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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, characterization, and antimicrobial screening of some Mannich base sydnone derivatives

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Abstract The title compounds (**5a–j**), (**6a–j**), and (**7a–j**) were prepared via a four-step procedure using starting material 4-methoxyaniline (**1**). The structure of all synthesized compounds was confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR, and CHN analysis. The synthesized compounds were tested for their antibacterial and antifungal activity (MIC) in vitro against organisms viz. *B. subtilis*, *S. aureus*, *E. coli*, *P. aeruginosa*, and *C. albicans* taking ciprofloxacin, ampicillin, streptomycin, penicillin-G, fluconazole, and nystatin as the standard drugs. Some of the compounds have shown significant activities.

Keywords Sydnone · Benzothiazole · Benzimidazole · Mannich · Antimicrobial activity

Introduction

Mesoionic compounds are heterocyclic betaines that are very useful in medicinal chemistry because of their well-known range of pharmacological activities and low toxicity. Sydnones are the most important class of mesoionic compounds because they possess different physiologic activities depending on the substituent in the heterocyclic ring (Greco *et al.*,1962; Yeh *et al.*,1989). Sydnones have attained importance due to their unusual structure (Stefaniak and Jazwinski, 1995; Papageorgiou *et al.*, 1983), chemical properties (Satoshi *et al.*, 2004), and synthetic utility (Jogul and Badami, 2006). A hydrogen atom at the 4th position of the sydnone ring allows substitution with a wide variety of electrophiles, such as bromination, nitration, acylation, and sulfonation. It seems to be possible to substitute the 4th position by electron-releasing groups such as the methylene group by Mannich reaction (Tien *et al.*, 1981). A large number of sydnone derivatives have been synthesized as they serve as vital biologic agents viz, antibacterial, antifungal (Bansode and Kamble, 2012; Patel and Asundaria, 2012), antitumor (Marija *et al.*, 2011), antioxidant (Shih and Ke, 2004), anticancer (Satyanarayana *et al.*, 2004), anti-inflammatory, analgesic, and antiviral (Kamble *et al.*, 2009; Deshpande and Pai, 2012; Pandey and Mukesh, 2006) activities.

Benzothiazoles have drawn attention as promising structural units in the field of medicinal chemistry. They were reported to exhibit a variety of biologic activities such as anti-HIV (Hadizadeh and Mehrparvar, 2004), anti-inflammatory, analgesic (Venkatesh and Pandeya, 2009a; Hosni and Abdulla, 2008), antifungal (Pattan and Narendra babu, 2002), antibacterial (Vibhute, 2001), antitumor (Yuichi, 2005), antitubercular (Amini *et al.*, 2008), anticancer (Devmurari *et al.*, 2010), etc.

Benzimidazole nucleus is an important heterocyclic ring because of its synthetic utility and broad range of pharmacological activities like antibacterial, antifungal (Sanja *et al.*, 2007; Lal *et al.*, 2011), antitubercular (Joshi *et al.*, 2001), anticonvulsant (Srivastava *et al.*, 2000), antidepressant (Sharma *et al.*, 1999), etc.

Therefore, we focused our attention on the synthesis of some sydnones and their Mannich derivatives containing benzothiazole and benzimidazole moieties with a view to evaluate their antibacterial and antifungal activity.

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Results and discussion

Chemistry

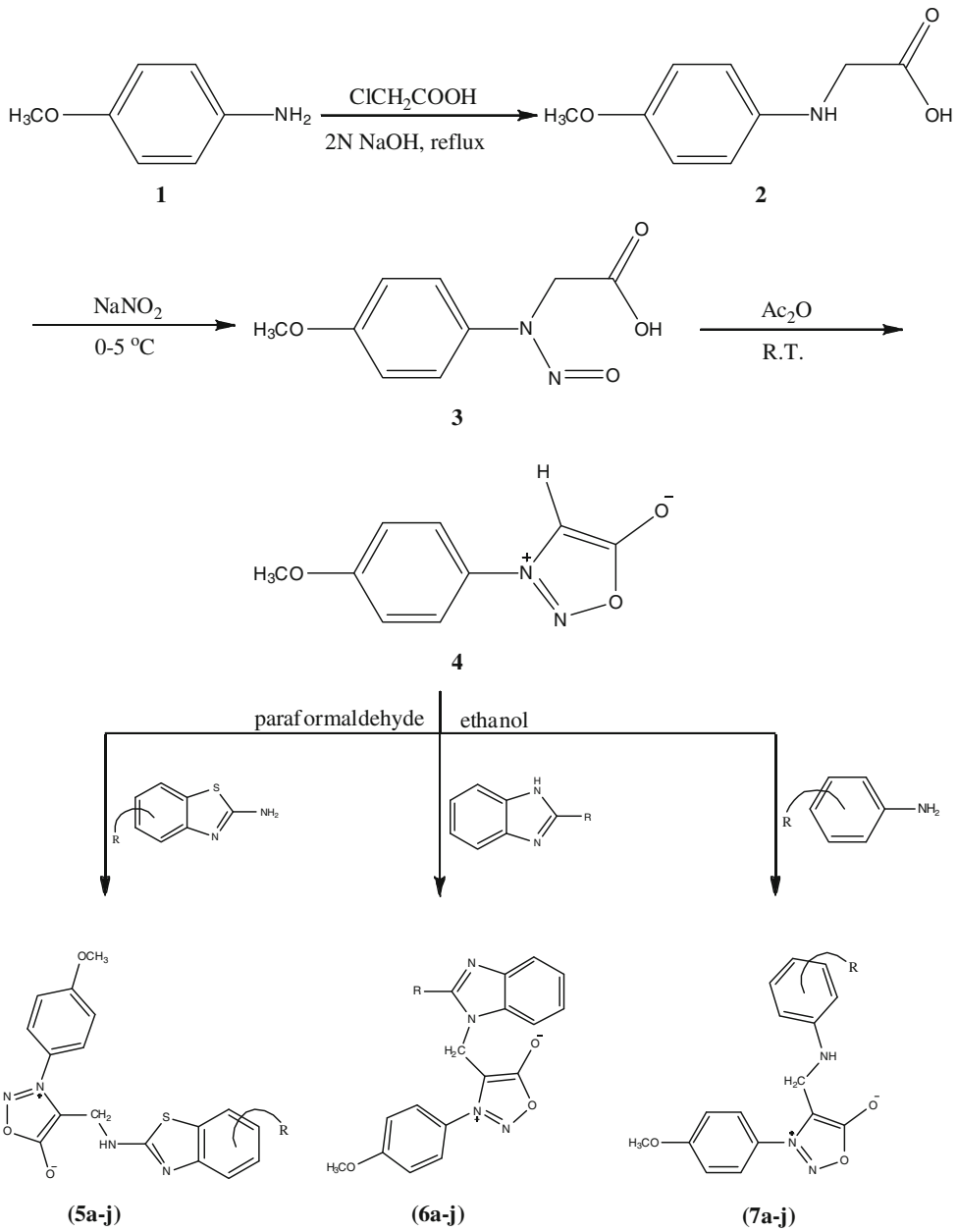
The synthesis of methylene-based sydnones containing benzothiazoles (**5a–j**), benzimidazoles (**6a–j**), and 1° amines (**7a–j**) derivatives is shown in the Scheme 1. Synthesis of 3-(4-methoxyphenyl)sydnone (**4**) was accomplished by a three-step procedure. Compound **(4)** was reacted with paraformaldehyde, benzothiazoles, benzimidazoles, and 1° amines to give (**5a–j**), (**6a–j**), and (**7a–j**) as shown in Scheme 1.

