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DMAP-catalysed synthesis, antibacterial activity evaluation, cytotoxicity and docking studies of some heterocyclic molecules bearing sulfonamide moiety

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DMAP has been shown to be a highly efficient nucleophilic catalyst when compared to triethylamine and pyridine using acetonitrile as solvent for the synthesis of a series of novel *N*- heterocyclic sulfonamide derivatives. The influence of the reaction parameters, like choice of solvent, catalyst, amount of catalyst and reaction time on product yield has been studied. Antibacterial screening involving a range of sulfonamide analogues as new peptide deformylase (PDF) inhibitors have been focused. The molecules show significant antibacterial activity (MIC value 6.2 − 3.1 µg/mL) against *B. subtilis*, *S. pyrogenes*, *P. vulgaris* and *P. mirabilis*. Potential *in silico* docking studies have been in conjugation with *in vitro* antibacterial results. Molecular docking of all compounds with PDF enzyme (PDB code: 1G2A) explain how certain moieties play significant roles in increasing the binding interactions and stabilizing the protein-ligand complexes. The compounds also confirm low extent of cytotoxicity when tested on HEL and HeLa cell lines.

Keywords: DMAP, sulfonamides, antibacterial activity, molecular docking, peptide deformylase inhibitor

Heterocyclic cores indisputably play key roles in the field of medicinal chemistry[1,2]. Nitrogen containing heterocycles bearing sulfonamide moieties, especially aryl derivatives, have been the focus of attention, because of their broad range of exciting biological properties, like carbonic anhydrase inhibitors, antibacterials, anticancer, anti-inflammatory, antifungal and antiviral agents[3-7]. Pathogenic bacteria rapidly developing resistance towards the clinically used antibiotics make it tougher to eliminate infections from the affected human beings. As a result, developing new class of antibacterial drugs with minimum adverse effects is of immense importance in order to fight the increasing danger of antibiotic drug resistance[8-10]. Selection of antibacterial drug targets wholly depends on the reality that is ideology on which antibiotic mechanism works is sharp dissimilarities between cellular metabolism in bacteria and humans. Peptide deformylase (PDF), identified to be most suitable and valuable target, in view of the fact that there is no comparable protein present in humans[11,12]. Furthermore, as both heterocyclic rings and sulfonamide moiety possess a wide range of biological activities, many synthetic methods have been reported for the preparation of sulfonamide and their derivatives[13,14]. Amidst published procedures, for the synthesis of *N*-heterocyclic sulfonamides, employing pyridine as a base for sulfonylation of amines with sulfonyl chlorides is still one of the most popular method[15,16].

As compared to pyridine, 4-(N,N-dimethylamino) pyridine is a remarkable nucleophilic catalyst and possess higher basicity. DMAP shows versatile catalytic role in miscellaneous synthetic transformations, *e.g.*, acylations, alkylations, silylations, esterifications, *N*-sulfonyl monocyclic β-lactams synthesis, *etc*. as it behaves as a stronger nucleophile relatively than a base[17-19].

Results and Discussion

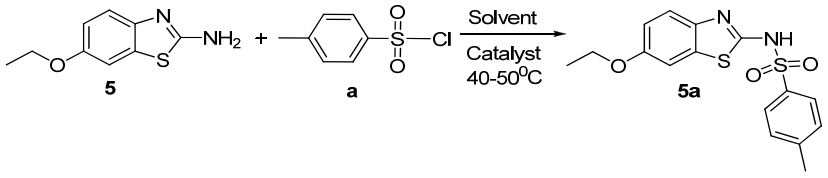
In continuation of our previous published article[20], here in the current communication we detailed a simple DMAP-intervened approach for the adequate sulfonation of heterocyclic amines and eighteen *N*-substituted heteroarylsulfonamide derivatives (synthesized through different chemical synthetic method compared to previous work) *via* one-pot, two component reaction between *N*-containing heterocycles, **1**(1-*H*-benzimidazole), **2**(2-Cl-1-*H*-benzimidazole), **3** (1-*H*-indazole), **4**(5-NO_2-indazole), **5**(2-amino-6-ethoxy-benzothiazole), **6**(2-amino-thiazole), **7**(5,6-dibromo-2-Cl-benzimidazole), and aromatic sulfonyl chlorides, likep-toluene sulfonyl chloride (**a**), 4-chloro-benzene-sulfonyl chloride (**b**)

and 4-nitro-benzene-sulfonyl chloride (**c**). All compounds were subjected to antibacterial screeningacross two gram-+ve (*B. subtilis*, *S. pyrogenes*) and two gram −ve bacterial strains (*P. vulgaris*,*P. mirabilis*). Molecular docking results of all compounds into active site of PDF enzyme (1G2A) explained that certain moieties played an important role in increasing binding interaction and this indicated towards possible mechanism of action of these compounds.

