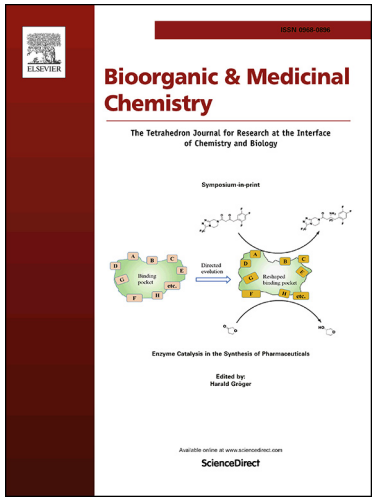
Accepted Manuscript



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Synthesis and urease inhibitory potential of benzophenone sulfonamide hybrid *in vitro* and *in silico*

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Abstract: This study deals with the synthesis of benzophenone sulfonamides hybrids (**1-31**) and screening against urease enzyme *in vitro*. Studies showed that several synthetic compounds were found to have good urease enzyme inhibitory activity. Compounds **1 (*N*'-((4'-Hydroxyphenyl)(phenyl)methylene)-4''-nitrobenzenesulfonohydrazide), 2 (*N*'-((4'-Hydroxyphenyl)(phenyl)methylene)-3''-nitrobenzenesulfonohydrazide), 3 (*N*'-((4'-Hydroxyphenyl)(phenyl)methylene)-4''-methoxybenzenesulfonohydrazide), 4 (3'',5''-Dichloro-2''-hydroxy-*N*'-((4'-hydroxyphenyl)(phenyl)methylene)benzenesulfonohydrazide)**, **6 (2'',4''-Dichloro-*N*'-((4'-hydroxyphenyl)(phenyl)methylene)benzenesulfonohydrazide)**, **8 (5-(Dimethylamino)-*N*'-((4-hydroxyphenyl)(phenyl)methylene)naphthalene-1-sulfono hydrazide)**, **10 (2''-Chloro-*N*'-((4'-hydroxyphenyl)(phenyl)methylene)benzenesulfonohydrazide)**, **12 (*N*'-((4'-Hydroxyphenyl)(phenyl)methylene)benzenesulfonohydrazide)** have found to be potently active having an IC_{50} value in the range of 3.90-17.99 μM. These compounds showed superior activity than standard acetohydroxamic acid (IC_{50} = 29.20 ± 1.01 μM). Moreover, *in silico* studies on most active compounds were also performed to understand the binding interaction of most active compounds with active sites of urease enzyme. Structures of all the synthetic compounds were elucidated by ^{1}H-NMR, ^{13}C-NMR, EI-MS and FAB-MS spectroscopic techniques.

Keywords: Benzophenone sulfonamide hybrid; urease; *in vitro*; *in silico.*

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1. Introduction

Sulfonamide chemically containing sulfamoyl (SO_2NH) group is derivatives of amide. The first sulfonamide drug identified in 1932 was the prontosil and used as antibacterial agent [1]. Sulfonamides executed as competitive inhibitors due to resemblance with PABA (*p*-amino benzoic acid) and hence, block the synthesis of folic acid thus ultimately block the growth of bacteria [2]. Sulfonamide is biologically significant class of compound, because it is well absorbed orally and excreted in urine. Thus, it has less toxicity, increased reactivity, and cost effective [3] molecues. Sulfonamides are mainly used as antibacterial drugs [4] but they also have anticancer [5], antiinflammatory [6], antiviral [7], antiobesity [8], and carbonic anhydrase inhibitory activities [9]. Sulfonamide synthesis takes place by nucleophilic substitution of NH group to sulfonyl chloride. Sulfonamide functionality has also found application in food additives and in animal husbandry [10].

Benzophenone also called as benzoyl benzene structurally has two phenyl group joined together through a carbonyl group. Benzopheonone nucleus chemically have nature of secondary metabolite *i.e.* polyketide. Naturally benzophenone molecules found in *Garcinia cochinchinensis*, and *Clusiacea* family and it can also be obtained synthetically. The ability of benzophenones as chemotherapeutic agent especially as anticancer [11], antimicrobial [12], antiHIV [13], antiinflammatory [14], antioxidant and urease inhibitory activity is well documented. Benzophenone nucleus also has importance in field of agriculture as one of the fungicide *i.e.* fluomorph also have benzophenone as key skeleton.

Urease also known as urease aminohydrolase, is a nickel containing metaloenzyme have enzyme commission number of (EC 3.5.1.5). Urease enzyme is distributed from prokaryotes to eukaryotes [15]. Main function of urease involves degradation of urea into carbon dioxide and ammonia [16]. In human, there is no any urease enzyme is present but they form urea which is the end product of protein metabolism and normally it excreted from body in the form of urine. Since, if human is infected from bacteria such as with *Helicobacter pyroli* which contains virulence factor *i.e.* urease enzyme. Urease enzyme is seem to be presence in variety of pathogenic bacteria. It plays a major role in colonization of a host organism and in protection of bacterial cells in host tissues therefore, urease has toxic effect on human [17]. Urease enzyme in pathogeneic bacteria degraded human urea into carbon dioxide and ammonia as a results of

which human defence mechanism releases increased amount of stomach acid which ultimately causes gastric and dueodenal ulcers [18].

To overcome the urease activity of pathogenic bacteria, our research group has been engaged in designing small, cost effective, and less toxic urease inhibitor since two decades [19-27]. Since, sulfonamide molecules showed good antibacterial and urease inhibitory activity [28,29]. In addition, fine urease inhibitory activity of benozophenone derivative is also previously reported by our research group [30] (Figure-1). Therefore, in this study, we have synthesized and characterized thirty-one (31) hybrids of benzophenone sulfonamide and screened them against urease enzyme *in vitro*. *In silico* study has also been performed to understand binding mode of active compound against urease enzyme. To the best of our knowledge compounds **13**, **24**, **27** and **31** are previously known [31], while remaining compounds are new.

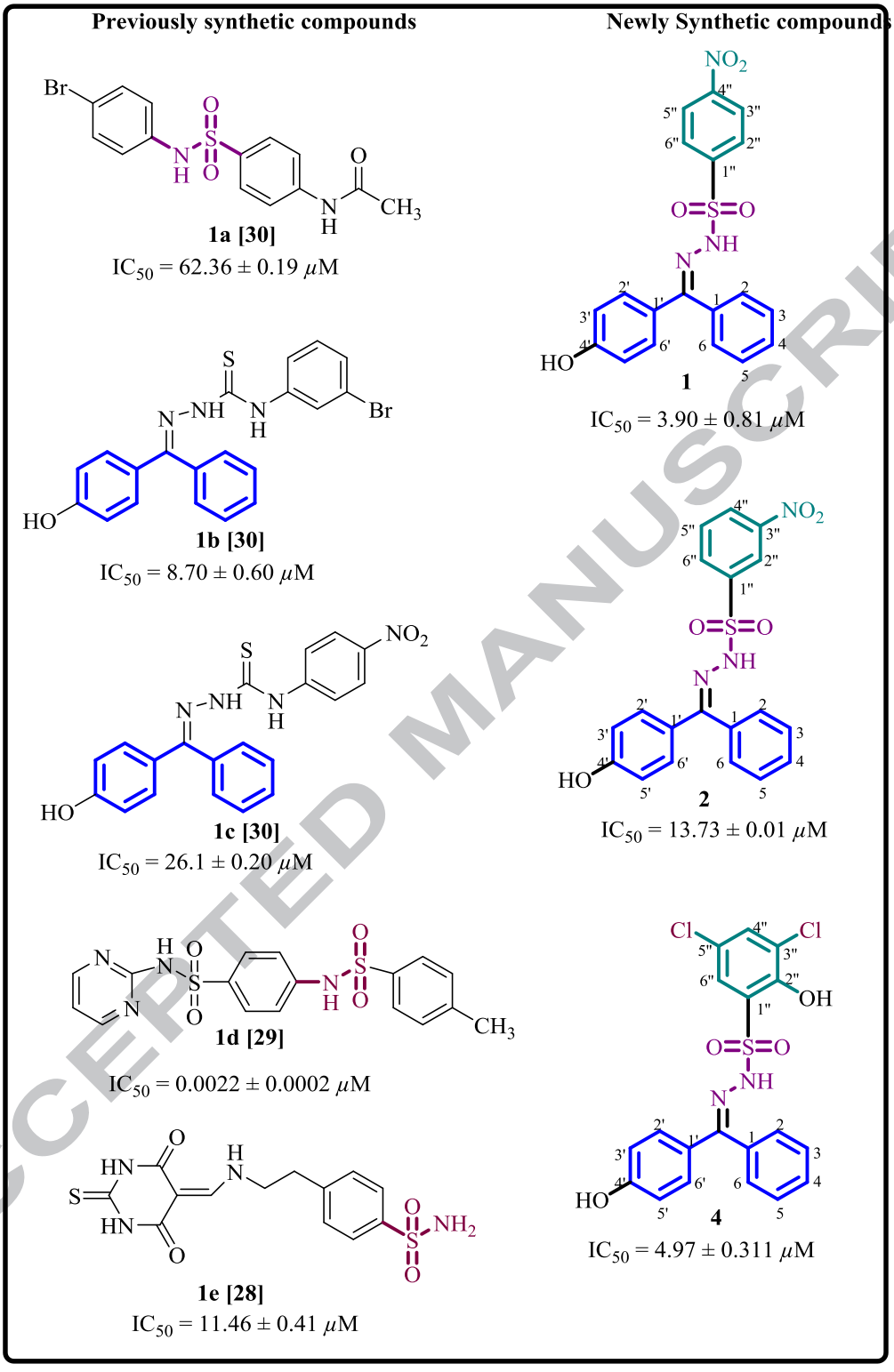
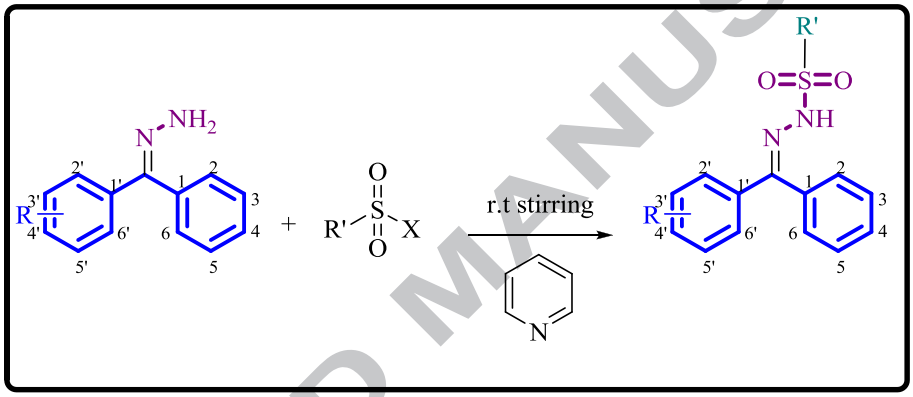


Figure-1: Rationale of current sudy

2 Results and discussion

2.1 Chemistry

Benzophenone sulfonamide hybrids have been synthesized by the reaction of benzophenone and 4′-hydroxy benzophenone hydrazones with differently substituted sulfonyl chloride, respectively. Synthesis has been performed by stirring a reaction mixture at room temperature in the presence of pyridine acting as base as well as solvent which results in precipitation. Reaction was also performed by taking acetonitrile as solvent and pyridine as a base but no results were obtained. Chemical structures of these synthetic analogues were characterized by ^{1}H-NMR, ^{13}C-NMR, EI-MS and FAB-MS techniques Table-1.



Scheme-1: Synthesis of benzophenone sulfonamide hybrid 1-31

2.2 Spectroscopic studies of active compound *N*'-((4'-hydroxyphenyl)(phenyl)methylene)-4''-methoxybenzenesulfonohydrazide (3)

Active compound **3** is randomly selected for describing detailed characterizing of the structure of the synthetic benzophenone sulfonamide. For understanding hydrocarbon skeleton NMR spectra of compound **3** *i.e.* proton and carbon spectra were run in deuterated dimethyl sulfoxide on a Bruker Avance AM 300 MHz instrument.