Substituted benzothiazoles (Venkatesh and Pandeya, 2009b) and benzimidazoles (Messmary *et al.*, 2010) were synthesized by the reported process.

The structures of all the synthesized compounds were confirmed by elemental analysis and spectral studies. The IR spectra of compound **4** showed two characteristic bands at 3,112 and 1,749 cm^{-1} due to the C–H and >C=O stretching of the sydnone, and ^1H NMR (DMSO d_6) spectra of compound **4** showed a singlet at δ 3.89 ppm due to the methoxy and δ 7.21 ppm, characteristic of the proton at C_4 of the sydnone. The absence of a sharp band at around 3,112 cm^{-1} is due to the formation of Mannich bases in title compounds.

The IR spectrum of compounds (**5a–j**), (**6a–j**), and (**7a–j**) displayed absorption bands between 1,760 and 1,718 cm^{-1}, which is characteristic of the carbonyl group of sydnones and also showed 1,250–1,210, 1,050–1,010, and 2,940–2,850 cm^{-1}

Scheme 1 Synthetic route of compound **5a–j**, **6a–j**, and **7a–j**



characteristic of C–O–C_{asy}, C–O–C_{sym}, and CH_2 groups, respectively. Some additional peaks appear due to the substitution in the aromatic ring showing an absorption band at 2,238 cm^{-1} (C≡N), 1,650–1,490 cm^{-1} ($NO_{2\ asy}$), 1,360–1,310 cm^{-1} ($NO_{2\ sym}$), 1,350–1,120 cm^{-1} (C–F), 850–800 cm^{-1} (C–Cl), and 690–510 cm^{-1} (C–Br). Furthermore, in ^{1}H NMR spectra, common signals are in the range of δ 5.0–4.72 ppm for (NH) group, δ 3.82–3.98 ppm for (OCH_3) group, and δ 3.26–3.6 ppm for (–CH_2–) group. ^{13}C NMR spectra exhibited confirmatory signals for the carbonyl carbon around δ 169.00 ppm, methoxy carbon around δ 56.75 ppm, and methylene carbon around δ 51 ppm.

Antimicrobial activity

All of the synthesized compounds were tested for their antibacterial and antifungal activity on four important bacterial stains (Gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus* and Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*) and one fungal strain (*Candida albicans*), taking ciprofloxacin, ampicillin, streptomycin, penicillin-G, fluconazole, and nystatin as the standard drugs. Most of the compounds have shown antibacterial and antifungal activity.

Compound **5d** (R = 4-NO_2) is most active against all bacterial and fungal strains, whereas compound **5f** (R = 6-NO_2), **5j** (R = CN), and **7g** (R = 4-OC_2H_5) displayed excellent activity against Gram-positive bacteria *B. subtilis* and *S. aureus*. Compound **5 g** (R = 6-CH_3) is most active only against Gram-positive bacteria *B. subtilis* and compound **6j** (R = 2-NO_2) is most active only against Gram-positive bacteria *S. aureus*. Compound **6i** (R = 4-NO_2) is most active against Gram-negative bacteria *E. coli* compared with the standard drugs ciprofloxacin and ampicillin. Compound **5c**, **5h**, **7a**, and **7g** showed moderate to good activity and the rest of compounds were moderate to less active against these species as compared to the standard drugs.

Antifungal screening data showed that compound **5d** (R = 4-NO2) exhibited high activity and compound **5c** and **7d** (R = 6-Br and 4-Cl) showed excellent activity against *C. albicans*. Compound **5b**, **5f–h**, and **5i** (R = 6-Cl, 6-NO_2, 6-CH_3, 6-OCH_3, and 6-OC_2H_5) showed good activity and the rest of the compounds were moderate to less active against *C. albicans* compared to the standard drugs fluconazole and nystatin.

