higher anticonvulsant activity. Other substituents at various positions are next in the order of activity. It is evident from the anticonvulsant activity that electron donating groups seemed to be necessary moieties in showing higher anticonvulsant activity and *in vitro* docking studies have confirmed the same [34].



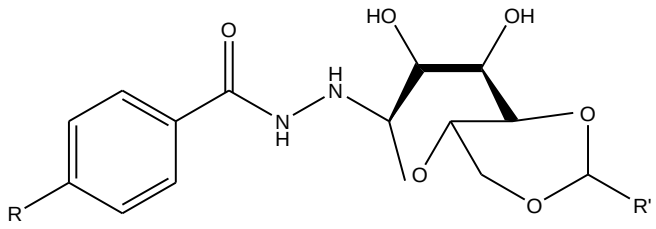
VII B

Miscellaneous activities performed with benzohydrazides

Synthesis of new N-substituted 4-(ethyl methyl amino) benzohydrazide derivatives (1-8) was synthesized using an efficient synthesis method. Reaction of these compounds with thiosalicylic acid give a new series of 1, 3-benzothiazin-4-one derivatives (9-16).The spectral (IR,1H NMR,13C NMR) and elemental analysis confirmed the structure of synthesized compounds. Their chemical transformation was studied [35].



Synthesis & design of long alkyl chain substituted benzohydrazide N-glycosylamines or sugar-benzohydrazides: low molecular weight organogelators. The synthesised (8-19) derivatives can form stable gels in organic solvents through Hydrogen bonding &Van Der Walls interaction [36].



R, R’ = Long alkyl chains.

Synthesis of 4-(1H-Azol-1-ylmethyl) benzohydrazides and their Acyclic and Heterocyclic derivatives from methyl 4-(bromomethyl) benzoate, azoles, and hydrazine hydrate. Reactions of 4-(1H-imidazol-1-ylmethyl) benzohydrazide with carbonyl compounds gave hydrazones whose tautomerism was studied. From the hydrazides, 1, 3, 4-oxadiazoles, 1, 2, 4-triazole-5-thione, and N-benzoyl-N-alkyl (aryl) sulfonyl hydrazones were synthesized [37].

Conclusion

Benzohydrazides are selected as the main target molecules for this review as bioactive heterocyclic compounds because of their distinct biological and clinical applications. Due to its distinct biological activity, researchers synthesized variety of benzohydrazide derivatives and screened them for their various biological activities viz. anticonvulsant, antimicrobial, antimycobacterial, anticancer, antiviral, antibacterial, other miscellaneous activities. These observations based on the present review have been guiding for the development of new benzohydrazides that possess varied biological activities.