In ^{1}H-NMR spectrum, the most downfield signals at δ_H 10.23 showed the presence of SO_2NH group in the molecule. The phenolic proton resonated at δ_H 9.85. In aryl region the most downfielded protons resonate as doublet at δ_H 7.85 ($J_{2,3/6,5}$ for H-2, H-6). Protons 3, 4, 5 resonate as triplet atδ_H 7.72 ($J_{3(2,4)/4(3,5)/5(4,6)}$ for H-3, H-4, H-5). In aromatic region of proton NMR spectrum, an aryl *ortho* protons resonate as doublet at δ_H 7.24 ($J_{2'',3''/6'',5''}$ for H-2″, H-6″). While the H-3″, H-5″ protons neighbour to methoxy group also appear as doublet at δ_H 7.14 ($J_{3'',2''/5'',6''}$ for H-3″, H-5″). The most upfield signals in aromatic region is assigned to 4′-substituted hydroxyl

benzophenone part, these upfield protons of aromatic region appeared as doublets at δ_H 7.05 ($J_{2',3'/6',5'}$ for H-2′, H-6′) and δ_H 6.88 ($J_{3',2'/5',6'}$ for H-3′, H-5′) (Figure-2).

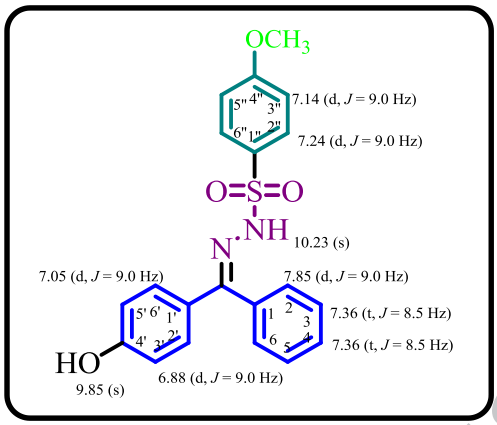


Figure-2: ^{1}H-NMR analysis of compound **3**.

Broad band spectrum of compound **3** showed total of 14 carbons present in the structure. Out of which there are 6 quaternary, 7 methines and 1 methoxy carbons. While from DEPT-135, it was also proven that there is no any methylene group in the structure. Iminic carbon showed most downfield signal at δ_C 162.5. In aromatic region the most downfield signal was supposed to be C-1″ at δ_C 158.3. Aryl aromatic carbon attached to methoxy group that is C-4″ resonate at δ_C 154.5. The two carbons (C-3′, C-5′) of benzophenone resonated at the most upfield region of δ_C 115.4, this is due to the mesomeric effect of the adjacent hydroxy group. All other aromatic carbons resonate at their usual aromatic range (Figure-3).

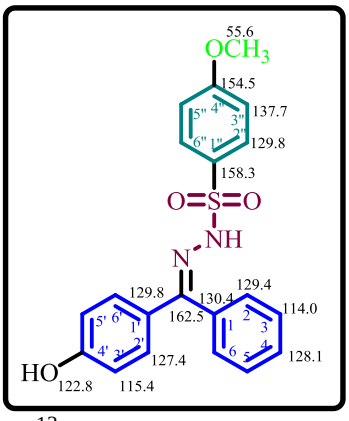


Figure-3: ^{13}C-NMR analysis of compound **3**.

FAB-MS technique was used for determining mass of compound **3** which gave mass *m/z* 383 $[M+H]^+$.

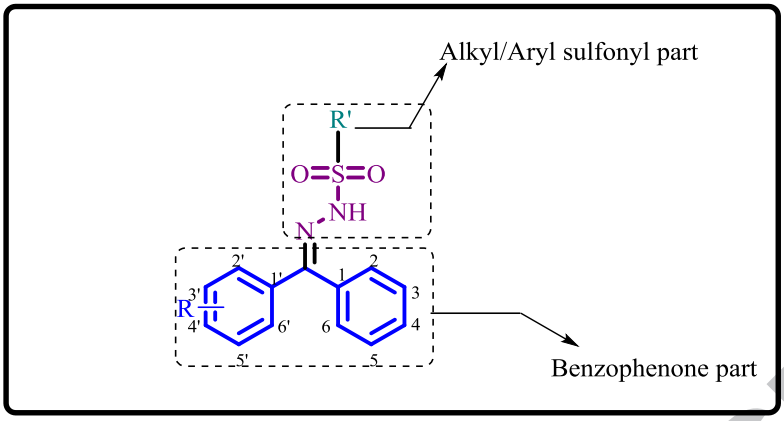


Figure-4: General structure of synthetic benzophenone sulfonamide

2.3 Structure-Activity Relationships (SAR)

Thirty-one (31) benzophenone sulfonamides were synthesized and screened for urease inhibition activity. Enzyme inhibition studies suggested that urease inhibition activity of this class of compounds not only depend on benzophenone part but also at different substitution of alkyl/aryl sulfonyl part (Figure-4). The limited review at structure-activity relationship reveals that hydroxylated benzophenone part has showed good inhibitory activity. Moreover, amongst hydroxylated benzophenone part various substituents at alkyl/aryl sulfonyl part responsible for varying degree of activity.

Amongst these synthetic compounds, twelve compounds have hydroxyl group at 4′-position of benzophenone part while nineteen compounds were without hydroxyl group at benzophenone part. Amongst all synthetic compounds, seventeen compounds showed good to weak inhibitory activity with IC_{50} values of 3.90-71.63 μM. Most active compound **1** (IC_{50} = 3.90 ± 0.81 μM) found to be about 10-fold more active than acetohydroxamic acid (IC_{50} = 29.20 ± 1.01 μM) which was used as the standard and a detailed SAR is discussed in forthcoming paragraphs.

As mentioned earlier, compound **1** having hydroxyl group at 4′- site of benzophenone and nitro group at 4″- position of aryl sulfonyl part was found to be most active compound of series, however, switching nitro group to 3″- position of aryl sulfonyl part as in compound **2** (IC_{50} = 13.73 ± 0.01 μM) a decreased activity was observed. Removal of hydroxy group from benzophenone part and shifting of nitro group to 2″/3″/4″-positions, respectively, resulted in inactive compounds **19**, **20**, and **21** (Figure-5) which indicates that the nitro group is only effective when it is in combination of hydroxyl group at benzophenone part.

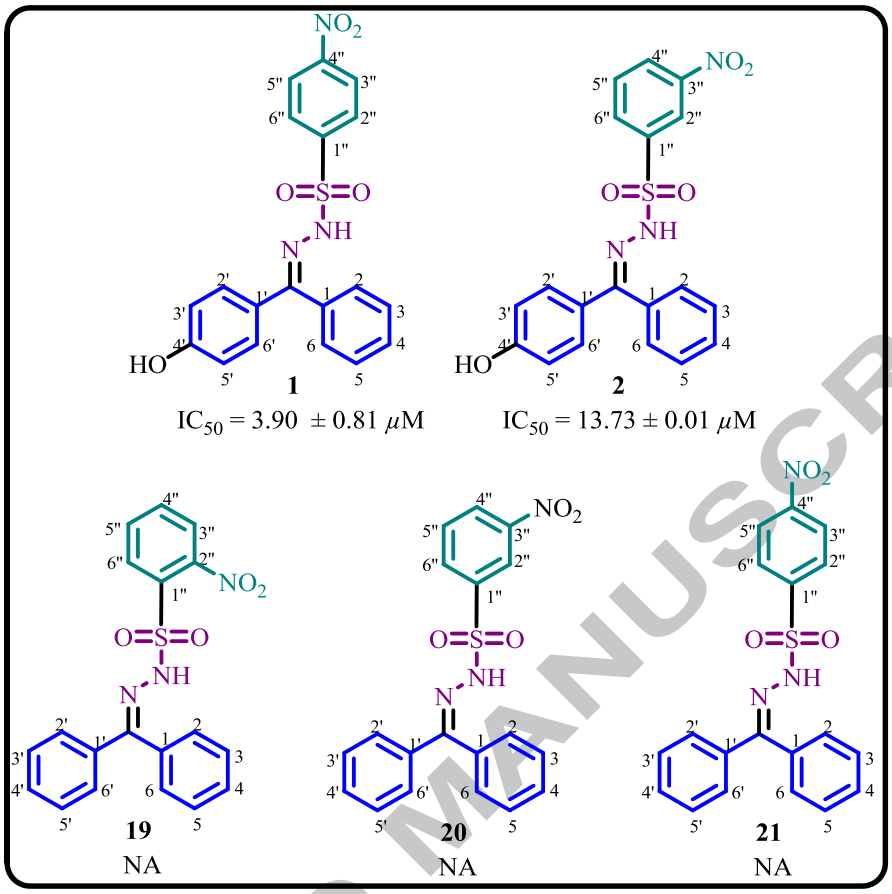


Figure-5: SAR of nitro substituted aryl sulfonyl part

However, nitro group in combination with chloro group at aryl sulfonyl part in absence of hydroxyl group at benzophenone part, as in compounds **22** and **25** showed no any activity. Nevertheles, compound **24** (IC_{50} = 68.9 9 ± 0.71 μM) having dinitro substituent at 2″,4″-positions of aryl sulfonyl benzophenone, and compound **23** (IC_{50} = 68.99 ± 0.65 μM) having methyl group at 2″- position and nitro group at 5″-position in combination of non-hydroxylated benzophenone was found to be weakly active (Figure-6).

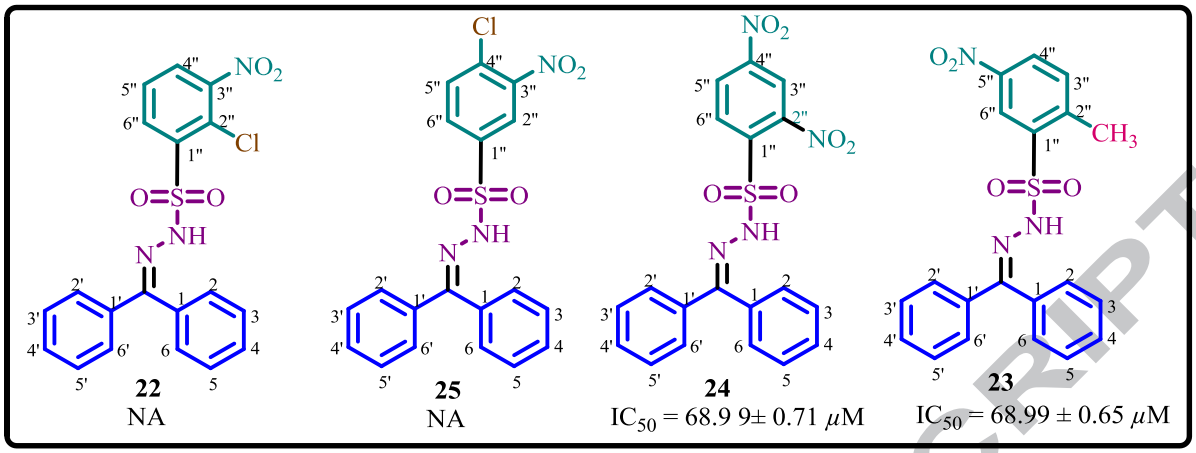


Figure-6: SAR of disubstituted *i.e.* nitro and chloro substituted aryl sulfonyl part

In hydroxylated benzophenone molecules, compound **3** (IC_{50} = 14.51 ± 1.14 μM) having methoxy group at 4″-position of aryl sulfonyl part showed good inhibitory activity. However, non-hydroxylated compounds **27** and **28** having methoxy groups at 4″-position and at 2″ and 4″-positions, respectively, were found to be inactive (Figure-7).