Conclusions

Various benzothiazole, benzimidazole, and 1° amine substituted Mannich base sydnones were synthesized, characterized by spectral data, elemental analysis, and evaluated for their antimicrobial activity.

Benzothiazole and 1° amine containing sydnones showed good activity as compared to benzimidazole containing sydnone derivatives.

It should be noted that 4-nitro benzothiazole containing sydnone showed good activity against all bacterial and fungal strains.

Most of the compounds were found to have good activity against Gram-positive bacterial strains and fungal strains as compared to Gram-negative bacterial strains.

Experimental

All the melting points reported are uncorrected and were recorded using an electro-thermal melting point apparatus. Elemental analysis (C, H, N) was performed on Thermo Scientific FLASH 2000 at G.N.F.C. (Gujarat Narmada Valley Fertilizer Company Ltd., Bharuch). Infrared spectra was recorded with a Thermo Scientific Nicolet iS10 FT-IR Spectrophotometer at the Department of Chemistry, Veer Narmad South Gujarat University, in the frequency range 4,000–400 cm^{-1} with samples embedded in KBr disks. Proton nuclear magnetic resonance (^{1}H NMR) spectra of the compound were recorded with a Bruker Avance II 400 NMR and carbon (^{13}C) NMR spectra of the compounds were recorded with a Bruker Avance II 400 NMR spectrometer using DMSO-d_6 as a solvent and tetramethylsilane (TMS) as an internal reference at sophisticated analytical instrument facilities (SAIF), Chandigarh. Thin-layer chromatography analyses were performed using aluminum-backed silica-gel plates (Merck 60 F524) and examined under short wave ultraviolet (UV) light.

The general procedure for synthesis of the compounds (**5a–j**, **6a–j**, and **7a–j**)

*Synthesis of 2-((4-methoxyphenyl)amino)acetic acid (**2**)*

This step, a condensation, involved neutralizing an aqueous solution of chloroacetic acid (0.94 g, 0.01 mol) with an equimolar equivalent of 2 *N* NaOH and adding this solution to an aqueous solution of 4-methoxy aniline (1.23 g, 0.01 mol) over a period of 4 h. This reaction mixture was heated for 12 h and the clear liquor was then vacuum filtered while hot to remove any decomposition product and refrigerated overnight. The resulting crystals were again filtered to obtain compound **2**. Yield 82 %, m.p. 130–135 °C. IR: (KBr) ν (cm^{-1}): 3,470 (O–H of acid), 1,770 (>C=O of acid), 1,600, 1,509 (C=C of aromatic), 1,242, 1,047 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.82 (s, 3H, OCH_3), 4.11 (s, 2H, CH_2), 9.3 (s, 1H, COOH), 6.56 (s, 1H, NH), 6.88–7.23 (m, 4H, Ar–H); ^{13}C

NMR (DMSO-d_6): δ (ppm): 45.92, 55.73, 114.32, 118.26, 139.10, 150.07, 172.08.

*Synthesis of 2-((4-methoxyphenyl)(nitroso)amino)acetic acid (**3**)*

To an ice-cooled solution of **2** (1.81 g, 0.01 mol) in 40 ml of water, a solution of (0.69 g, 0.01 mol) sodium nitrite in 5 ml of water was added drop by drop with stirring. After stirring for another 2 h and leaving the solution to stand overnight, the reaction mixture was filtered through a Buckner funnel, and the nitroso compound was precipitated by adding concentrated hydrochloric acid to the filtrate. Yellowish needles were obtained as product, yield 78 %, m.p. 101–105 °C. IR: (KBr) ν (cm^{-1}): 3,450 (O–H of acid), 1,763 (>C=O of acid), 1,614, 1,513 (C=C of aromatic), 1,570, 1,328 (N=O), 1,242, 1,047 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.82 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2), 9.0 (s, 1H, COOH), 6.91–7.47 (m, 4H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 55.62, 62.42, 115.29, 121.19, 134.66, 159.9, 172.92.

*Synthesis of 3-(4-methoxyphenyl)sydnone (**4**)*

A mixture of **3** (2.65 g, 0.0126 mol) and acetic anhydride (15 ml) was stirred at room temperature for 12 h in the dark. The solution was poured slowly into cold water which was very well stirred. The pH of the content was adjusted to 7.0 with 10 % sodium bicarbonate solution. The crude sydnone obtained was washed well with water and dried. Recrystallization from 95 % ethanol afforded a yield of 98 % of light yellow needles, m.p. 120–124 °C. IR: (KBr) ν (cm^{-1}): 3,112 (C–H of sydnone), 1,749 (>C=O of sydnone), 1,249, 1,040 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.89 (s, 3H, OCH_3), 7.21 (s, 1H, sydnone), 7.48–8.25 (m, 4H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 55.8, 121.19, 123.4, 134.66, 159.9, 172.92.

General synthesis of compounds **5a–j**, **6a–j** and **7a–j**

A mixture of compound **4** (1.29 g, 0.00679 mol), 0.25 gm paraformaldehyde, substituted benzothiazoles, substituted benzimidazoles, and substituted 1° amines (0.084 mol) was added to 10 ml of acetic acid and 10 ml ethanol and the whole mixture was heated at (70 °C) for 3 h. After cooling, ethanol was distilled and 20 ml of water was added and neutralized with aqueous sodium bicarbonate to afford the crude product. Recrystallization from 95 % ethanol yielded 55–60 % of compounds **5a–j, 6a–j**, and **7a–j** as crystalline solid.