References

1. Devi Prasan O, Kandikere RP. J Org Chem. 2013; 78(23):12136-12143.
2. Shaofengm D, Dilip KSM, James WH. Org Lett. 2008; 10(8):1541-1544.
3. Ahmed O, Gulhan TZ, Zafer AP, Mehlika DA. J Serb Chem Soc. 2012; 77(2):141-146.
4. Gurkok G, Altanlar N, Suzen S, Chemotherapy, 2009; 55(1):1519.
5. Fattorusso C, Campiani G, Kukreja G, Persico M. J Med Chem. 2008; 151(5):1333-1343.
6. Lima LM, Frattani FS, Dos Santos JL, Castro HC, Fraga CA, Zingali RB *et al*. European Journal Med Chem. 2008; 43(2):348-356.
7. Rafat MM, Daisy HF, Ola KS, Molecules, 2011; 16:16-27.
8. Zaher AE, Hicham HD, Nouria AA, Mohammed HE. ARKIVOC 2007; (ii):273-315.
9. Govindasami T, Anjana P, Nithya P, Ashutosh P. International Journal of Organic Chemistry. 2011; 1:71-77.
10. Rollas S, Kucukguzel SG. Biological Activities of Hydrazone Derivatives, Molecules. 2007; 12:19101939.
11. Shikha G, Shilpi G, Anis M, Hemant K, Khushbu S. Green Chemical Route towards Synthesis of Novel Acid Hydrazones. Int. J Gr. Herb. Chem. 2012; 1(2):140-144.
12. Visagaperumal D, Jaya Kumar R, Vijayaraj R, Anbalagan N. Microwave induced synthesis of some new 3substituted-1, 3-thiazolidin-4-ones for their potent anti microbial and antitubercular activities. Int. J Chem Tech. Res. 2009; 1(4):1048-1051.
13. Vicini P, Geronikaki A, Incerti M, Busonera B, Poni G, Cabras CA, Colla PL. Synthesis and Biological Evaluation of Benzo [d] isothiazole, Benzothiazole and Thiazole Schiff Bases. Bioorg. Med. Chem. 2003; 11:4785-4789.
14. Sharma RN, Sharma KP, Dixit SN. Synthesis, characterization and biological activities of some new acid hydrazones. Oriental J Chem. 2010; 26(1):69-74.
15. Haripriya V, Laxminarayana E, Chary MT. Synthesis and anti-bacterial activity of some novel quinaxaline-benzohydrazides. Indian Journal of Chemistry. 2016; 55(B):207-212.
16. KShashikala, Eppakayala L, Chary MT. Synthesis and antibacterial activity of novel Imidazo [1,2-a]pyrimidin2yl) methylene) benzohydrazides. Indian Journal of Heterocyclic Chemistry. 2015; (25):119-122.
17. Jubie S, Ashish W, Sabaritha K, Nishanthini P, Thomas A, Antony J. Synthesis and *In-vitro* Anti-Cancer Screening of N1[(Substituted Phenyl) Benzylidene] Benzohydrazides. J Pharm. Sci. & Res. 2016; 8(7):582-585.
18. Kumar P, Narsimhan B, Ramasamy K, Mani V, Mishra RK, Majeed ABA. Synthesis,antimicrobial,anticancer evaluation & QSAR studies of 2/3-bromo-N’-(substituted benzylidene/3-phenylallylidene)benzohydrazides.Arabian journal of Chemistry. 2017;10:3740-3748.
19. Saini M, Kumar P, Kumar M, Ramasamy K, Mani V, Mishra RK *et al*. Synthesis, *In-vitro* anti-microbial, anticancer evaluation and QSAR studies of N′-(substituted)-4-(butan-2-lideneamino) benzohydrazides. Arabian Journal of Chemistry. 2014; 7:448-460.
20. Katiyar A, Hegde M, Kumar S, Gopalakrishnan V, Bhatelia KD, Ananthaswamy K *et al*. Synthesis and