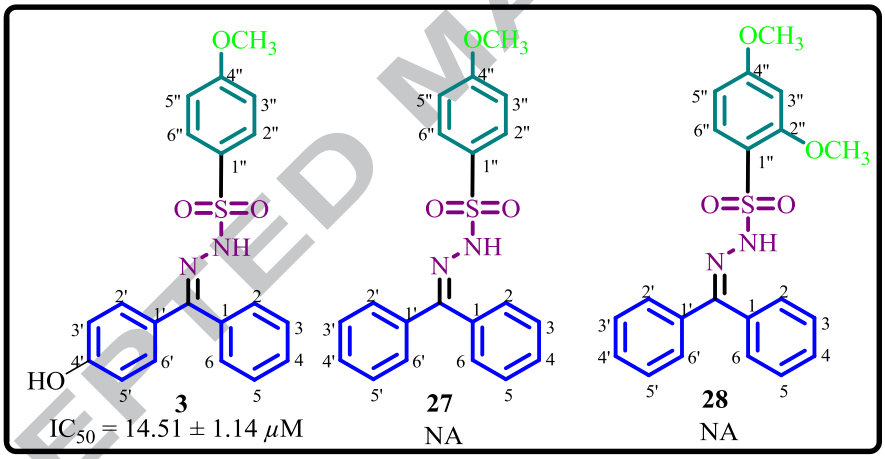


Figure-7: SAR of methoxy substituted aryl sulfonyl part

Compound **4** (IC_{50} = 4.97 ± 0.31 μM) having hydroxylated benzophenone part and in aryl sulfonyl part hydroxyl group at 2″-position and chloro group at 3″,5″-positions was found to be second most active compound of the series. Nevertheles, compound without any hydroxyl group substitution at benzophenone as in compound **26** (IC_{50} = 71.63 ± 0.81 μM) showed weak inhibitory activity. Shifting of chloro group at 2″,4″-positions of aryl sulfonyl part and hydroxyl group at 4′-position makes compound **6** (IC_{50} = 17.99 ± 0.61 μM) showed good but relatively weak inhibitory activity than compound **4**. However, analogs having no hydroxyl group at benzophenone part, compound **18** was found to be completely inactive. Presence of only one

chloro group at 2″-position and hydroxyl group at 4′-positions as in compound **10** (IC_{50} = 16.91 ± 2.10 μM) showed comparable activity to compound **6**. However, removal of hydroxyl substituent from benzophenone part and chloro group at 2″-position of aryl sulfonyl part as in compound **14** made it completely inactive. However, shifting of chloro group at 2″-position without hydroxyl group at benzophenone part as in compound **16** (IC_{50} = 66.10 ± 0.11 μM) exhibited weak urease inhibitory activity. Chloro group at 4″-position and methyl group at 2″, 5″-positions of aryl sulfonyl part without hydroxyl group at benzophenone part as in compound **15** made it completely inactive. Trichloro substituted aryl sulfonyl part with chloro group at 2″,4″,5″-positions and hydroxyl group at 4′-position of aryl sulfonyl part as in compound **9** (IC_{50} = 57.88 ± 0.71 μM) showed weak inhibitory activity. Compound **17** with trichloro substituent at same positions of aryl sulfonyl part as in compound **9** but without hydroxyl group at benzophenone part made it completely inactive (Figure-8).

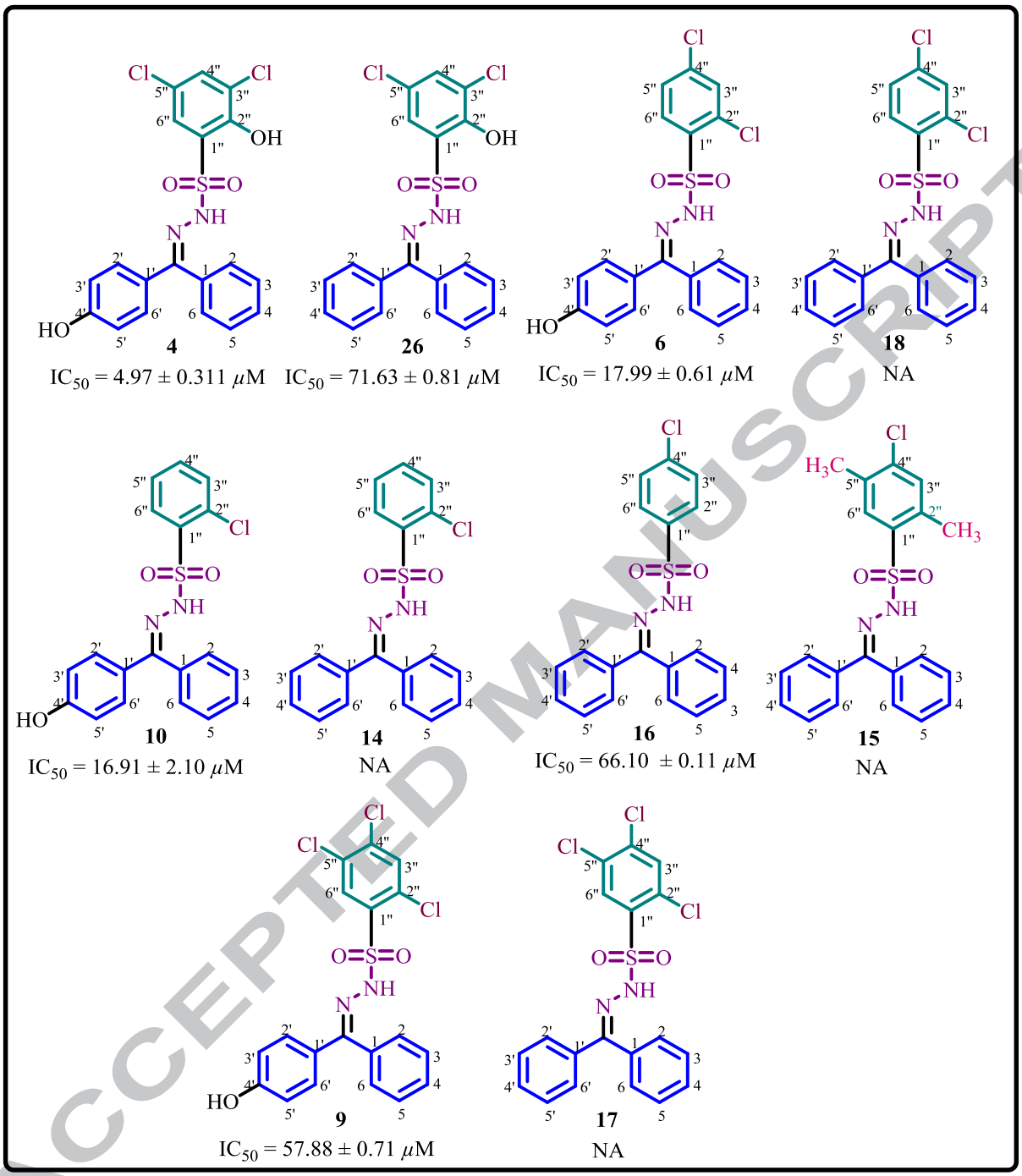


Figure-8: SAR of chloro, hydroxyl and methyl substituted aryl sulfonyl part

Compound **7** (IC_{50} = 55.04 ± 0.54 μM) with hydroxyl group at benzophenone part and chloroethane residue at aryl sulfonyl part made it weakly active. Only methyl substituent instead of aryl sulfonyl part as in compound **11** (IC_{50} = 43.39 ± 0.41 μM) demonstrated weak inhibitory activity. Compound **31** with no any substituent at benzophenone part and have butyl chain instead of aryl position made it completely inactive (Figure-9).

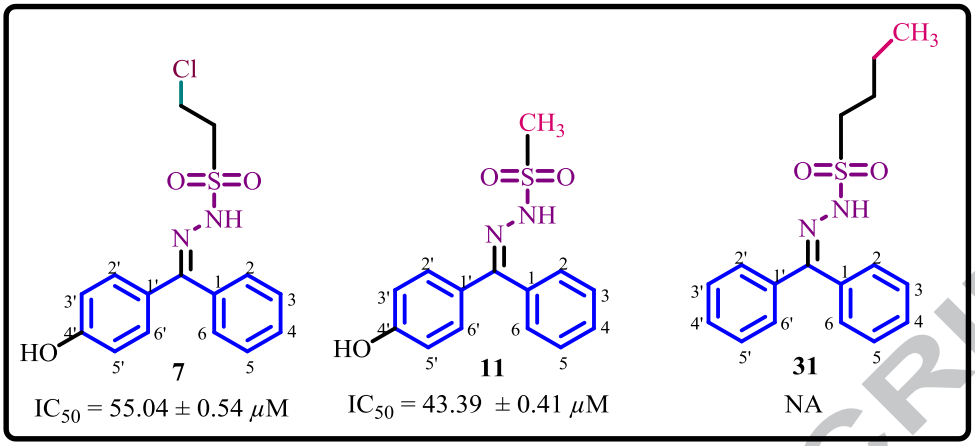


Figure-9: SAR of alkyl substituted aryl sulfonyl part

Benzene ring at aryl sulfonyl part without hydroxyl group substituent at benzophenone part as in compound **13** showed no any activity. Exchanging of benzene with naphthalene ring as in compound **29** also is ineffective. However, *N*,*N*-dimethylnaphthalene as aryl sulfonyl part as in compound **30** (IC_{50} = 72.19 ± 0.60 μM) found to be weakly active. Whereas, compound **8** (IC_{50} = 5.70 ± 0.19 μM) with hydroxylated benzophenone has same other functionalities of compound **30** was found to be third most active compound of the series (Figure-10).

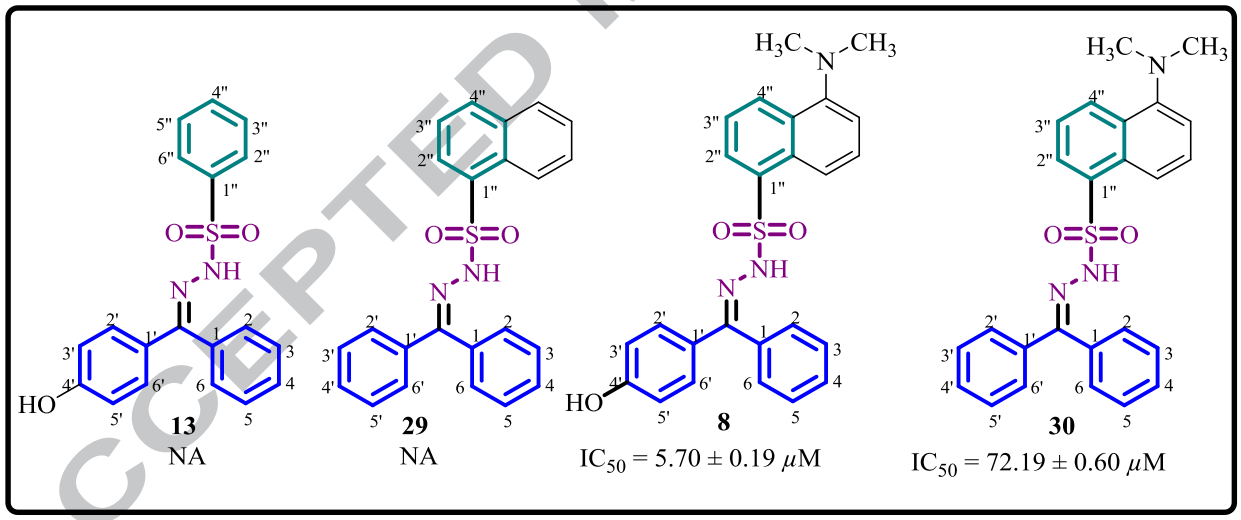
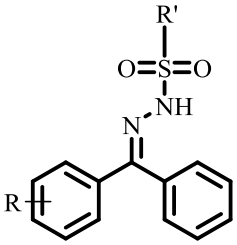
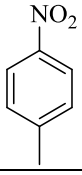
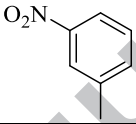
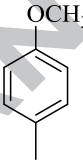
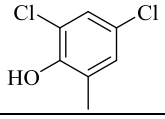
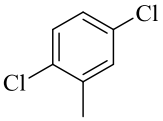
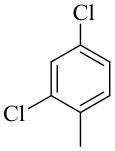
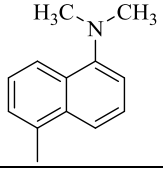
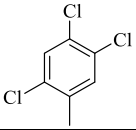
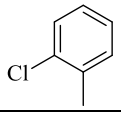
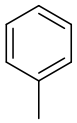
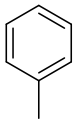
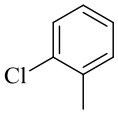
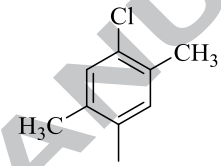
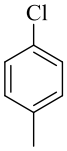
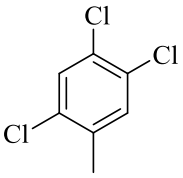
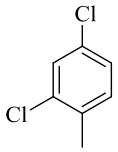
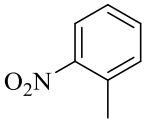
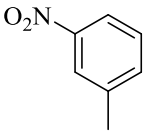
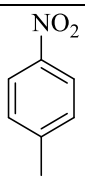


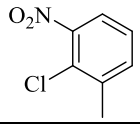
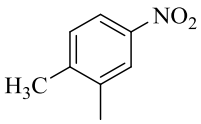
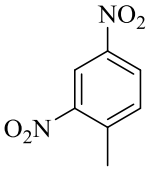
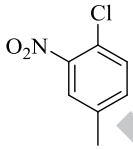
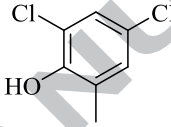
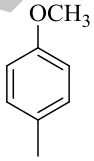
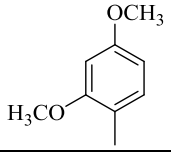
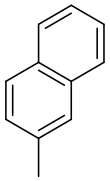
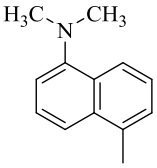
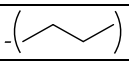
Figure-10: SAR of benzene and *N*,*N*-dimethyl naphthyl substituted aryl sulfonyl part