All the sydnone derivatives were prepared by the same method. Their physical constants and antimicrobial activity are given in Tables 1 and 2, respectively.

*4-(((substitutedbenzo[d]thiazol-2-yl)amino)methyl)-3-(4-methoxyphenyl)-sydnone (**5a–j**)*

(5a) IR: (KBr) ν (cm^{-1}): 3,260 (NH), 2,917, 2,850 (–CH_2–), 1,746 (>C=O of sydnone), 1,237, 1,040 (C–O–C of methoxy), 1,173 (C–F); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.32 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 4.90 (s, 1H, NH), 6.92–7.86 (m, 7H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 51.10, 56.75, 108.32, 113.61, 116.20, 117.54, 124.92, 130.75, 132.10, 138.95, 148.61, 157.60, 159.95, 170.14, 175.40; Anal. Calcd. for $C_{17}H_{13}FN_4O_3S$: C, 54.83; H, 3.52; N, 15.05. Found: C, 54.71; H, 3.49; N, 15.01.

(5b) IR: (KBr) ν (cm^{-1}): 3,265 (NH), 2,924, 2,864 (–CH_2–), 1,753 (>C=O of sydnone), 1,240, 1,047 (C–O–C of methoxy), 757 (C–Cl); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.38 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 4.95 (s, 1H, NH), 7.10–8.20 (m, 7H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 52.20, 55.89, 115.95, 118.32, 120.95, 125.90, 128.95, 130.24, 132.33, 137.65, 150.92, 162.88, 169.25, 174.90; Anal. Calcd. for $C_{17}H_{13}N_4O_3ClS$: C, 52.51; H, 3.37; N, 14.41. Found: C, 52.45; H, 3.32; N, 14.38.

(5c) IR: (KBr) ν (cm^{-1}): 3,274 (NH), 2,933, 2,887 (–CH_2–), 1,757 (>C=O of sydnone), 1,228, 1,046 (C–O–C of methoxy), 596 (C–Br); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.29 (s, 2H, CH_2), 3.94 (s, 3H, OCH_3), 4.86 (s, 1H, NH), 6.82–7.89 (m, 7H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 51.75, 56.20, 116.20, 117.32, 118.45, 123.92, 124.95, 127.85, 130.87, 132.81, 138.98, 151.90, 163.24, 168.70, 175.22; Anal. Calcd. for $C_{17}H_{13}N_4O_3BrS$: C, 47.12; H, 3.02; N, 12.93. Found: C, 47.15; H, 2.99; N, 12.89.

(5d) IR: (KBr) ν (cm^{-1}): 3,257 (NH), 2,917, 2,847 (–CH_2–), 1,752 (>C=O of sydnone), 1,550, 1,356 (–NO_2), 1,254, 1,048 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.35 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 4.98 (s, 1H, NH), 6.92–8.05 (m, 7H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 52.32, 57.30, 115.91, 122.33, 125.10, 125.60, 126.82, 128.20, 130.74, 137.82, 142.92, 144.90, 163.22, 168.92, 174.88; Anal. Calcd. for $C_{17}H_{13}N_5O_5S$: C, 51.12; H, 3.28; N, 17.54. Found: C, 51.05; H, 3.22; N, 17.47.

(5e) IR: (KBr) ν (cm^{-1}): 3,267 (NH), 2,930, 2,851 (–CH_2–), 1,747 (>C=O of sydnone), 1,533, 1,365 (–NO_2), 1,237, 1,056 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.28 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3), 4.93 (s, 1H, NH), 7.10–8.34 (m, 7H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 52.30, 56.72, 116.24, 117.42, 119.34, 122.74, 124.92, 130.92, 136.80, 139.21, 146.82, 149.84, 163.54, 169.34, 174.62; Anal. Calcd. for $C_{17}H_{13}N_5O_5S$: C, 51.12; H, 3.28; N, 17.54. Found: C, 51.07; H, 3.21; N, 17.49.

(5f) IR: (KBr) ν (cm^{-1}): 3,283 (NH), 2,937, 2,865 (–CH_2–), 1,754 (>C=O of sydnone), 1,521, 1,327 (–NO_2), 1,212, 1,048 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.32 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 4.89 (s, 1H, NH), 7.09–8.54 (m, 7H, Ar–H); ^{13}C NMR (DMSO-d_6): δ