We commenced our study by taking 2-amino-6-ethoxy-benzothiazole (**5**) and *p*-toluene sulfonyl chloride (**a**) as the model substrates in the presence of different polar aprotic solvents, like ethyl acetate (EtOAc) and acetonitrile (CH_3CN) at 40-50°C in the absence of catalyst (Table I, entries 1 and 5). Very low yield of desired product was obtained in these set of reaction conditions even after lengthened reaction time. In order to examine the effect of solvents on the reaction rate, EtOAc and CH_3CN were further investigated in the existence of different base catalysts, *i.e.* triethyl amine (TEA), pyridine and DMAP. Results clearly revealed that higher yield of the product **5a** was obtained in the case of CH_3CN as solvent, with all three catalysts (Table I, entries 6-8), as compared to EtOAc (Table I, entries 2-4) and reaction time was reduced to approximately 2 hours in case of CH_3CN as solvent. Therefore, CH_3CN was the best solvent for this organic reaction. Further, analyzing the effect of various bases, like TEA, pyridine and DMAP as catalyst on reaction rate, it was concluded that the best results, *i.e.*, faster completion of reaction and the maximal product yield-89% was attained with DMAP as a base (Table I, entry 8). TEA proved to be the poorest base for this reaction as very low yield and high time was required for completion of the reaction. The analysis indicated that pyridine as catalyst resulted in better yield when compared to TEA. Furthermore, the influence of the amount of DMAP was examined to optimize the reaction conditions. When the amount of DMAP catalyst was decreased from 2 mmol to 1.7 mmol and 1.5 mmol, the yield of compound **5a** remained the same (Table I, entries 9 and 10). With further decreasing the amount of DMAP to 1.3 mmol and 1.0 mmol, the yield of the product decreased to 75% and 70%, respectively.

It was further noticed that the yield of product **5a** was not significantly enhanced when amount of DMAP catalyst was increased from 2.0 mmol to 2.2 mmol (Table I, entry 13) and hence 1.5 mmol amount of DMAP as catalyst was sufficient enough to catalyse the reaction and was supposed to be the optimum amount for the reaction. Further, a little better yield was obtained when DMAP preactivatedsulfonyl chloride was allowed to react with amine in comparison to heating a mixture of all three together.

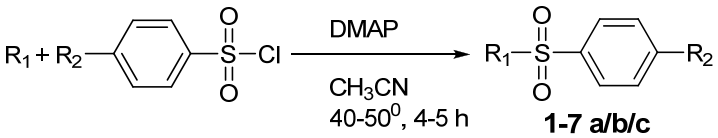
Table I — Escalation of the reaction conditions for the synthesis of **5a**[a]

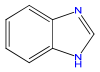
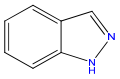
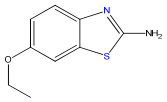
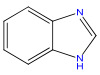
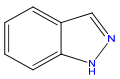
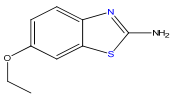
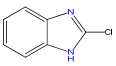
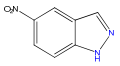
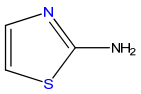
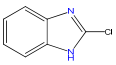
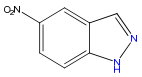
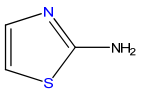
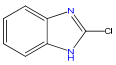
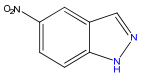
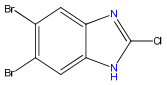
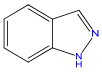
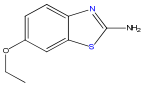
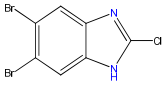