Table-1: Synthetic compound 1-31 with urease inhibitory activities *in vitro*



Compound No.	R	R´	IC_{50} ± SEM[a] [μM]
1	OH		3.90 ± 0.81
2	OH		13.73 ± 0.01
3	OH		14.51 ± 1.14
4	OH		4.97 ± 0.31
5	OH		31.20 ± 0.16
6	OH		17.99 ± 0.61
7	OH	*n*-Ethyl chloride	55.04 ± 0.54
8	OH		5.70 ± 0.19
9	OH		57.88 ± 0.71
10	OH		16.91 ± 2.10
11	OH	-CH_3	43.39 ± 0.41

12	OH		16.30±1.10
13	H		NA[b]
14	H		NA[b]
15	H		NA[b]
16	H		66.10 ± 0.11
17	H		NA[b]
18	H		NA[b]
19	H		NA[b]
20	H		NA[b]
21	H		NA[b]

22	H		NA[b]
23	H		68.99 ± 0.65
24	H		68.9 9± 0.71
25	H		NA[b]
26	H		71.63 ± 0.81
27	H		NA[b]
28	H		NA[b]
29	H		NA[b]
30	H		72.19 ± 0.60
31	H		NA[b]
Acetohydroxamic acid			29.20 ± 1.01

SEM[a] = Standard Error of the Mean; NA.[b] = Not Active

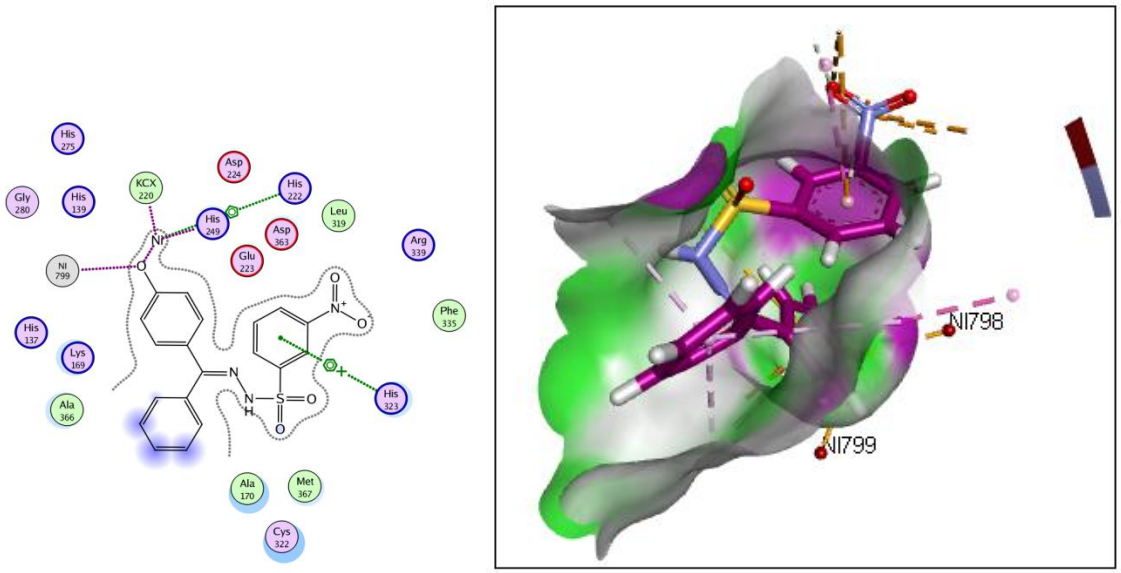
2.4 Computational studies:

In order to under the binding mode of these newly synthesized compounds, molecular docking was performed. From the docking conformation of the compounds, it was revealed that compound **1** (IC_{50} = 3.90 ± 0.81, docking score = -21.4737), showed arene-cation interaction with catalytic residue His323 and also established linkages with both nickel of the active site of the urease enzyme as shown in Figure 11(a). The presence of -NO_2 group at *para* position made it most active compound in the series. The second most active compound was compound **4** (IC_{50} = 4.97 ± 0.31, docking score = -21.3977) showed similar interactions, one of the oxygen of the phenyl moiety of ligand contact with nickel and second phenyl moiety formed arene-cation linkage with His323 as shown in(Figure 11(b)).Compound **1** and **4**, both exhibited the excellent biological activities against the urease enzyme, however, if compared compound **1** with the compound **4** having slight difference in the activities, due to the presence of -Cl group on *ortho* position, -OH and -Clgroups at *meta* positions which made compound **4** the second most active compound and in the series. The third most active compound **8** (IC_{50} = 5.70±0.19, docking score = -21.2256) showed one arene-cation contact with the His323 residue of the binding pocket of the urease enzyme. The oxygen of phenyl moiety of sulfonohydrazide showed hydrogen bonding with His275 and also established contact with nickel (Figure-11c). The fourth one active compound is **2** (IC_{50} = 6.10 ± 0.01, docking score = -20.7057) which showed one arene-cation interaction with the catalytic residue His 323 of the enzyme. The oxygen of the phenyl moiety mediates interaction with both nickel as shown in (Figure-11d). Compound **3** showed two arene-cation interactions, one with His323 and second with nickel, the second nickel involved in interaction with His249, His222, and KCX220 which established contact with oxygen of the phenyl residue of the benzenesulfonohydrazide of the active site of the urease enzyme shown in (Figure-11e). The presence of -OMe group at *meta* position made it fifth most active compound of the series. Compound **6** (IC_{50} = 17.99 ± 0.61, docking score = -20.544), oxygen of the phenyl moiety interact with both nickel. The ligand also showed arene action cationcontact with His323 of the active site of the urease (Figure-11f). Compound **6** have -Cl groups at *ortho* and *para* positions which made it sixth most active compound of the series. The 7^{th} most active compound **12** (IC_{50} = 16.30 ± 1.10, docking score = -20.2789) mediate arene-arene interaction with catalytic residue His323 and also phenyl oxygen contact with nickel which subsequently showed binding with His222, His249 and KXC220 (modified lysine) (Figure-11g). 8^{th} most active compound **10**

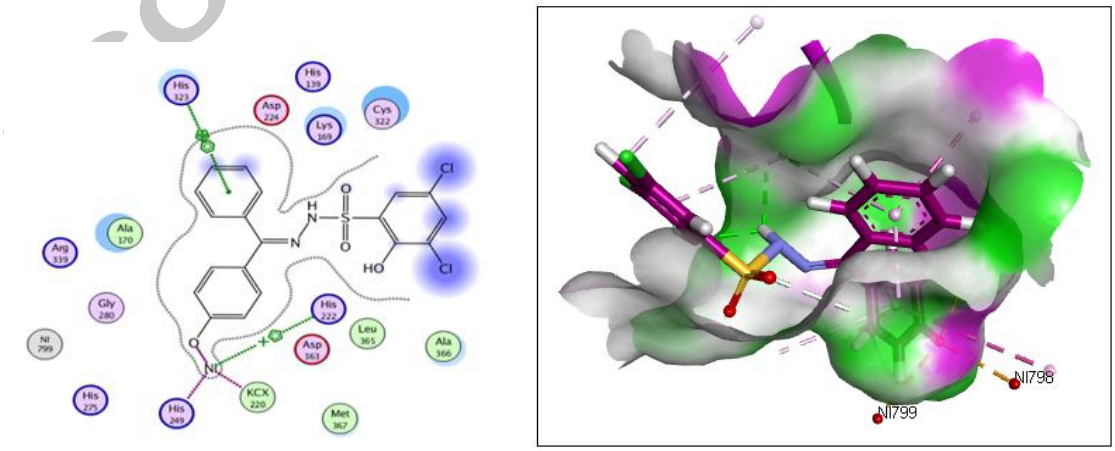
(IC_{50} = 16.91 ± 2.10, docking score = -20.2587) exhibited similar interactions as shown by compound **12** (Figure-11h). Both compounds showed excellent biological activities they have slight difference in their structures at position *ortho* (-Cl in compound **10**) while no any substitution at aryl sulfonyl part, make compound **12**.

Compounds **1-4**, **6**, **8**, **10**, **12** of the series showed good inhibitory activities as compared to the standard acetohydroxamic acid compound (IC_{50} = 29.20 ± 1.01 μM, docking score = -5.8103) and these compounds of the series are well fitted in the active site of the urease enzyme. The control, acetohydroxamic acid makes one hydrogen bond with the active site residues Asp224. The basic catalytic residues His323 and Arg339 of the urease made two hydrogen bonds with two oxygen moieties of the standard compound (Figure-11g). Overall a good correlation was observed between the docking study and biological evaluation of active compounds.

a)



b)



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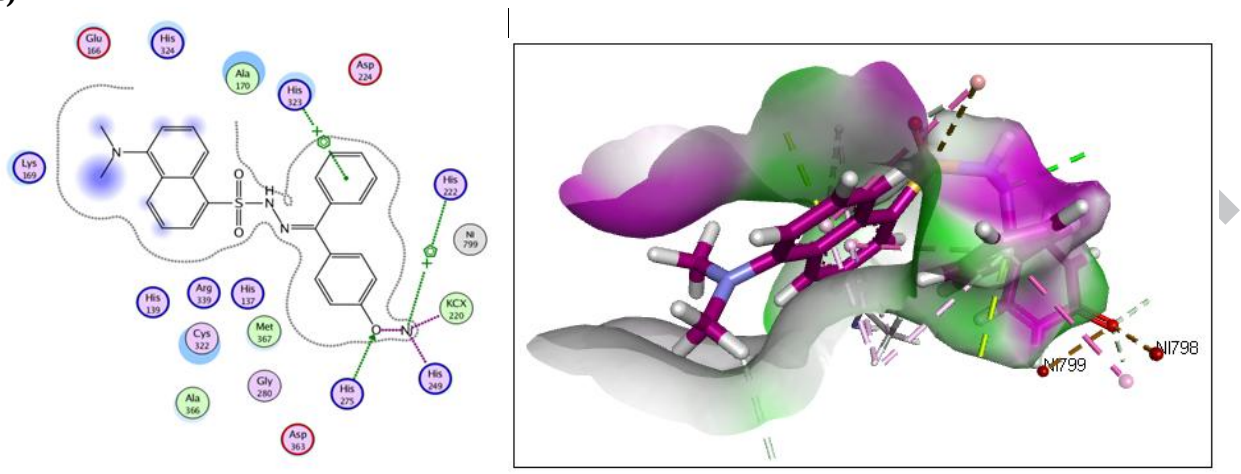
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Ala 170
Asp 224
His 123
Lys 169
His 222
Ni 799
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Arg 339
His 137
KCX 220
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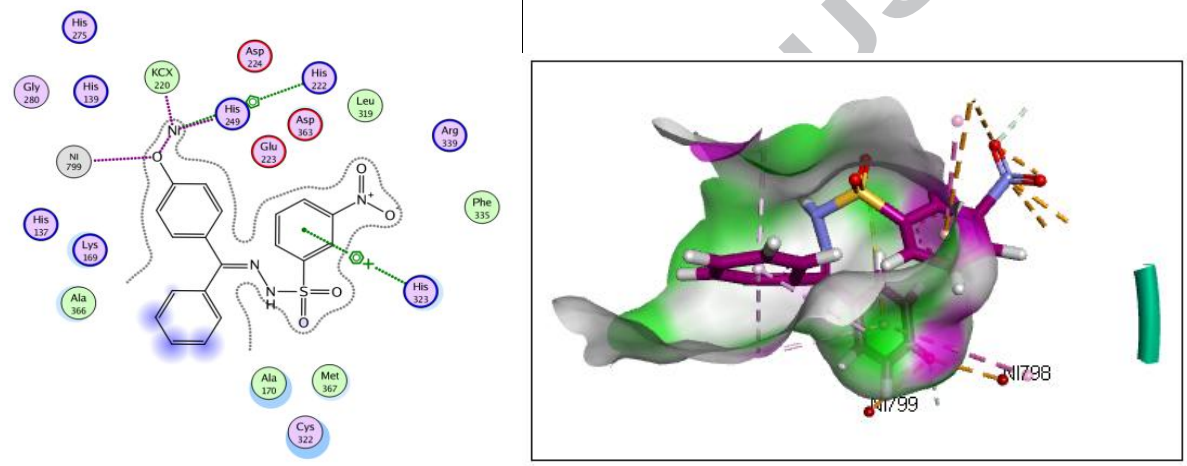
Met 367
His 249
Gly 280
His 275
Ala 366
Asp 363
NI798
NI799