Table 1 Physical constant of the synthesized compounds

Compound	R	Yield (%)	MP (°C)	Molecular formula	Molecular weight
5a	6-F	61	125–128	$C_{17}H_{13}N_4O_3FS$	372.37
5b	6-Cl	64	105–108	$C_{17}H_{13}N_4O_3ClS$	388.83
5c	6-Br	70	120–123	$C_{17}H_{13}N_4O_3BrS$	433.28
5d	4-NO_2	72	100–103	$C_{17}H_{13}N_5O_5S$	399.38
5e	5-NO_2	80	205–208	$C_{17}H_{13}N_5O_5S$	399.38
5f	6-NO_2	68	215–218	$C_{17}H_{13}N_5O_5S$	399.38
5g	6-CH_3	82	95–98	$C_{18}H_{16}N_4O_3S$	368.41
5h	6-OCH_3	75	162–165	$C_{18}H_{16}N_4O_4S$	384.41
5i	6-OC_2H_5	85	122–125	$C_{19}H_{18}N_4O_4S$	398.44
5j	6-CN	82	111–114	$C_{18}H_{13}N_5O_3S$	379.39
6a	H	74	136–139	$C_{17}H_{14}N_4O_3$	322.32
6b	3,4-di Cl Ph	69	188–191	$C_{23}H_{16}N_4O_3Cl_2$	467.30
6c	2,4-di Cl Ph	65	125–128	$C_{23}H_{16}N_4O_3Cl_2$	467.30
6d	4-OCH_3 Ph	69	155–158	$C_{24}H_{20}N_4O_4$	428.44
6e	2-Br Ph	55	138–141	$C_{23}H_{17}N_4O_3Br$	477.31
6f	3-Br Ph	59	112–115	$C_{23}H_{17}N_4O_3Br$	477.31
6g	4-Cl Ph	61	185–188	$C_{23}H_{17}N_4O_3Cl$	432.86
6h	3-NO_2, 4-OCH_3 Ph	65	152–155	$C_{24}H_{19}N_5O_6$	473.44
6i	4-NO_2	54	181–184	$C_{23}H_{17}N_5O_5$	443.41
6j	2-NO_2	62	178–181	$C_{23}H_{17}N_5O_5$	443.41
7a	4-OCH_3	58	105–108	$C_{17}H_{17}N_3O_4$	327.33
7b	4-NO_2 Ph	63	156–159	$C_{16}H_{14}N_4O_5$	342.31
7c	2-NO_2 Ph	62	138–141	$C_{16}H_{14}N_4O_5$	342.31
7d	4-Cl	69	122–125	$C_{16}H_{14}N_3O_3Cl$	331.75
7e	4-Br	65	108–111	$C_{16}H_{14}N_3O_3Br$	376.20
7f	4-CH_3	72	118–121	$C_{17}H_{17}N_3O_3$	311.34
7g	4-OC_2H_5	68	121–124	$C_{18}H_{19}N_3O_4$	341.36
7h	2-Cl	74	131–134	$C_{16}H_{14}N_3O_3Cl$	331.75
7i	2,5-di Cl	62	115–118	$C_{16}H_{13}N_3O_3Cl_2$	366.20
7j	4-F	70	128–131	$C_{16}H_{14}N_3O_3F$	315.30

(ppm): 51.92, 57.20, 116.44, 117.34, 119.12, 121.32, 125.34, 130.89, 131.22, 138.74, 144.24, 160.22, 162.81, 168.21, 175.24; Anal. Calcd. for $C_{17}H_{13}N_5O_5S$: C, 51.12; H, 3.28; N, 17.54. Found: C, 51.10; H, 3.24; N, 17.50.

(5g) IR: (KBr) ν (cm^{-1}): 3,281 (NH), 2,986 (–CH_3), 2,940, 2,853 (–CH_2–), 1,743 (>C=O of sydnone), 1,241, 1,037 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 2.42 (s, 3H, CH_3), 3.34 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 4.95 (s, 1H, NH), 6.80–8.00 (m, 7H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 51.44, 56.82, 116.22, 117.22, 121.34, 125.24, 126.72, 131.10, 131.82, 134.20, 138.70, 149.82, 162.89, 169.71, 174.24; Anal. Calcd. for $C_{18}H_{16}N_4O_3S$: C, 58.68; H, 4.38; N, 15.21. Found: C, 58.72; H, 4.34; N, 15.18.

(5h) IR: (KBr) ν (cm^{-1}): 3,272 (NH), 2,921, 2,857 (–CH_2–), 1,737 (>C=O of sydnone), 1,249, 1,063 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.26 (s, 2H, CH_2), 3.83, 3.98 (s, 6H, OCH_3), 4.80 (s, 1H, NH), 6.89–8.12 (m, 7H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 51.44, 56.82, 116.22, 117.22, 121.34, 125.24, 126.72, 131.10, 131.82, 134.20, 138.70, 149.82, 162.89, 169.71, 174.24; Anal. Calcd. for $C_{18}H_{16}N_4O_4S$: C, 56.24; H, 4.20; N, 14.57. Found: C, 56.20; H, 4.18; N, 14.51.

(5i) IR: (KBr) ν (cm^{-1}): 3,257 (NH), 2,976 (–CH_3), 2,937, 2,848 (–CH_2–), 1,742 (>C=O of sydnone), 1,253, 1,054 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 1.40 (t, 3H, CH_3), 3.35 (s, 2H, CH_2), 3.83 (q, 2H, OCH_2), 3.90 (s, 3H, OCH_3), 4.92 (s, 1H, NH), 7.05–8.48 (m, 7H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 14.80, 51.90, 56.82, 64.60, 105.12, 114.22, 116.23, 117.82, 125.22, 130.21, 131.45, 139.22, 144.72, 152.84, 163.62, 168.40, 175.23; Anal. Calcd. for $C_{19}H_{18}N_4O_4S$: C, 57.27; H, 4.55; N, 14.06. Found: C, 57.21; H, 4.50; N, 14.01.

(5j) IR: (KBr) ν (cm^{-1}): 3,270 (NH), 2,937, 2,851 (–CH_2–), 2,238 (C≡N), 1,754 (>C=O of sydnone), 1,253, 1,034 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ

Table 2 Antibacterial and antifungal activity of synthesized compounds

Compound	Minimum inhibition concentration (μ/ml) and inhibition of zone at 300 (μ/ml)									
	Gram-positive				Gram-negative				Fungal species	
	B. subtilis		*S. aureus*		*E. coli*		*P. aeruginosa*		*C. albicans*	
	IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC
5a	12	200	12	300	12	300	10	500	13	200
5b	15	200	14	200	13	200	13	200	16	100
5c	15	100	18	100	11	300	12	200	21	80
5d	30	20	27	20	23	40	18	100	32	20
5e	10	500	10	500	12	300	10	500	14	200
5f	18	40	16	80	12	300	16	200	17	100
5g	18	60	15	200	12	300	10	500	17	100
5h	12	200	14	100	13	200	14	200	15	100
5i	13	200	14	200	13	300	13	200	14	200
5j	17	60	16	80	12	300	10	500	17	100
6a	11	300	11	300	10	500	10	500	12	300
6b	12	200	11	300	13	300	14	300	15	200
6c	10	500	10	500	12	300	12	300	16	200
6d	12	200	11	300	15	300	12	300	14	200
6e	12	300	10	500	14	200	13	200	13	200
6f	10	500	10	500	12	300	10	500	14	200
6g	12	300	12	300	15	200	10	500	14	200
6h	10	500	10	500	14	200	16	200	16	200
6i	12	300	10	500	18	60	12	300	12	200
6j	12	300	21	40	14	200	10	500	14	200
7a	18	100	16	80	12	200	14	100	20	200
7b	12	200	10	500	14	200	14	200	14	200
7c	13	200	11	300	14	200	13	200	14	200
7d	13	200	12	200	13	300	13	300	18	80
7e	13	200	10	300	12	300	13	200	15	200
7f	14	200	13	200	13	200	13	200	16	200
7g	16	80	17	40	13	200	15	100	16	200
7h	12	300	12	300	12	300	10	500	12	300
7i	12	300	11	300	10	500	10	500	13	300
7j	16	200	14	200	17	100	11	300	17	100
Ciprofloxacin	31	50	30	50	26	25	23	25	–	–
Ampicillin	26	100	30	250	31	100	29	100	–	–
Streptomycin	40	0.25	40	0.125	28	1.0	34	0.5	–	–
Penicillin-G	35	0.25	45	0.125	30	0.5	38	0.25	–	–
Fluconazole	–	–	–	–	–	–	–	–	25	100
Nystatin	–	–	–	–	–	–	–	–	28	100

(ppm): 3.29 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 4.87 (s, 1H, NH), 7.10–7.96 (m, 7H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 51.94, 57.20, 104.40, 115.98, 117.22, 118.60, 125.43, 126.20, 129.23, 130.80, 131.41, 138.74, 156.82, 162.72, 168.24, 175.25; Anal. Calcd. for $C_{18}H_{13}N_5O_3S$: C, 56.98; H, 3.45; N, 18.46. Found: C, 57.03; H, 3.39; N, 18.40.

*3-(4-methoxyphenyl)-4-((2-substituted-1H-benzo[d]imidazol-1-yl)methyl)-sydnone (**6a–j**)*

(6a) IR: (KBr) ν (cm^{-1}): 2,935, 2,867 (–CH_2–), 1,734 (>C=O of sydnone), 1,247, 1,050 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 2.13 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3), 7.02–7.85 (m, 8H, Ar–H); ^{13}C NMR (DMSO-d_6):

δ (ppm): 52.10, 57.10, 109.92, 115.84, 119.71, 123.00, 125.12, 130.87, 134.24, 138.98, 143.80, 144.24, 163.89, 168.74; Anal. Calcd. for $C_{17}H_{14}N_4O_3$: C, 63.35; H, 4.38; N, 17.38. Found: C, 63.29; H, 4.36; N, 17.35.

(6b) IR: (KBr) ν (cm^{-1}): 2,937, 2,860 (–CH_2–), 1741 (>C=O of sydnone), 1,236, 1,049 (C–O–C of methoxy), 848 (C–Cl); ^{1}H NMR (DMSO-d_6): δ (ppm): 2.16 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 6.98–7.93 (m, 11H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 52.78, 57.34, 116.34, 118.81, 119.44, 122.98, 125.33, 126.98, 128.95, 129.98, 130.78, 131.05, 132.71, 133.44, 137.83, 139.54, 141.91, 152.94, 163.84, 169.20; Anal. Calcd. for $C_{23}H_{16}N_4O_3Cl_2$: C, 59.11; H, 3.45; N, 11.99. Found: C, 59.06; H, 3.41; N, 12.03.

(6c) IR: (KBr) ν (cm^{-1}): 2,925, 2,857 (–CH_2–), 1,753 (>C=O of sydnone), 1,245, 1,039 (C–O–C of methoxy), 834 (C–Cl); ^{1}H NMR (DMSO-d_6): δ (ppm): 2.13 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 7.11–7.95 (m, 11H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 51.90, 56.94, 116.21, 119.41, 120.00, 122.91, 124.91, 127.34, 130.11, 130.89, 131.80, 133.71, 136.11, 136.80, 137.90, 139.24, 142.34, 152.94, 162.94, 170.12; Anal. Calcd. for $C_{23}H_{16}N_4O_3Cl_2$: C, 59.11; H, 3.45; N, 11.99. Found: C, 59.07; H, 3.42; N, 12.02.

(6d) IR: (KBr) ν (cm^{-1}): 2,937, 2,854 (–CH_2–), 1760 (>C=O of sydnone), 1,237, 1,021 (C–O-C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 2.11 (s, 2H, CH_2), 3.84, 3.88 (s, 6H, OCH_3), 6.93–8.09 (m, 11H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 51.88, 56.97, 113.92, 116.24, 119.22, 119.78, 122.81, 123.34, 125.32, 130.81, 131.23, 137.82, 138.74, 142.34, 153.45, 160.62, 163.64, 170.12; Anal. Calcd. for $C_{24}H_{20}N_4O_4$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.22; H, 4.67; N, 13.04.