Entry	Solvent	Catalyst (mmol)	Time (h:min)	Yield %)[b]
1	EtOAc	–	8:00	10
2	EtOAc	TEA (2.0)	9:00	45
3	EtOAc	Pyridine (2.0)	7:30	52
4	EtOAc	DMAP (2.0)	6:00	60
5	CH_3CN	DMAP (2.0)	8:00	15
6	CH_3CN	TEA (2.0)	6:30	50
7	CH_3CN	Pyridine (2.0)	5:00	65
8	CH_3CN	DMAP (2.0)	4:30	88
9	CH_3CN	DMAP (1.7)	4:30	88
10	CH_3CN	DMAP (1.5)	4:30	88
11.	CH_3CN	DMAP (1.3)	5:00	75
12	CH_3CN	DMAP (1.0)	5:00	70
13	CH_3CN	DMAP (2.2)	4:30	89

[a] Conditions: 2-amino, 6-ethoxy benzothiazole(1.0 mmol) and 4-nitro benzenesulfonyl chloride (2.0 mmol).
[b] Isolated yields.

Table II — DMAP catalysed formation of *N*-heteroarylsulfonamides derivatives **1-7 (a/b/c)** using different heterocycles and substituted benzene sulfonyl chloride as substrates[a]



Compd	R_1	R_2	Yield[b] (%)	Compd	R_1	R_2	Yield[b] (%)	Compd	R_1	R_2	Yield[b] (%)
1a		CH_3	89	**3b**		Cl	84	**5b**		Cl	86
1b		Cl	85	**3c**		NO_2	73	**5c**		NO_2	88
2a		CH_3	87	**4a**		CH_3	82	**6a**		CH_3	85
2b		Cl	83	**4b**		Cl	80	**6b**		Cl	82
2c		NO_2	80	**4c**		NO_2	78	**7a**		CH_3	89
3a		CH_3	88	**5a**		CH_3	90	**7c**		NO_2	81

[a]Conditions: Heterocycles (R_1-1mmol), sulfonyl chlorides (R_2-2mmol), DMAP (1.5 mmol) in the presence of solvent acetonitrile (5 mL) for 4-5 h.
[b]Isolated yields.

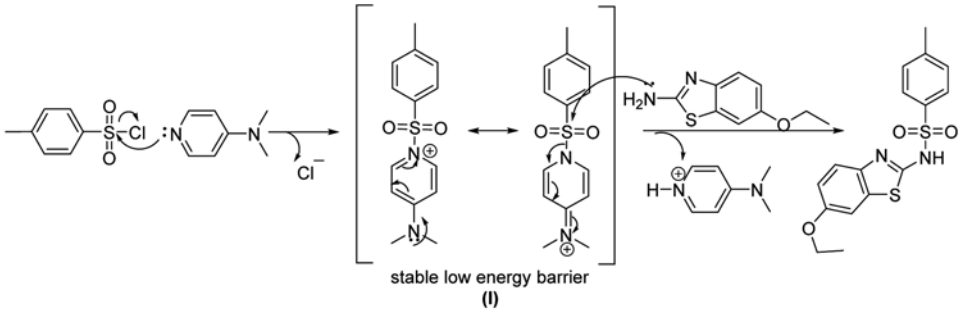
With the retained optimized reaction condition, a series of *N*-heteroarylsulfonamide derivatives **1-7(a/b/c)** were synthesized to test the generalization and extent/range of this novel procedure and the findings are summed-up in Table II. It was concluded that sulfonamides with electron-donating substituents (-CH_3) on the *p*-position of benzene ring of sulfonyl chloride afforded the corresponding products in yield ranging between 82-90% and substrates containing electron-withdrawing groups (-Cl, NO_2) at *p*-position of the phenyl group resulted in the desired products in yields ranging between 73-88%. Thus, in every case, the reaction progressed to result in the formation of desired products in great yields.

On the basis of optimized reaction conditions and relevant literature survey[21-24], we proposed a probable strategy for the production of compound **5a**employing DMAP as catalyst (Scheme I). At first, the nucleophilic base DMAP attacks at the electrophilic centre of sulfonyl chloride resulting in the generation of stable lower efficiency barrier sulfonyl-DMAP transition state**(I)** with loss of chlorine. This activation of sulfonyl chloride was followed by the *N*-nucleophilic attack of primary amine **(5),** which led to the generation of product **(5a)** and $DMAPH^+$. As DMAP's nitrogen atom is extra nucleophilic as compared to amino group in heterocycle and the intermediate **(I)** is also much more active than benzene sulfonyl chloride, the product formation is quite rapid when DMAP is present as compared to its absence.