d)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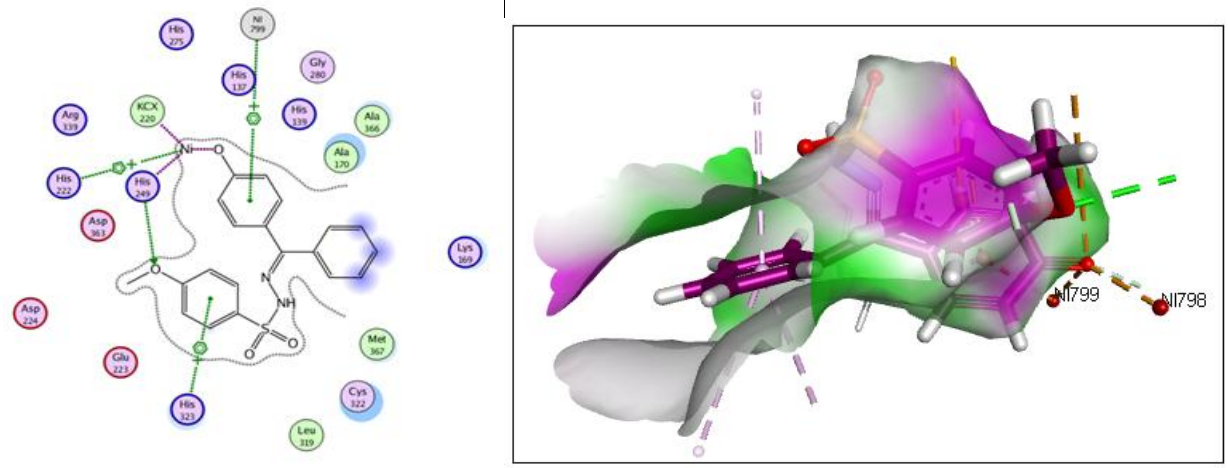
NI798
NI799

e)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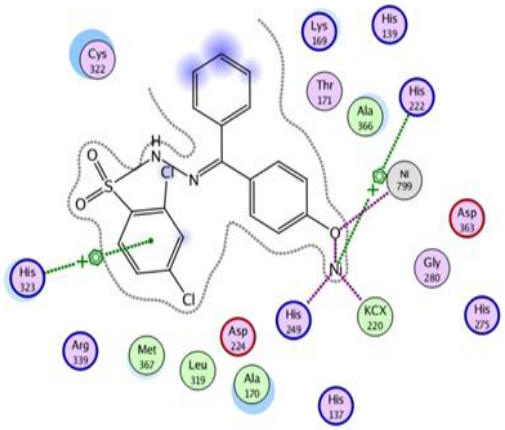
Glu 223
Cys 322
His 323
Leu 319
NI799
NI798

f)


Cys 322
His 139
Lys 169
Thr 171
His 222
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Gly 280
His 323
Cl
His 249
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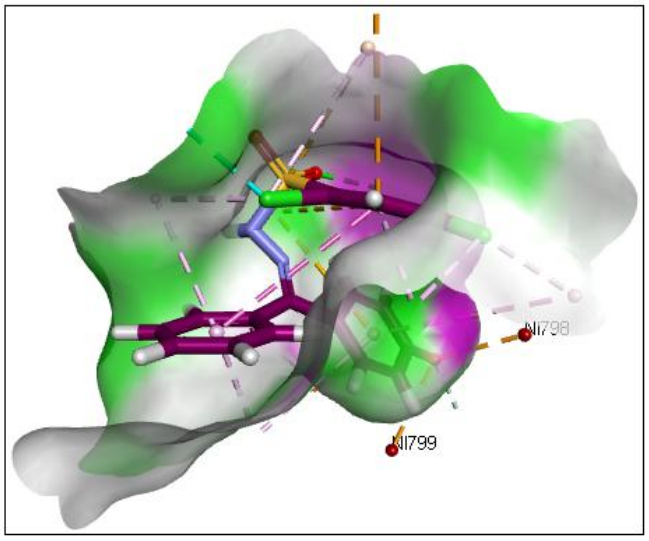
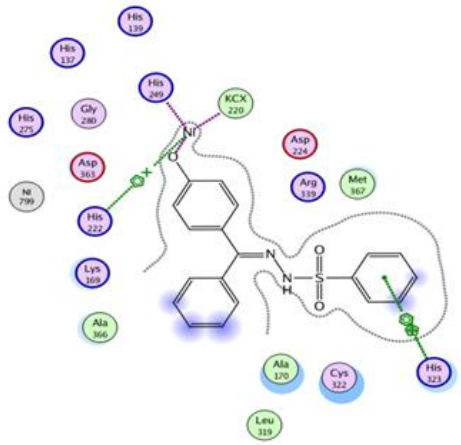
Asp 224
Arg 339
Met 367
Leu 319
Ala 170
His 137


NI798
NI799

g)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His 137
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KCX 220
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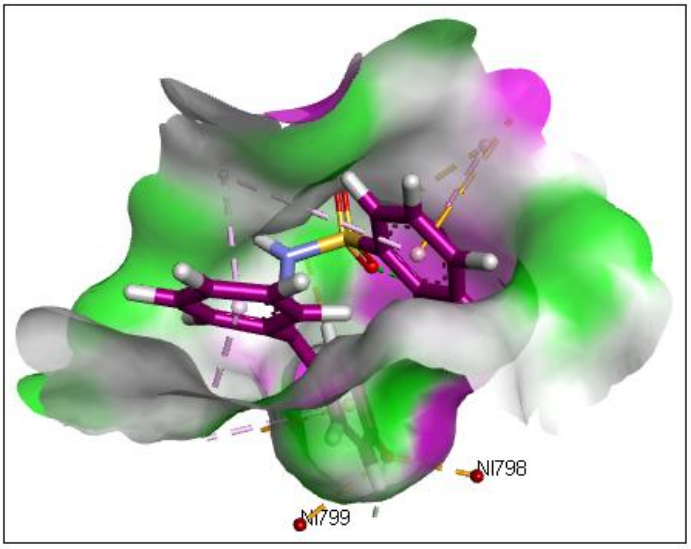
Cys 322
His 323
Leu 319


NI798
NI799

h)

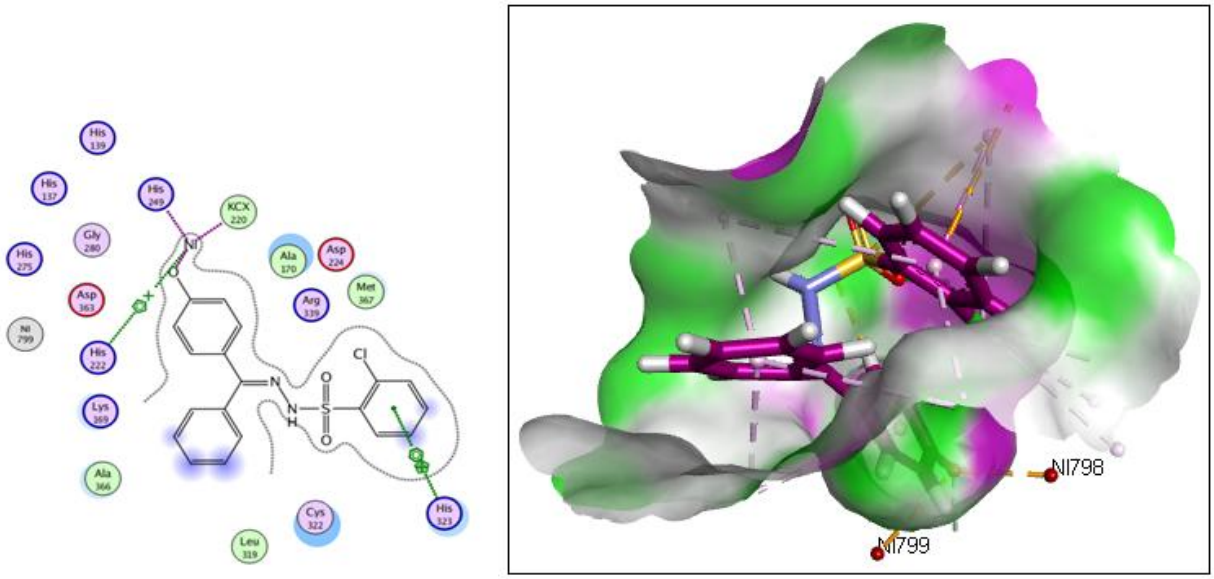


Figure-11: Docking conformation of compound **1** (a), compound **4** (b) **8** (c), compound **2** (d) and **3** (e) compound **6** (f), compound **12** (g), compound **10** (h)

a)

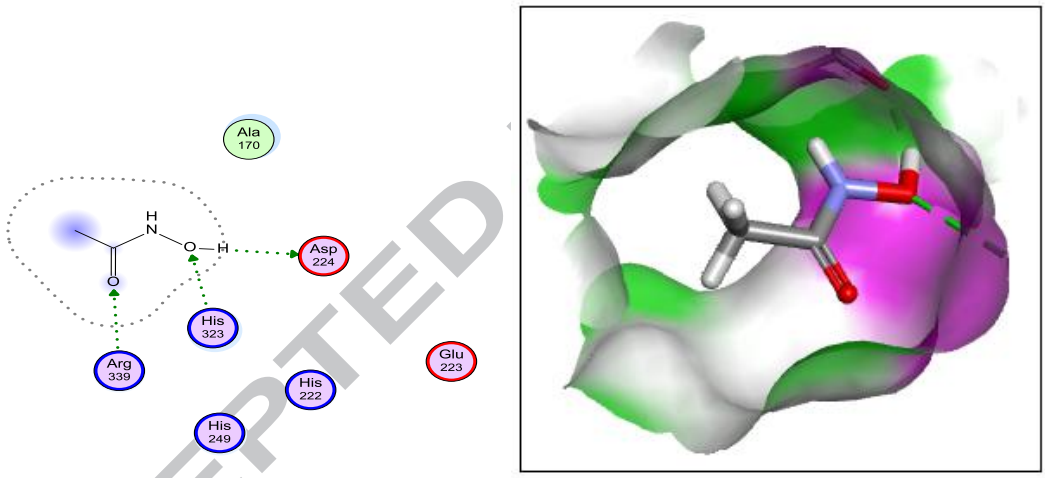


Figure-12: Docking conformation acetohydroxamic acid (a) in the active site of urease.

3 Conclusion

This study deals with the synthesis of benzophenone sulfonamides (**1-31**) and their urease inhibitory potential. Amongst thirty-one compounds, seventeen (**1-12**, **16**, **23**, **24**, **26**, **30**) demonstrated good to moderate inhibitory potential having an IC_{50} value range of 3.90-71.63 μM. Compounds **1-4**, **6**, **8**, **10**, **12** showed superior activity (IC_{50} = 3.90 - 17.99 μM) than the standard acetohydroxamic acid (IC_{50} = 29.20 ± 1.01). Limited structure-activity relationship revealed that compounds having hydroxyl group at benzophenone part displayed good inhibitory activity than non-hydroxyl benzophenone part. However, different substitution at aryl sulfonyl

part also responsible for varying degree of activity. Moreover, computational studies of most active compounds showed good binding interaction between active compound and urease enzyme. Decisively this study provides some leads compounds as urease inhibitors.

4. Experimental:

4.1 Material and Methods:

Pyridines, benzophenone hydrazone, 4'-hydroxy benzophenone hydrazone, varyingly substitute sulfonyl chloride and hexane, were purchased from Sigma-Aldrich, USA and used as received without purification. Thin layer chromatography (TLC) was performed on pre-coated silica gel aluminium plates (Kieselgel 60, 254, E. Merck). UV wavelength 254 and 365 nm were used for TLC visualization. Melting points of all the compounds were determined on Stuart® SMP10 melting point apparatus and are uncorrected. ^{1}H-NMR experiments were performed out on Bruker Avance AM 300, 400, and 500 MHz machines. EI-MS and FAB-MS was recorded on a Finnigan MAT-311A (Germany) mass spectrometer. ^{13}C-NMR experiments were carried on Bruker Avance AM 300 and 400 MHz instruments at 75, 100, and 150 MHz, respectively. Infrared (IR) spectra were recorded on JASCO IR-A-302 spectrophotometer.