evaluation of the biological activity of N'-[2-oxo1,2 dihydro-3H-indol-3ylidene] benzohydrazides as potential anticancer agents. Royal Society of Chemistry, 2015, 1-37.
21. Tahlan S, Kumar P, Ramasamy K, Mani V, Mishra RK, Majeed ABA *et al*. Synthesis, antimicrobial, anticancer evaluation and QSAR studies of N'-substituted benzylidene/2-hydroxynaphthalen-1-ylmethylene/3-phenylallylidene/5-oxopentylidene -4-(2-oxo-2-(4H-1,2,4-triazol-4-yl) ethyl amino benzohydrazide s. Arabian Journal of Chemistry, 2013.
22. Kankanala K, Reddy VR, Devi YP, Mangamoori LN, Rambabu D, Mukkanti K *et al*. Nonsteroidal Anti-inflammatory Drug-based N-Allylidene Benzohydrazides and 1-Acyl-2-pyrazolines: Their Synthesis as Potential Cytotoxic Agents *In vitro*. Journal of Heterocyclic Chemistry, 2014.
23. Kumar P, Narsimhan B, Ramasamy K, Mani V, Mishra RK, Majeed Abdul AB *et al*. N'-[4-[(Substituted imino)methyl]benzylidene]-substituted benzohydrazides: synthesis, antimicrobial, antiviral, and anticancer evaluation, and QSAR studies. Montash Chem. 2013; 144:825-849.
24. Raparti V, Chitre T, Bothara K, Kumar V, Dangre S, Khachane C *et al*. Novel 4-(morpholin-4-yl)-N '-(arylidene) benzohydrazides: Synthesis, antimycobacterial activity and QSAR investigations. European Journal of Medicinal Chemistry. 2009; 44(10):3954-3960.
25. Bhole RP, Borkar DD, Bhusari KP, Patil PA. Design and Synthesis of p-hydroxybenzohydrazide derivatives for their Antimycobacterial Activity. Journal of the Korean Chemical Society. 2012; 56(2).
26. Kumar P, Narsimhan B, Ramasamy K, Mani V, Mishra RK, Majeed Abdul AB *et al*. N'-[4-[(Substituted imino)methyl] benzylidene]-substituted benzohydrazides: synthesis, antimicrobial, antiviral, and anticancer evaluation, and QSAR studies. Montash Chem 2013; 144: 825-849.
27. Kumar P, Narsimhan B, Ramasamy K, Mani V, Mishra RK, Majeed ABA. Synthesis, antimicrobial, anticancer evaluation & QSAR studies of 2/3-bromo-N'-(substituted benzylidene/3-phenylallylidene) benzohydrazides. Arabian journal of Chemistry. 2017; 10:3740-3748.
28. Chandole SS, Shirodkar SG. Synthesis of Biological Active N'-(1-(4-Hydroxycumarinyl) Ethylidene) Benzohydrazides. JCPR. 2017; 9(11):145-149.
29. Saini M, Kumar P, Kumar M, Ramasamy K, Mani V, Mishra RK *et al*. Synthesis, *In-vitro* anti-microbial, anticancer evaluation and QSAR studies of N′-(substituted)-4-(butan-2-lideneamino) benzohydrazides. Arabian Journal of Chemistry. 2014; 7:448–460.
30. Tahlan S, Kumar P, Ramasamy K, Mani V, Mishra RK, Majeed ABA *et al*. Synthesis, antimicrobial, anticancer evaluation and QSAR studies of N'-substituted benzylidene/2-hydroxynaphthalen-1-ylmethylene/3-phenylallylidene/5-oxopentylidene-4-(2-oxo-2-(4H-1,2,4-triazol-4-yl) ethyl amino benzohydrazide s. Arabian Journal of Chemistry, 2013.
31. Kumar P, Narsimhan B, Ramasamy K, Mani V, Mishra RK, Majeed Abdul AB *et al*. N'-[4-[(Substituted imino) methyl] benzylidene]-substituted benzohydrazides: synthesis, antimicrobial, antiviral, and anticancer evaluation, and QSAR studies. Montash Chem. 2013; 144:825-849.
32. Shaikh SS. Synthesis and Antimicrobial Activities of N ′′′′ -[(2-Chloro-6-methoxy quinolin-3-yl) methylidene] substituted Benzohydrazide. Chem Sci Trans. 2013; 2(3):950-954.
33. Padmaja A, Laxmi K, Palreddy RR, Choudhary SD. A study on Structural Aspects and Biological Activity of (E)-N'[2Hydroxybenzylidene] benzohydrazide and its Metal Complexes. IOSR-JAC. 2014; 7:12-22.
34. Madhiraa S, Mandavaa K, Mandab S, Ra SP, TVijayalaxmi. Synthesis and Evaluation of Some Novel N, NDialkylaminoalkoxy-2-Oxo-Indole-3-Ylidene Benzohydrazides as Anticonvulsant Agents. IOSR – JPBS. 2017; 12:84-93.
35. Al-Ebaisat HS. Synthesis of some N-substituted 4-(ethyl methyl amino) benzohydrazide derivatives and their chemical transformations. IJCS. 2015; 3(1):30-34.
36. Soundarajan K, Periyasamya R, Das TM. Design and synthesis of sugar-benzohydrazides: low molecular weight organogelators. Royal Society of Chemistry Advances. 2016; 6:81838-81846.
37. Osyanin VA, Purygin PP, Belousova ZP. Synthesis of 4-(1H-Azol-1-ylmethyl) benzohydrazides and Their Acyclic and Heterocyclic Derivatives. Russian Journal of General Chemistry. 2005; 75(1):111-117.