Materials and Methods

General information related to synthesis of N-heterocyclic compounds

All chemicals and reagents were purchased from Sigma-Aldrich Chemical Company, USA and



Scheme I — Plausible mechanism of reaction of formation of *N*-(6-ethoxybenzothiazol-2-yl)-4- methylbenzenesulfonamide**5a**

E. Merck India Ltd, India. All reactions were carried out in oven dried apparatus using dried and distilled solvents. Column chromatography was carried out over silica gel (100-200 mesh). Compounds were confirmed by TLC, using silica gel 60F254 aluminium sheets and visualized by ultraviolet light at 254 nm. Melting points were recorded on electro thermal apparatus using open capillary tubes and are uncorrected.^{1}H and ^{13}C NMR spectra were recorded on BRUKER-AV400 spectrometer (Bruker Co., Faellanden, Switzerland) in DMSO-d_6(^{1}H at 400 MHz and ^{13}C at 100 MHz). Chemical shifts (δ) are expressed in parts per million (ppm) and *J* (coupling constant) values are expressed in Hz. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Mass spectra were recorded on Micromass Q-Tof (ESI-HRMS). The elemental analyses were performed on a Perkin-Elmer 240-C analyses equipment.

Experimental Section

General synthesis of N-heterocyclic sulfonamide derivatives 1-7(a/b/c)

A solution of sulfonyl chloride **a-c** (2 mmol) and dimethyl amino pyridine (1.5 mmol) in acetonitrile (5 mL) was stirred at RT for 20-30 min. After 30 min. compound **1** (or **2/ 3/ 4/ 5/ 6/ 7**; 1 mmol) was added to the stirred solution. The reaction mixture was heated for 4-5 h at 40-50°C. The advancement of the reaction and utilization of reactants into productwas predicted through TLC analysis. The resultant blend was dehydrated under vacuum and the dried mixture was divided between EtOAc and aqueous $NaHCO_3$ solution. The organic portion was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. Decontamination of the crude product was done by column chromatography and recrystallisation from ethanol.

1-Tosyl-1*H*-benzimidazole, 1a: Crystal like white powder. Yield 86%. m.p.112-115°C. R_f - 0.55 (DCM:Hexane :: 5:5); ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 2.38 (s, 3H,), 6.93-6.95 (m, 1H), 6.99-7.01 (m, 2H,), 7.28 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 8.02 (s, 1H), 9.08 (s, 1H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 21.3, 116.4, 117.6, 128.1, 128.3, 129.8, 130.9, 137.8, 138.6, 141.8, 145.1, 146.6. Anal.Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29; S, 11.77. Found: C, 61.73; H, 4.42; N, 10.28; S, 11.75%.

1-(4-Chlorophenylsulfonyl)-1*H*-benzimidazole, 1b: Cream coloured crystal powder. Yield 88%.m.p.187-188°C. R_f - 0.54 (DCM:Hexane :: 5:5) ; ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 6.91-6.94 (m, 1H), 6.99-7.01 (m, 2H), 7.29 (d, *J* = 8.2 Hz,2H), 7.58 (d, *J* = 8.2 Hz, 2H), 8.03 (s, 1H), 8.97 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 112.6, 121.1, 122.9, 126.8, 129.5, 129.9, 131.3, 135.2, 139.9, 140.6, 143.9. Anal.Calcd for $C_{13}H_9ClN_2O_2S$: C, 53.34; H, 3.10; N, 9.57; Cl, 12.11; S, 10.95. Found: C, 53.33; H, 3.8; N, 9.56; Cl, 12.09, S, 10.96%.

2-Chloro-1-tosyl-1*H*–benzimidazole, 2a: Off white coloured powder. Yield 87%.m.p.97-98°C. R_f - 0.57 (DCM:Hexane :: 5:5); ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 2.38 (s, 3H), 6.91-6.93 (m, 1H), 6.99-7.01 (m, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 8.04 (s, 1H), 9.0 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 21.6, 112.9, 115.7, 123.5, 126.6, 128.6, 130.5, 130.9, 134.8, 138.9, 139.8, 141.9. Anal.Calcd for $C_{14}H_{11}ClN_2O_2S$: C, 54.81; H, 3.61; N, 9.13; Cl, 11.56; S, 10.45. Found: C, 54.79; H, 3.63; N, 9.12; Cl, 11.54; S, 10.46%.