4.2. Urease inhibitory assay

Spectrophotometically urease inhibition assay was performed. For urease inhibition assay 5 μL of synthetic compound was incubated with 25 μL of urease solution (1 U/well) (250 μL) at 30 $^{\circ}$C for 15 minute. After that, 55 μL substrate urea with 100 mM concentration was added and the plate was again incubated at 30 $^{\circ}$C. After incubation 70 μL of basic reagent (0.5% w/v NaOH and 0.1% NaOCl) and 45 μL of carbolic acid (1% w/v carbolic acid and 0.005% w/v $Na_2[Fe(CN)_5NO]$) were added at each well. Again plate was incubated for 50 min at 30 $^{\circ}$C. Rate of production ammonia was used for determining urease inhibitory activity by following Weatherburn method and change in absorbance was monitored at 630 nm on a ELISA plate reader (Spectra Max M2, Molecular Devices, CA, USA). Acetohydroxamic acid was used as a standard compound [32].

4.3. Methodology

Molecular docking

The molecular docking was performed by using MOE-Dock implemented in the Molecular Operating Environment (MOE), using the default parameters [33]. The X-ray crystallographic structure of *Bacillus pasteurii* (PDB Code: 4UBP) was downloaded from the protein databank [34]. All molecules of water were removed from the structure of the protein. Then, hydrogen's were added, and the energy minimization was carried out using a default force field. 3D structure of all the compounds was built using the Molecular Builder program implemented in MOE. Finally, a database was created in which all the ligands were converted into their respective 3D structures and this database was used as input file MOE-docking. Subsequently, the energy of compounds present in the database was minimized up to 0.05 Gradient using MMFF94x force field and add hydrogen to the compounds. The database was docked into the active site of protein using the Triangular Matching docking method and 10 conformations of each Ligand protein complex were generated with docking score (S). Each complex was analyzed for interactions and their 3D images were taken.

General procedures for the synthesis of compound 1-31

The synthesis of benzophenone sulfonamide has been performed by stirring the reaction of benzophenone hydrazone (1 mmol) and 4′-hydroxy benzophenone hydrazone (1 mmol) with differently substituted sulfonyl chloride (1 mmol) respectively in 10 mL of pyridine. Stirring of reaction mixture was carried out at for 24 hours. After completion of reaction, reaction mixture was poured in ice cold water. Which results in precipitation, these precipitate were filter dry and then washed with hexane. Chemical structures of these synthetic analogues were characterized by ^{1}H-NMR, ^{13}C-NMR, EI-MS and FAB-MS spectroscopy.

***N'*-((4'-Hydroxyphenyl)(phenyl)methylene)-4''-nitrobenzenesulfonohydrazide (1)**

Yield: 89%; m.p 165-168 $^{\circ}$C; R_f: 0.38 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.64 (s, 1H, NH), 9.96 (s, 1H, OH), 8.06 (m, 2H, H-3″, H-5″), 7.91 (m, 2H, H-2″, H-6″), 7.37 (m, 2H, H-2, H-6), 7.31 (m, 1H, H-4), 7.26(m, 2H, H-3, H-5), 7.11 (d, 2H, $J_{2',3'/6',5'}$ = 8.4 Hz, H-2′, H-6′), 6.93 (d, 2H, $J_{3',2'/5',6'}$ = 8.7 Hz, H-3′, H-5′); FAB-MS *m/z* 398 $[M+H]^+$.

***N*'-((4'-Hydroxyphenyl)(phenyl)methylene)-3''-nitrobenzenesulfonohydrazide (2)**

Yield: 90%; m.p 170-172 °C; R_f: 0.39 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.71 (d, 1H, J = 78.0 Hz, NH), 9.93 (d, 1H, J = 15.0 Hz, OH), 8.65 (s, 1H, H-2″). 8.53 (d, 1H, $J_{6'',5''}$ = 8.4 Hz, H-6″), 8.34 (d, 1H, $J_{4'',5''}$ = 7.8 Hz, H-4″), 7.97 (t, 1H, $J_{5''(4'',6'')}$ = 7.8 Hz, H-5″), 7.50 (m, 1H, H-4), 7.36 (m, 4H, H-2, H-3, H-5, H-6), 7.21 (m, 2H, H-2′, H-6′), 7.07 (d, 1H, $J_{2',3'}$ = 8.4 Hz, H-3′), 6.86 (d, 1H, $J_{5',6'}$ = 8.4 Hz, H-5′); FAB-MS *m/z* 398 $[M+H]^+$

***N*'-((4'-Hydroxyphenyl)(phenyl)methylene)-4''-methoxybenzenesulfonohydrazide (3)**

Yield: 90%; m.p 168-170 °C; R_f: 0.39 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.23 (s, 1H, NH), 9.85 (s, 1H, OH), 7.85 (d, 2H, $J_{2,3/6,5}$ = 9.0 Hz, H-2, H-6), 7.36 (t, 3H, $J_{3(4,5)/4(3,5)/5(4,6)}$= 8.5 Hz, H-3, H-4, H-5), 7.24 (d, 2H, $J_{2'',3''/6'',5''}$ = 9.0 Hz, H-2″, H-6″), 7.14 (d, 2H, $J_{3'',2''/5'',6''}$ = 9.0 Hz, H-3″, H-5″), 7.05 (d, 2H, $J_{2',3'/6',5'}$ = 8.4 Hz, H-2′, H-6′), 6.88 (d, 2H, $J_{3',2'/5',6'}$ = 8.7 Hz, H-3′, H-5′); ^{13}C-NMR: (75.0 MHz, DMSO-d_6): δ_C 162.5 (C=N), 158.3 (C-1″), 154.5 (C-4″), 137.7 (C-3″, C-5″), 130.4 (C-1), 129.8 (C-1′), 129.4 (C-2, C-6), 128.1 (C-4) 127.4 (C-2′, C-6′), 122.8 (C-4′), 115.4 (C-3′, C-5′), 114.0 (C-3, C-5), 55.6 (C-4″-OCH_3); FAB-MS *m/z* 383 $[M+H]^+$.

3'',5''-Dichloro-2''-hydroxy-*N*'-((4'-hydroxyphenyl)(phenyl)methylene)benzenesulfonohydrazide (4)

Yield: 89%; m.p 178-180 °C; R_f: 0.37 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.09 (s, 1H, NH), 8.59 (d, 1H, $J_{4'',6''}$ = 2.4 Hz, H-4″), 8.59 (d, 1H, $J_{6'',4''}$ = 2.4 Hz, H-6″), 7.58 (m, 5H, H-2, H-3, H-4, H-5, H-6), 7.18 (d, 2H, $J_{2',3'/6',5'}$ = 8.4 Hz, H-2′, H-6′), 6.98 (d, 2H, $J_{3',2'}$ = $J_{5',6'}$ = 8.7 Hz, H-3′, H-5′); FAB-MS *m/z* 438 $[M+H]^+$.

2'',5''-Dichloro-*N*'-((4'-hydroxyphenyl)(phenyl)methylene)benzenesulfonohydrazide (5)

Yield: 83%; m.p 118-120 °C; R_f: 0.37 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.74 (s, 1H, NH), 9.93 (s, 1H, OH), 7.97 (d, 1H, $J_{6'',3''}$ = 1.5Hz, H-6″), 7.77 (d, 2H, $J_{3'',4''}$ = $J_{4'',3''}$ = 7.5 Hz, H-3″, H-4″), 7.36 (m, 2H, H-3, H-5), 7.22 (d, 3H, $J_{2,3/6,5/4,3}$ = 6.9 Hz, H-2, H-6, H-4), 7.10 (d, 2H, $J_{2',3'/6',5'}$ = 7.5 Hz, H-2′, H-6′), 6.91 (d, 2H, $J_{3',2'/5',6'}$ = 7.5 Hz, H-3′, H-5′); FAB-MS *m/z* 421 $[M+H]^+$.

2'',4''-Dichloro-*N*'-((4'-hydroxyphenyl)(phenyl)methylene)benzenesulfonohydrazide (6)

Yield: 91%; m.p 168-170 °C; R_f: 0.37 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.90 (s, 1H, NH), 7.99 (s, 1H, OH), 7.79 (dd, 1H, $J_{5'',6''}$ = 6.6 Hz, $J_{5'',3''}$ = 2.1 Hz, H-5''), 7.75 (d, 1H, $J_{6'',5''}$ = 7.5 Hz, H-6''), 7.55 (m, 3H, H-2, H-6, H-H-3''), 7.38 (t, 1H, $J_{4(5,6)}$ = H-4), 7.33 (t, 2H, $J_{3(2,4)\ /5(4,6)}$ = H-3, H-5), 7.27 (m, 2H, H-2', H-6'), 7.24 (m, 2H, H-3', H-5'); ^{13}C-NMR: (100.0 MHz, DMSO-d_6): δ_C 155.5 (C=N), 138.0 (C-1''), 136.8 (C-2''), 134.3 (C-4''), 133.7 (C-1'), 132.1 (C-1), 132.0 (C-3, C-5), 130.8 (C-4'), 129.9 (C-2, C-6), 129.8 (C-3''), 129.6 (C-5''), 129.0 (C-6''), 128.6 (C-3', C-5'), 128.4 (C-4), 127.2 (C-2', C-6'); FAB-MS *m/z* 421 $[M+H]^+$.

2''-Chloro-*N*'-((4'-hydroxyphenyl)(phenyl)methylene)ethanesulfonohydrazide (7)

Yield: 90%; m.p 172-174 °C; R_f: 0.39 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.39 (s, 1H, NH), 9.19 (d, 1H, J = 5.7 Hz, OH), 8.64 (t, 1H, $J_{4(3,5)}$ = 7.5 Hz, H-4), 8.18 (t, 2H, $J_{3(2,4)/5(4,6)}$ = 7.5 Hz, H-3, H-5), 7.55 (m, 2H, H-2, H-6), 7.41 (m, 4H, H-2', H-3', H-5', H-6'), 5.10 (t, 2H, $J_{CH2(CH2)}$ = 6.0 Hz, CH_2), 4.19 (t, 2H, $J_{CH2(CH2)}$ = 6.0 Hz, CH_2); ^{13}C-NMR: (75.0 MHz, DMSO-d_6): δ_C 155.8 (C=N), 146.1 (C-1''), 145.5 (C-1'), 136.9 (C-1), 129.9 (C-2, C-6), 129.5 (C-2', C-6'), 128.3 (C-4), 127.6 (C-4'), 127.6 (C-3, C-5), 54.7 (CH_2), 49.2 (CH_2); FAB-MS *m/z* 339 $[M+H]^+$.

5-(Dimethylamino)-*N*'-((4-hydroxyphenyl)(phenyl)methylene)naphthalene-1-sulfono-hydrazide (8)

Yield: 87%; m.p 130-132 °C; R_f: 0.36 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 11.03 (m, 1H, NH), 8.50 (m, 2H, H-3', H-'), 8.40 (m, 2H, H-2', H-6'), 7.69 (m, 4H, H-2, H-6, H-3, H-5), 7.27 (m, 4H, H-4, H-2'', H-3'', H-4'',), 7.02 (m, 1H, H-6''), 6.95 (m, 2H, H-7'', H-8''), 2.77 (s, 6H, $N(CH_3)_2$); FAB-MS *m/z* 446 $[M+H]^+$.

2'',4'',5''-Trichloro-*N*'-((4'-hydroxyphenyl)(phenyl)methylene)benzenesulfonohydrazide (9)

Yield: 89%; m.p 165-167 °C; R_f: 0.35 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.93 (s, 1H, NH), 9.90 (s, 1H, OH), 8.66, (m, 1H, H-3''), 8.40 (m, 1H, H-6''), 7.75 (d, 1H, $J_{4(3,5)}$ = 7.5 Hz, H-4), 7.39, (m, 2H, H-2, H-6), 7.21 (m, 2H, H-3, H-5), 7.09 (d, 2H, $J_{2',3'/6',5'}$ = 8.4 Hz, H-2', H-6'), 6.89 (d, 2H, $J_{3',2'/5',6'}$ = 8.7 Hz, H-3', H-5'); ^{13}C-NMR: (150.0 MHz, DMSO-d_6):

δ_C 148.5 (C=N), 142.6 (C-1″), 139.3 (C-4″), 138.6 (C-5″), 134.2 (C-2″), 133.1 (C-2, C-6), 133.0 (C-1′), 132.3 (C-4′), 131.5 (C-1), 131.4 (C-3′, C-5′), 131.3 (C-2′, C-6′), 128.2 (C-3″), 127.3 (C-6″), 125.3 (C-3, C-5), 122.9, (C-3,C-5); FAB-MS *m/z* 456 $[M+H]^+$.