(6e) IR: (KBr) ν (cm^{-1}): 2,928, 2,862 (–CH_2–), 1,752 (>C=O of sydnone), 1,220, 1,045 (C–O–C of methoxy), 588 (C–Br); ^{1}H NMR (DMSO-d_6): δ (ppm): 2.15 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 6.85–7.94 (m, 12H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 52.12, 57.21, 115.92, 119.12, 119.81, 120.22, 122.89, 125.23, 128.21, 129.54, 130.72, 131.11, 132.48, 136.89, 139.21, 140.10, 142.54, 153.34, 162.94, 169.78; Anal. Calcd. for $C_{23}H_{17}N_4O_3Br$: C, 57.88; H, 3.59; N, 11.74. Found: C, 57.81; H, 3.55; N, 11.70.

(6f) IR: (KBr) ν (cm^{-1}): 2,918, 2,840 (–CH_2–), 1,749 (>C=O of sydnone), 1,241, 1,019 (C–O–C of methoxy), 592 (C–Br); ^{1}H NMR (DMSO-d_6): δ (ppm): 2.17 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 7.05–8.14 (m, 12H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 51.92, 56.80, 116.21, 118.91, 119.50, 121.95, 123.21, 125.10, 128.22, 126.64, 130.52, 131.62, 131.92, 132.80, 136.94, 139.11, 141.85, 152.92, 162.34, 168.94; Anal. Calcd. for $C_{23}H_{17}N_4O_3Br$: C, 57.88; H, 3.59; N, 11.74. Found: C, 57.84; H, 3.58; N, 11.71.

(6g) IR: (KBr) ν (cm^{-1}): 2,937, 2,852 (–CH_2–), 1,761 (>C=O of sydnone), 1,246, 1,037 (C–O–C of methoxy), 757 (C–Cl); ^{1}H NMR (DMSO-d_6): δ (ppm): 2.13 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 6.97–8.05 (m, 12H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 52.05, 57.12, 116.32, 119.20, 119.80, 122.91, 125.10, 128.64, 128.98, 129.40, 130.82, 134.40, 137.71, 138.82, 142.89, 152.91, 163.84, 169.12; Anal. Calcd. for $C_{23}H_{17}N_4O_3Cl$: C, 63.82; H, 3.96; N, 12.94. Found: C, 63.86; H, 3.90; N, 12.91.

(6h) IR: (KBr) ν (cm^{-1}): 2,922, 2,860 (–CH_2–), 1,746 (>C=O of sydnone), 1,555, 1,346 (–NO_2), 1,235, 1,022 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 2.14 (s, 2H, CH_2), 3.84, 3.87 (s, 6H, OCH_3), 6.89–7.98 (m, 11H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 52.11, 56.44, 57.34, 114.82, 115.94, 119.11, 119.86, 123.34, 123.92, 124.22, 125.50, 130.72, 135.81, 136.42, 137.80, 139.24, 142.41, 153.24, 154.41, 162.80, 169.21; Anal. Calcd. for $C_{24}H_{19}N_5O_6$: C, 60.89; H, 4.05; N, 14.79. Found: C, 60.80; H, 3.99; N, 14.72.

(6i) IR: (KBr) ν (cm^{-1}): 2,936, 2,857 (–CH_2–), 1,741 (>C=O of sydnone), 1,531, 1,342 (–NO_2), 1,232, 1,034 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 2.18 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 6.95–8.05 (m, 12H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 52.34, 57.11, 115.81, 118.10, 119.50, 122.24, 124.34, 125.92, 127.82, 130.94, 136.60, 137.22, 139.89, 141.81, 147.22, 153.22, 162.81, 169.22; Anal. Calcd. for $C_{23}H_{17}N_5O_5$: C, 62.30; H, 3.86; N, 15.79. Found: C, 62.22; H, 3.80; N, 15.72.

(6j) IR: (KBr) ν (cm^{-1}): 2,917, 2,867 (–CH_2–), 1,759 (>C=O of sydnone), 1,545, 1,324 (–NO_2), 1,226, 1,022 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 2.14 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3), 7.04–8.21 (m, 12H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 51.85, 56.89, 114.30, 119.10, 119.74, 120.62, 122.42, 123.24, 124.44, 126.22, 129.72, 132.89, 135.26, 137.72, 138.98, 142.34, 149.51, 153.30, 161.00, 170.10; Anal. Calcd. for $C_{23}H_{17}N_5O_5$: C, 62.30; H, 3.86; N, 15.79. Found: C, 62.21; H, 3.84; N, 15.71.

*3-(4-methoxyphenyl)-4-(((substitutedphenyl)amino)methyl)-sydnone (**7a–j**)*

(7a) IR: (KBr) ν (cm^{-1}): 3,264 (NH), 2,936, 2,847 (–CH_2–), 1,754 (>C=O of sydnone), 1,244, 1,033 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.30 (s, 2H, CH_2), 3.84, 3.88 (s, 6H, OCH_3), 4.79 (s, 1H, NH), 6.85–7.92 (m, 8H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 51.10, 56.24, 113.32, 115.22, 116.44, 125.25, 130.64, 139.10, 140.89, 151.62, 162.82, 169.30; Anal. Calcd. for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.23; N, 12.84. Found: C, 62.28; H, 5.19; N, 12.80.

(7b) IR: (KBr) ν (cm^{-1}): 3,257 (NH), 2,952, 2,841 (–CH_2–), 1,744 (>C=O of sydnone), 1,507, 1,357 (–NO_2), 1,231, 1,025 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.28 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 4.84 (s, 1H, NH), 6.92-8.05 (m, 8H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 52.24, 57.20, 114.40, 116.32, 125.20, 127.41,

130.72, 136.31, 138.84, 154.49, 162.90, 168.82; Anal. Calcd. for $C_{16}H_{14}N_4O_5$: C, 56.14; H, 4.12; N, 16.37. Found: C, 56.06; H, 4.09; N, 16.32.

