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Synthesis, Characterization, Antiproliferative and Apoptosis Inducing Effects of Novel *s*-Triazine Derivatives

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Supplementary Material:

- 1. Spectral discussion of compounds 6a and 12b
- Molecular docking Results (2D structure of compounds 5a-d, 6a-c, 8a-c, 9a-b, 12a-c, and 13a-c)
- 3. List of Figures

Figure. S1 ¹H NMR spectrum of compound 7b

Figure. S2 ¹H-¹H COSY spectrum of compound 7b

Figure. S3 HSQC spectrum of compound 7b

Figure. S4 ¹H NMR spectrum of compound 4a

Figure. S5 ¹³C NMR spectrum of compound 4a

Figure. S6 ¹H NMR spectrum of compound 6a

Figure. S7 ¹³C NMR spectrum of compound 6a

Figure. S8 HMBC spectrum of compound 6a
Figure. S9 ¹H NMR spectrum of compound 11
Figure. S10 ¹³C NMR spectrum of compound 11
Figure. S11 ¹H NMR spectrum of compound 12b
Figure. S12 ¹³C NMR spectrum of compound 12b
Figure. S13 ¹H-¹H -COSY spectrum of compound 12b
Figure. S14 HSQC spectrum of compound 12b
Figure. S15 HMBC spectrum of compound 12b

1. Spectral discussion of compounds 6a and 12b

The IR spectra of compounds **7b** showed a strong band at 1580 cm⁻¹ (Figure S1-3 Supplementary data) that attributed to azomethine v (–CH=N) stretching. In addition, a band at 3450 cm⁻¹, is assigned to the –OH group present in the Schiff compound. Hence the IR spectral data illustrate the formation of the Schiff derivatives. Furthermore, s-Triazine derivatives show another important band in the region 1576 cm⁻¹ ascribed to –C=N stretching vibration of s-Triazine ring and the –C^T–O– absorption is observed as a distinct band at 1363–1374 cm⁻¹ (**6a**). This is attributed to the involvement of carbon atom of triazine ring in hydroxyl linkage. Hence the IR spectral data illustrate the formation of the morpholino based 1,3,5-triazine Schiff base derivatives. Moreover, the absence of bands around 3200 and 3350-3400 cm⁻¹ due to secondary amine (–NH) stretching and –OH stretching of morpholine and phenol respectively indicates the condensation of secondary amine and Schiff base in s-triazine derivatives. Further, the structure

was assigned by chemical shifts and coupling constant obtained from NMR spectral data. In ¹H NMR spectrum, singlets at 8.72 & 8.96 ppm (**4a** and **7a**) (Figures S1-5 Supplementary data) are assigned for azomethine (-CH=N) group. Another sharp singlet at 10.61–13.75 ppm with an integral value corresponding to one proton suggests the presence of a hydroxyl group (Ph-OH). Moreover, in the ¹³C spectrum of compounds **4a** and **7a** absorptions due to azomethine (-CH=N) carbon at 163.0 and 162.5 ppm confirmed the formation of Schiff base compounds. Surprisingly, all the fluorine substituted phenyl carbons resonate as doublets due to the presence of highly electronegative fluorine present in the phenyl heterocyclic ring. Generally, fluorine atom substituted compounds show off splitting two separate signals adjacent to each other.



The NMR spectroscopic assignment of compounds 6a and 12b

Compounds **6a** and **12b** were taken as a representative compound and the signals were assigned based on the correlations in the 2D spectra. The 1D (¹H & ¹³C NMR) and 2D NMR (HMBC) spectra of compound **6a** are shown in Figures S6-8 (Supplementary data (S)) for the remaining compounds, the signals were assigned based on the spectral values compound **6a**. In ¹H NMR spectrum, the singlet at 9.76 ppm is assigned for azomethine (–CH=N) group. Beside

the absence of –OH and –NH peaks confirm the condensation between Schiff base and morpholine to form s-Triazine scaffold derivatives. Moreover, two triplets due to C-2" proton and C-2" proton of the morpholine moiety resonates closely at 3.73 and 3.98 ppm respectively with apiece eight integral values for presence of two morpholine moieties confirmed the formation of compound **6a** in di-morpholino based s-triazine Schiff base derivatives. In ¹³C spectra, peaks at 191.0 ppm and 163.7 ppm were unambiguously assigned to C-2 and C-4/C-6 carbons, and the azomethine (–CH=N) carbon absorbs at 163.0 ppm (C-14). Further, this assignment was substantiated by HMBC analysis. The HMBC spectrum reveals that the signal at 7.75 ppm (C-9 hydrogen) showing γ correlation with C-6 s-triazine carbon at 191.0 ppm, and imine carbon (–CH=N) at 163.4 ppm. Moreover, the signal at 163.4 ppm shows beta correlation with C-10 proton (Figure S8). In addition, The C-2" and C-4" protons also show β correlation with C-2 and C-4 s-triazine carbons at 163.7 ppm. Based on the hetero-nuclear correlation, compound **6a** confirms the formation morpholine based s-triazine Schiff base scaffold derivatives.

In ¹H NMR spectrum of **12b**, the broad singlet appeared in the region of 10.78 ppm with one proton integral and one sharp singlet appeared in the region of 9.76 ppm with one proton integral, respectively assigned to –NH proton and –CH=N azomethine proton for compound **12b** (Figure S11). In ¹H spectra (¹H-¹H COSY), peaks at 6.96 ppm and 7.74 ppm were unambiguously assigned to C-9 and C-10 protons, respectively. Moreover, compound **12b** shows two up field (having one methyl and one methane at carbon 14' and 15') signals appeared at 1.28 and 2.49 ppm confirmed by the ¹H–¹H COSY correlation (Figure S13). Further, this assignment was substantiated by HSQC analysis (Figure S14). In 13C NMR spectrum of compound **12b**, the signals at 14.59 and 63.67 ppm in the aliphatic region are assigned to 14' and 15' carbons of the

ethoxybenzo[d]thiazol ring, respectively. Another six chemical shift values observed at 115.83, 120.8, 126.4, 129.5, 132.0, and 163.3 ppm are assigned for (C-9, C-19, C-17, C-18, C-10 and C-14 (-CH=N) carbons of the Schiff base moiety) shows one bond correlation with signal at 6.96, 7.40, 7.27, 7.40, 7.74, 9.76 ppm. In addition, the HMBC (Figure S15) spectrum reveals that the signal at 7.74 ppm (132.0 ppm, H-9 hydrogen) shows gamma correlation with C-6 and C-14 at, s-triazine carbon at 190.9 ppm and 163.3 ppm (-C=NH) azomethine carbon (Fig. 5). Also the signal at 162.5 ppm shows α correlation with 7.74 ppm (H-9), moreover, the signal at 6.96 ppm shows α correlation with 128.3 ppm (C-10) and β correlation with 162.5 ppm (C-8).

2. Molecular Docking Results (2D structure of compounds 5a-d, 6a-c, 8a-c, 9a-b, 12a-c, and

13a-c)





Compound 5a



Compound 5b



Compound 5d





Compound 6a

Compound 6b





Compound 6c



Compound 8b

Compound 8a



Compound 8c





Compound

9a

Compound 9b





Compound 12b



Compound 13b



Compound 13c

3. List of Figures



Figure. S1



Figure. S2



Figure. S3



Figure. S4

Figure. S5

Figure. S6

Figure. S7

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- $\rightarrow \beta$ correlation
- $\rightarrow \gamma$ correlation

Figure. S8

Figure. S9

Figure. S10

Figure. S15