2''-Chloro-*N*'-((4'-hydroxyphenyl)(phenyl)methylene)benzenesulfonohydrazide (10)

Yield: 87%; m.p 130-132 °C; R_f: 0.35 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.33 (s, 1H, NH), 9.92 (s, 1H, OH), 8.05 (d, 1H, $J_{3'',4''}$ = 7.8Hz, H-3″), 7.69 (m, 2H, H-2, H-6), 7.62 (m, 1H, H-4), 7.34 (m, 3H, H-3, H-5, H-5″), 7.19 (d, 2H, $J_{3'',4''/6'',5''}$ = 8.4 Hz H-3″, H-6″), 7.10 (d, 2H, $J_{2',3'/6',5'}$ = 8.4 Hz, H-2′, H-6′), 6.93 (d, 2H, $J_{3',2'/5',6'}$ = 8.4 Hz, H-3′, H-5′); FAB-MS *m/z* 387 $[M+H]^+$.

***N*'-((4'-Hydroxyphenyl)(phenyl)methylene)methanesulfonohydrazide (11)**

Yield: 89%; m.p 145-147 °C; R_f: 0.37 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 8.68 (s, 1H, NH), 7.67 (s, 1H, OH), 7.65 (m, 2H, H-3, H-5),7.57 (d, 2H, $J_{2,3/6,5}$ = 6.0 Hz, H-2, H-6), 7.52 (d, 2H, $J_{2',3'/6',5'}$ = 6.0 Hz, H-2′, H-6′), 7.48 (d, 2H, $J_{3',2'/5',6'}$ = 7.2 Hz, H-3′, H-5′), 6.91 (d, 1H, $J_{4(3,5)}$ = 7.8 Hz, H-4), 2.33 (s, 3H, S-CH_3); FAB-MS *m/z* 291 $[M+H]^+$.

***N*'-((4'-Hydroxyphenyl)(phenyl)methylene)benzenesulfonohydrazide (12)**

Yield: 86%; m.p 193-195 °C; R_f: 0.38 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.44 (s, 1H, NH), 9.87 (s, 1H, OH), 7.92 (d, 2H, $J_{2,3}$ = $J_{6,5}$ = 6.9Hz, H-2, H-6), 7.67 (m, 3H, H-3, H-5, H-4), 7.36 (m, 3H, H-3″, H-5″, H-4″), 7.22 (d, 2H, $J_{2'',3''/6'',5''}$ = 6.9 Hz, H-2″, H-6″), 7.06 (d, 2H, $J_{2',3'/6',5'}$ = 8.4 Hz, H-2′, H-6′), 6.88 (d, 2H, $J_{3',2'/5',6'}$ = 8.4 Hz, H-3′, H-5′); FAB-MS *m/z* 353 $[M+H]^+$.

***N*'-(Diphenylmethylene)benzenesulfonohydrazide (13)**

Yield: 85%; m.p 165-167 °C; R_f: 0.40 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.51(s, 1H, NH), 7.93 (d, 2H, $J_{2,3/}J_{6,5}$ = 8.4 Hz, H-2, H-6), 7.66 (m, 1H, H-4″), 7.52 (m, 1H, H-4), 7.44 (m, 1H, H-4′), 7.37 (m, 4H, H-2″, H-6″, H-3″, H-5″), 7.29 (m, 4H, H-3, H-5, H-3′, H-5′), 7.22 (m, 2H, H-2′, H-6′); EI-MS: *m/z* (rel. abund.%), 336 $[M]^+$ (5.8), 283 (95.5), 257 (13.6), 195 (100.0), 180 (38.6), 165 (64.5), 77 (40.9).

2''-Chloro-*N'*-(diphenylmethylene)benzenesulfonohydrazide (14)

Yield: 88%; m.p 120-122 °C; R_f: 0.38 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.57 (s, 1H, NH), 8.06 (d, 1H, $J_{3'',4''}$ = 7.5 Hz, H-3''), 7.69 (d, 2H, $J_{2,3/6,5}$ = 8.4Hz, H-2, H-6), 7.62 (m, 2H, H-3, H-5), 7.56 (d, 2H, $J_{4'\,(3',5')/4(3,5)}$ = 8.4 Hz, 2H, H-4, H-4'), 7.36 (m, 1H, H-6''), 7.30 (t, 2H, $J_{4''(3'',5'')/5''(4'',6'')}$ = 8.4 Hz, H-4'', H-5''), 7.26 (m, 2H, H-3', H-5'), 7.17 (d, 2H, , $J_{2',3'/6',5'}$ = 8.4 Hz, H-2', H-6'); FAB-MS m/z 371 $[M+H]^+$.

4''-Chloro-*N*'-(diphenylmethylene)-2'',5''-dimethylbenzenesulfonohydrazide (15)

Yield: 88%; m.p 170-172 °C; R_f: 0.39 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 10.64 (s, 1H, NH), 7.87 (s, 1H, H-3''), 7.52 (m, 4H, H-6'', H-4, H-4', H-5), 7.36 (m, 3H, H-3, H-3', H-5'), 7.22 (m, 4H, H-2, H-6,H-2', H-6'), 2.59 (s, 3H, 2''-CH_3), 2.37 (s, 3H, 6''-CH_3); EI-MS *m/z* (% rel. abund.): 400 $[M+2]^+$ (14.1), 398 $[M]^+$ (32.6), 360 (67.6), 283 (84.5), 195 (100.0), 165 (91.1), 92 (27.0), 77 (56.9).

4''-Chloro-*N*'-(diphenylmethylene)benzenesulfonohydrazide (16)

Yield: 89%; m.p 180-182 °C; R_f: 0.39 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 7.60 (d, 4H, $J_{2,3/6,5/2'',3''/6'',5''}$ = 8.4 Hz, H-2, H-6, H-2'', H-6''), 7.47 (d, 2H, $J_{3'',2''/5'',6''}$ = 8.4 Hz, H-3'', H-5''), 7.37 (m, 7H, H-3, H-5, H-2', H-6', H-3', H-5', H-4), 7.28 (m, 1H, H-4'); ^{13}C-NMR: (100.0 MHz, DMSO-d_6): δ_C 159.0 (C=N), 147.2 (C-1''), 137.4 (C-4''), 137.4 (C-1''), 135.0 (C-1''), 132.9 (C-1'), 129.9 (C-1), 128.9 (C-2, C-6), 128.8 (C-2', C-6'), 128.3 (C-2'', C-6''), 128.3 (C-3'', C-5''), 128.1 (C-4), 128.0 (C-3, C-5), 127.6 (C-3', C-5'), 127.4 (C-4'); FAB-MS *m/z* 371 $[M+H]^+$.

2,4,5-Trichloro-*N*'-(diphenylmethylene)benzenesulfonohydrazide (17)

Yield: 88%; m.p 140-142 °C; R_f: 0.37 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.96 (s, 1H, NH), 8.14 (s, 2H, H-3'', H-6''), 7.55 (m, 1H, H-4), 7.47 (m, 1H, H-4'), 7.37 (m, 4H, H-2, H-6, H-2', H-6'), 7.30 (m, 4H, H-3, H-5, H-3', H-5'); EI-MS *m/z* (% rel. abund.): 440$[M+2]^+$ (5.3), 437.0 $[M]^+$ (5.4), 360 (35.6), 283 (61.3), 195 (100.0), 165 (65.5).

2'',4''-Dichloro-*N*'-(diphenylmethylene)benzenesulfonohydrazide (18)

Yield: 90%; m.p 146-148 °C; R_f: 0.36 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.89 (s, 1H, NH), 7.99 (d, 1H, , $J_{3'',5''}$ = 2.1 Hz, H-3''), 7.78 (m, 1H, H-5''), 7.55 (m, 2H, H-4, H-6''), 7.47 (d, 2H, $J_{2,3/6,5}$ = 6.9 Hz, H-2, H-6), 7.37 (m, 3H, H-2', H-6', H-4'), 7.27 (m, 4H, H-3, H-5, H-3, H-5); FAB-MS *m/z* 405 $[M+H]^+$.

***N*'-(Diphenylmethylene)-2''-nitrobenzenesulfonohydrazide (19)**

Yield: 87%; m.p 144-146 °C; R_f: 0.39 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.71 (s, 1H, NH), 8.08 (m, 2H, H-3'', H-6''), 7.91 (m, 1H, H-5''), 7.56 (m, 1H, H-4''), 7.49 (d, 2H, $J_{2,3/}J_{6,5}$ = 6.0 Hz, H-2, H-6) 7.37 (m, 4H, H-2, H-6, H-4, H-4'), 7.29 (m, 4H, H-3, H-5, H-3', H-5'); EI-MS *m/z* (% rel. abund.): 381 $[M]^+$ (2.2), 360 (62.3), 283 (100.0), 257, (18.5), 195 (44.3), 180, (41.4), 165 (51.0).

***N*'-(Diphenylmethylene)-3′′-nitrobenzenesulfonohydrazide (20)**

Yield: 92%; m.p 230-232 °C; R_f: 0.40 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 8.32 (m, 4H, NH, H-2'', H-4'', H-6''), 8.19 (m, 3H, H-4, H-4', H-5''), 8.02 (d, 4H, $J_{2,3/6,5/2',3'/6',5'}$ = 7.8 Hz, H-2, H-6, H-2', H-6'), 7.67 (t, 4H, $J_{3(2,4)/5(6,4)/3'(2',4')/5'(6',4')}$ = 7.8 Hz, H-3, H-5, H-3', H-5'); FAB-MS *m/z* 382 $[M+H]^+$.

***N*'-(Diphenylmethylene)-4''-nitrobenzenesulfonohydrazide(21)**

Yield: 87%; m.p 150-152 °C; R_f: 0.38 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.83 (s, 1H, NH), 8.47 (d, 2H, $J_{3'',2''/5'',6''}$ = 9.0 Hz, H-3'', H-5''),8.18 (d, 2H, $J_{2'',3''/}J_{6'',5''}$ = 8.7 Hz, H-2'', H-6''), 7.53 (m, 2H, H-4, H-4'), 7.39 (m, 4H, H-2, H-6, H-2', H-6'), 7.26 (m, 4H, H-3, H-5, H-3', H-5'); EI-MS *m/z* (% rel. abund.): 381 $[M]^+$ (7.3), 360 (12.9), 283 (21.4), 195, (100.0), 165, (38.5).

2-Chloro-*N*'-(diphenylmethylene)-3-nitrobenzenesulfonohydrazide (22)

Yield: 90%; m.p 154-156 °C; R_f: 0.39 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 8.12 (s, 1H, H-NH), 7.86 (dd, 1H, $J_{6'',5''}$ = 6.6 Hz, $J_{6'',4''}$ = 2.1 Hz, H-6''), 7.74 (d, 1H, $J_{4'',5''}$

= 8.4 Hz, H-4″), 7.47 (d, 2H, $J_{2,3/6,5}$ = 6.9 Hz, H-2, H-6), 7.37 (m, 5H, H-3, H-5, H-3′, H-5′, H-5″), 7.29 (m, 4H, H-2′, H-6′, H-4, H-4′); FAB-MS *m/z* 416 $[M+H]^+$.

_N_'-(Diphenylmethylene)-2''-methyl-5''-nitrobenzenesulfonohydrazide (23)

Yield: 91%; m.p 160-162 °C; R_f: 0.40 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 11.01 (s, 1H, NH), 8.68 (d, 1H, $J_{6'',4''}$ = 2.4Hz, H-6″), 8.41 (dd, 1H, $J_{4'',3''}$ = 6.0 Hz, $J_{4'',6''}$ = 2.4 Hz, H-4″), 7.76 (d, 1H, $J_{3'',2''}$ = 8.4 Hz, H-3″), 7.54 (m, 3H, H-2, H-4, H-6), 7.37 (m, 3H, H-2′, H-4′, H-6′), 7.23 (m, 4H, H-3, H-5, H-3′, H-5′), 2.80 (s, 3H, H-2″-CH_3); EI-MS *m/z* (% rel. abund.): 395 $[M]^+$ (2.5), 195, (60.1), 165, (100.0), 137, (17.0), 91 (15.5), 77 (13.2).

_N_'-(Diphenylmethylene)-2'',4''-dinitrobenzenesulfonohydrazide (24)

Yield: 90%; m.p 155-156 °C; R_f: 0.38 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 11.31 (s, 1H, NH), 8.97 (m, 1H, H-3″), 8.70 (d, 1H, $J_{4(3,5)}$ = 7.5 Hz, H-4), 8.42 (dd, 1H, $J_{5'',6''}$ = 6.0 Hz, $J_{5'',3''}$ = 2.4 Hz, H-5″), 8.30 (d, 1H, $J_{6'',5''}$ = 8.7 Hz, H-6″), 8.15 (d, 1H, $J_{4'\,(3',5')}$ = 9.0 Hz, H-4′), 7.56 (m, 8H, H-2, H-6, H-2′, H-6′, H-3, H-5, H-3′, H-5′); FAB-MS *m/z* 427 $[M+H]^+$.