(7c) IR: (KBr) ν (cm^{-1}): 3,282 (NH), 2,945, 2,832 (–CH_2–), 1,761 (>C=O of sydnone), 1,532, 1,341 (–NO_2), 1,244, 1,060 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.30 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3), 4.60 (s, 1H, NH), 6.82–7.92 (m, 8H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 51.82, 56.44, 114.20, 115.92, 118.00, 124.82, 126.00, 130.92, 131.94, 135.61, 138.95, 146.10, 163.92; Anal. Calcd. for $C_{16}H_{14}N_4O_5$: C, 56.14; H, 4.12; N, 16.37. Found: C, 56.08; H, 4.09; N, 16.32.

(7d) IR: (KBr) ν (cm^{-1}): 3,275 (NH), 2,937, 2,841 (–CH_2–), 1,752 (>C=O of sydnone), 1,234, 1,056 (C–O–C of methoxy), 769 (C–Cl); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.27 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 4.72 (s, 1H, NH), 7.05–8.14 (m, 8H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 52.30, 57.20, 114.90, 116.32, 125.60, 126.23, 129.54, 130.92, 138.82, 147.54, 163.84, 168.72; Anal. Calcd. for $C_{16}H_{14}N_3O_3Cl$: C, 57.93; H, 4.25; N, 12.67. Found: 57.82; H, 4.20; N, 12.64.

(7e) IR: (KBr) ν (cm^{-1}): 3,265 (NH), 2,922, 2,862 (–CH_2–), 1,743 (>C=O of sydnone), 1,221, 1,065 (C–O–C of methoxy), 584 (C–Br); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.31 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.81 (s, 1H, NH), 6.85–7.94 (m, 8H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 51.89, 56.82, 114.50, 115.24, 116.62, 125.10, 130.80, 132.82, 139.22, 148.35, 163.85, 168.92; Anal. Calcd. for $C_{16}H_{14}N_3O_3Br$: C, 51.08; H, 3.75; N, 11.17. Found: C, 51.00; H, 3.71; N, 11.13.

(7f) IR: (KBr) ν (cm^{-1}): 3,286 (NH), 2,987 (–CH_3), 2,942, 2,850 (–CH_2–), 1,752 (>C=O of sydnone), 1,236, 1,054 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 2.22 (s, 3H, CH_3), 3.33 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 4.74 (s, 1H, NH), 6.94–8.05 (m, 8H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 20.61, 52.34, 56.75, 112.85, 116.24, 125.45, 129.85, 130.10, 131.22, 138.95, 146.35, 162.98, 169.71; Anal. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.51; H, 5.45; N, 13.44.

(7g) IR: (KBr) ν (cm^{-1}): 3,282 (NH), 2,989 (–CH_3), 2,936, 2,857 (–CH_2–), 1,744 (>C=O of sydnone), 1,236, 1,051 (C–O–C of methoxy); ^{1}H NMR (DMSO-d_6): δ (ppm): 1.37 (t, 3H, CH_3), 3.26 (s, 2H, CH_2), 3.60 (q, 2H, OCH_2), 3.83 (s, 3H, OCH_3), 4.76 (s, 1H, NH), 6.94–8.14 (m, 8H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 14.70, 51.72, 57.34, 63.20, 112.81, 115.25, 116.35, 125.15, 130.56, 139.10, 140.54, 149.95, 163.60, 169.15; Anal. Calcd. for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31. Found: C, 63.40; H, 5.66; N, 12.26.

(7h) IR: (KBr) ν (cm^{-1}): 3,279 (NH), 2,924, 2,860 (–CH_2–), 1,753 (>C=O of sydnone), 1,245, 1,049 (C–O–C of methoxy), 844 (C–Cl); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.31 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 4.73 (s, 1H, NH), 7.04–8.16 (m, 8H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 52.41, 56.40, 114.54, 115.90, 122.61, 123.95, 125.50, 138.85, 143.80, 162.95, 169.55; Anal. Calcd. for $C_{16}H_{14}N_3O_3Cl$: C, 57.93; H, 4.25; N, 12.67. Found: 57.88; H, 4.21; N, 12.60.

(7i) IR: (KBr) ν (cm^{-1}): 3,275 (NH), 2,937, 2,856 (–CH_2–), 1,760 (>C=O of sydnone), 1,234, 1,060 (C–O–C of methoxy), 832 (C–Cl); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.26 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 4.80 (s, 1H, NH), 6.97–8.03 (m, 8H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 52.32, 57.25, 114.85, 116.50, 118.65, 120.12, 125.20, 129.34, 131.00, 133.25, 139.22, 145.22, 164.10, 168.91; Anal. Calcd. for $C_{16}H_{13}N_3O_3Cl_2$: C, 52.48; H, 3.58; N, 11.47. Found: C, 52.39; H, 3.51; N, 11.42.

(7j) IR: (KBr) ν (cm^{-1}): 3,264 (NH), 2,924, 2,867 (–CH_2–), 1,752 (>C=O of sydnone), 1,245, 1,037 (C–O–C of methoxy), 1,154 (C–F); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.33 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3), 4.77 (s, 1H, NH), 7.01–8.21 (m, 8H, Ar–H); ^{13}C NMR (DMSO-d_6): δ (ppm): 51.92, 569.94, 102.95, 114.32, 116.75, 124.86, 130.70, 137.50, 139.15, 144.85, 147.54, 163.56, 169.10; Anal. Calcd. for $C_{16}H_{14}N_3O_3F$: C, 60.95; H, 4.48; N, 13.33. Found: C, 60.88; H, 4.44; N, 13.29.

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