4'-Chloro-_N_'-(diphenylmethylene)-3''-nitrobenzenesulfonohydrazide (25)

Yield: 87%; m.p 168-170 °C; R_f: 0.36 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.76 (s, 1H, NH), 8.56 (d, 1H, $J_{2'',4''}$ = 2.0 Hz, H-2″), 8.19 (dd, 1H, $J_{5'',6''}$ = 6.6 Hz, $J_{5'',2''}$ = 2.0 Hz, H-5″), 8.09 (d, 1H, $J_{6'',5''}$ = 8.4 Hz, H-6″), 7.54 (m, 3H, H-2, H-4, H-6), 7.43 (m, 4H, H-3, H-5, H-3′, H-5′), 7.29 (m, 3H, H-2′, H-6′, H-4′); ^{13}C-NMR: (100.0 MHz, DMSO-d_6): δ_C 156.6 (C=N), 147.1 (C-1″), 138.5 (C-3″), 136.8 (C-4″), 132.9 (C-1′), 132.4 (C-1), 132.3 (C-4′), 130.1 (C-2, C-6), 129.6 (C-2″), 128.9 (C-3″), 128.8 (C-3′, C-5′), 128.4 (C-4), 127.5 (C-2, C-6), 125.2 (C-3, C-5); FAB-MS *m/z* 416 $[M+H]^+$.

3'',5''-Dichloro-_N'_-(diphenylmethylene)-2-hydroxybenzenesulfonohydrazide (26)

Yield: 89%; m.p 185-187 °C; R_f: 0.37 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 11.10 (s, 1H, NH), 9.88 (s, 1H, OH),7.94 (d, 1H, $J_{6'',4''}$ = 2.7Hz, H-6″), 7.72 (d, 1H, $J_{4'',6''}$ = 2.4 Hz, H-4″), 7.59 (m, 2H, H-2, H-6), 7.37 (m, 4H, H-4, H-4′, H-2′, H-6′), 7.29 (m, 4H, H-3, H-5, H-3′, H-5′); FAB-MS *m/z* 421 $[M+H]^+$.

_N_'-(Diphenylmethylene)-4''-methoxybenzenesulfonohydrazide (27)

Yield: 87%; m.p 160-162 °C; R_f: 0.38 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.27 (s, 1H, NH), 7.86 (d, 1H, $J_{4'(3',5')}$ = 8.7 Hz, H-4′), 7.52 (m, 2H, H-3, H-5), 7.47 (m, 3H, H-2, H-4, H-6), 7.37 (m, 4H, H-2′, H-6′, H-3′, H-5′), 7.29 (m, 2H, H-2″, H-6″), 7.15 (d, 2H, $J_{3'',2''/5'',6''}$ = 8.7 Hz, H-3″, H-5″); FAB-MS *m/z* 367 $[M+H]^+$.

_N_′-(Diphenylmethylene)-2″,4″-dimethoxybenzenesulfonohydrazide (28)

Yield: 90%; m.p 180-182 °C; R_f: 0.39 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 7.58 (d, 2H, $J_{2,3/6,5}$ = 8.4 Hz, H-2, H-6), 7.47 (d, 2H, $J_{2',3'/6',5'}$ = 7.2 Hz, H-2′, H-6′), 7.42 (m, 3H, H-4, H-4′, H-6″), 7.29 (m, 2H, H-3, H-5), 6.45 (d, 2H, $J_{3'',5''/5'',3''}$ = 2.4 Hz, H-3″, H-5″), 6.39 (m, 2H, H-3′, H-5′), 3.73 (s, 3H, 2″-OCH_3), 3.70 (s, 3H, 4″-OCH_3); ^{13}C-NMR: (100.0 MHz, DMSO-d_6): δ_C 160.9 (C=N), 159.0 (C-2″), 157.3 (C-4″), 137.4 (C-1″), 135.0 (C-1″), 129.9 (C-1′), 129.4 (C-1), 128.9 (C-2, C-6), 128.8 (C-2′, C-6′), 128.7 (C-3, C-5), 128.3 (C-3″), 128.1 (C-5″), 128.0 (C-4), 10.2.8 (C-3′, C-5′), 98.7 (C-4′); FAB-MS *m/z* 397 $[M+H]^+$.

_N_'-(Diphenylmethylene)naphthalene-2-sulfonohydrazide (29)

Yield: 88%; m.p 256-258 °C; R_f: 0.40 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.57 (s, 1H, NH), 8.58 (s, 1H, H-1″),8.23 (d, 1H, $J_{5'',6''}$ = 7.2Hz, H-5″), 8.16 (d, 1H, $J_{8'',7''}$ = 8.7 Hz, H-8″), 8.06 (d, 1H, $J_{4'',3''}$ = 8.7Hz, H-4″), 7.96 (dd, 1H, $J_{3'',4''}$ = 6.0 Hz, $J_{3'',1''}$ = 2.0 Hz, H-3″), 7.74 (m, 3H, H-2, H-4, H-6), 7.35 (m, 2H, H-3, H-5), 7.35 (m, 2H, H-6″, H-7″), 7.33 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′); ^{13}C-NMR: (75.0 MHz, DMSO-d_6): δ_C 159.0 (C=N), 154.7 (C-1″), 137.4 (C-4a″), 135.9 (C-2″), 135.0 (C-2, C-6), 132.5 (C-8″), 131.6 (C-8a), 129.9 (C-2′, C-6′), 129.3 (C-8a″), 129.7 (C-3′, C-5′), 129.3 (C-4), 129.2 (C-3, C-5), 128.9 (C-1), 128.8 (C-1′), 128.3 (C-6″), 128.1 (C-4′), 128.0 (C-5″), 127.8 (C-3″), 127.5 (C-4″), 127.2 (C-4), 123.1 (C-7″) ; EI-MS *m/z* (% rel. abund.): 386 $[M]^+$ (59.5), 321, (6.9), 195, (100.0), 166, (77.0), 128, (52.2), 92, (64.4).

5-(Dimethylamino)-_N_'-(diphenylmethylene)naphthalene-1-sulfonohydrazide (30)

Yield: 86%; m.p 250-252 °C; R_f: 0.39 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.84 (s, 1H, NH), 8.55 (t, 2H, $J_{3''(2'',4'')/7''(6'',8'')}$ = 9.6 Hz H-3″, H-7″), 8.24 (d, 1H, $J_{2'',3''}$ = 8.7 Hz, H-4″), 7.71, (d, 1H, $J_{8'',7''}$ = 8.4 Hz, H-8″), 7.65 (d, 1H, $J_{2'',3''}$ = 6.0 Hz, H-2″), 7.61 (d, 1H,

$J_{6'',7''}$ = 8.1 Hz, H-6″), 7.51 (m, 2H, H-2, H-6), 7.35 (m, 1H, H-4), 7.32 (m, 3H, H-2′, H-4′, H-6′), 7.16 (m, 4H, H-3, H-5, H-3′, H-5′), 2.81 (s, 6H, $N(CH_3)_2$; ^{13}C-NMR: (150.0 MHz, DMSO-d_6): δ_C 156.8 (C=N), 150.0 (C-1″), 148.3 (C-4a″), 146.0 (C-5″), 145.5 (C-6″), 140.8 (C-7″), 136.5 (C-8″), 135.8 (C-8a), 132.2 (C-2′, C-6′), 131.9 (C-8a″), 130.2 (C-3′, C-5′), 129.7 (C-4), 129.0 (C-3, C-5), 128.8 (C-1), 128.7 (C-1′), 128.5 (C-2, C-6), 128.4 (C-4′), 127.5 (C-2″), 127.1 (C-3″), 121.5 (C-4″), 119.9 (C-4); EI-MS *m/z* (% rel. abund.): 429 $[M]^+$ (5.2), 251, (100.0), 168, (45.3), 154, (20.5), 127, (11.7), 115, (11.6).

***N*'-(Diphenylmethylene)butane-1-sulfonohydrazide (31)**

Yield: 95%; m.p 188-190 °C; R_f: 0.42 (ethyl acetate/hexanes, 4:6); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 9.90 (s, 1H, NH), 7.54 (m, 2H, H-2, H-6), 7.47 (m, 1H, H-4), 7.39 (m, 4H, H-3, H-5, H-3′, H-5′), 7.35 (m, 1H, H-4′), 7.29 (m, 2H, H-2′, H-6′), 3.27 (t, 2H, $J_{CH2(CH2)}$ = 7.5 Hz, CH_2), 1.72 (m, 2H, CH_2), 1.47 (m, 2H, CH_2), 0.90 (t, 3H, $J_{CH3(CH2)}$ = 7.2 Hz, CH_3); FAB-MS *m/z* 317 $[M+H]^+$.

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Synthesis and urease inhibitory potential of benzophenone sulfonamide hybrid *in vitro* and *in silico*

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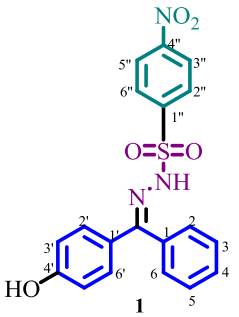
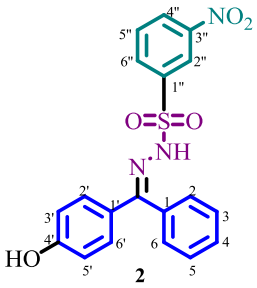


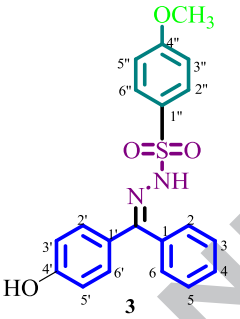
1

IC_{50} = 3.90 ± 0.81 μM



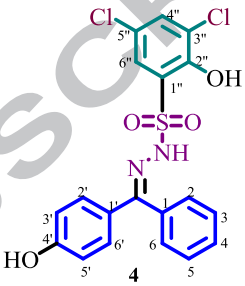
2

IC_{50} = 13.73 ± 0.01 μM



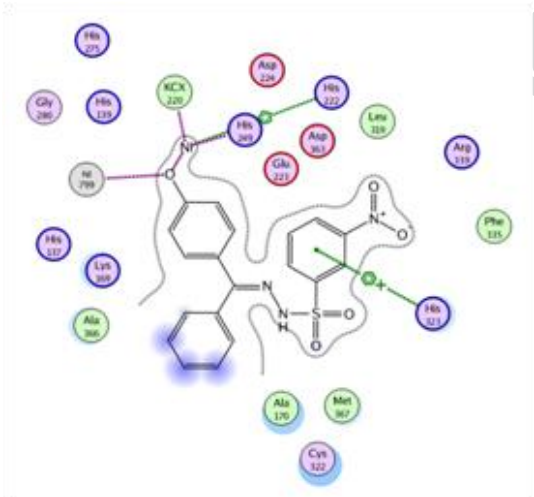
3

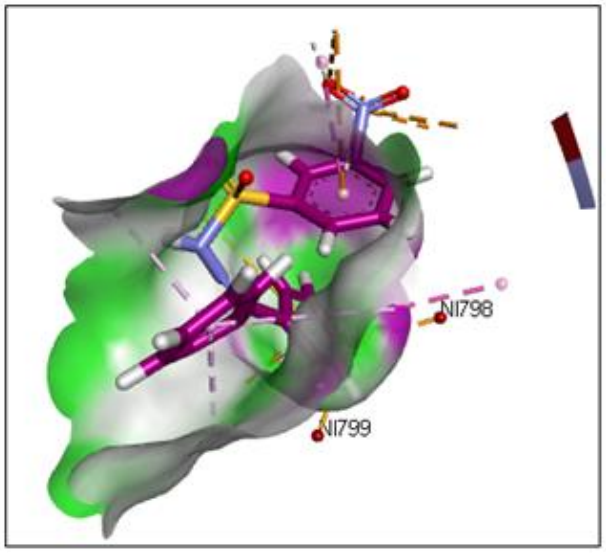
IC_{50} = 14.51 ± 1.14 μM



4

IC_{50} = 4.97 ± 0.311 μM





Molecular docking studies of most active compound 1

Research Highlight

- Syntheses of benzophenone sulfonamide analogs have been carried out.
- Structures of all synthetic compounds were elucidated by spectroscopic techniques.
- Urease inhibitory activity of synthetic compounds has been carried out.
- *In silico* studies of active analogs have been performed.
- Structure-activity relationship has been evaluated.