2-Chloro-1-(4-chlorophenylsulfonyl)-1*H*-benzimidazole, 2b: Dirty white powder. Yield 83%.m.p.146-148°C. R_f - 0.56 (DCM:Hexane :: 5:5); ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 7.21 (d, *J* = 3.0 Hz, 2H), 7.62 (d, *J* = 2.0 Hz, 2H), 7.95 (d, *J* = 5.8 Hz,

2H), 8.15 (d, J = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 112.8, 115.5, 123.6, 126.5, 129.8, 129.9, 130.8, 135.9, 138.9, 139.6, 141.9. Anal.Calcd for $C_{13}H_8Cl_2N_2O_2S$: C, 47.72; H, 2.46; N, 8.56; Cl, 21.67; S, 9.80. Found: C, 47.71; H, 2.48; N, 8.54; Cl. 21.65; S, 9.81%.

2-Chloro-1-(4-nitrophenylsulfonyl)-1*H*-benzimidazole, 2c: Creamish coloured powder. Yield 80%.m.p.162-163°C. R_f - 0.57 (DCM:Hexane :: 5:5); ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 7.41 (d, J = 3.2 Hz, 2H), 7.78 (d, J = 2.2 Hz, 2H), 7.98 (d, J = 5.9 Hz), 8.16 (d, J = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 112.9, 116.5, 123.8, 124.9, 126.6, 129.5, 131.2, 138.7, 140.9, 144.3, 152.7. Anal.Calcd for $C_{13}H_8ClN_3O_4S$: C, 46.23; H, 2.39; N, 12.44; Cl, 10.50, S, 9.49. Found: C, 46.22; H, 2.38; N, 12.45; Cl, 10.48; S, 9.51%.

1-Tosyl-1*H*-indazole, 3a: Dull white powder. Yield 88%.m.p.129-130°C. R_f - 0.57 (DCM:Hexane :: 5:5); ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 2.53 (s, 3H), 7.47 (t, J = 7.0 Hz, 1H), 7.71-7.75 (m, 1H), 7.93 (d, J = 8 Hz, 1H), 8.17-8.22 (m, 3H), 8.39 (d, J = 7.2 Hz, 2H), 8.87 (s, 1H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 21.4, 112.6, 122.5, 125.0, 125.9, 128.7, 130.2, 139.7, 141.0, 143.8, 150.8. Anal.Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29; S, 11.77. Found: C, 61.74; H, 4.45; N, 10.28; S, 11.75%.

1-(4-Chlorophenylsulfonyl)-1*H*-indazole, 3b: Creamish white coloured powder. Yield 84%.m.p.136-137°C. R_f - 0.56 (DCM:Hexane :: 5:5); ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 7.48 (t, J = 7.0 Hz, 1H), 7.71-7.75 (m, 1H), 7.89 (d, J = 8.4 Hz, 1H), 8.17-8.25 (m, 3H), 8.36-8.40 (m, 2H), 8.86 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 112.6, 122.5, 125.0, 125.9, 128.8, 130.2, 139.7, 141.0, 143.8, 150.8. Anal.Calcd for $C_{13}H_9ClN_2O_2S$: C, 53.34; H, 3.10; N, 9.57; Cl, 12.11; S, 10.9. Found: C, 53.32; H, 3.11; N, 9.56; Cl, 12.09; S, 10.91%.

1-(4-Nitrophenylsulfonyl)-1*H*-indazole, 3c: Cream coloured powder. Yield 73%.m.p.141-143°C. R_f - 0.55 (DCM:Hexane :: 5:5); ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 7.48 (t, J = 7.0 Hz, 1H), 7.71-7.75 (m,1H), 7.92 (d, J = 8Hz, 1H), 8.17-8.21(m, 3H), 8.36-8.40 (m, 2H), 8.67 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 112.5, 122.5, 125.1, 125.8, 128.8, 130.2, 139.6, 141.2, 143.7, 150.9. Anal.Calcd for $C_{13}H_9N_3O_4S$: C, 51.48; H, 2.99; N, 13.85; S, 10.57. Found: C, 51.46; H, 2.98; N, 13.87; S, 10.56%.

5-Nitro-1-tosyl-1*H*-indazole, 4a: Creamish white coloured powder. Yield 82%.m.p.192-193°C. R_f - 0.57 (DCM:Hexane :: 7:3); ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 2.32 (s, 3H), 7.44 (d, J = 8.1 Hz, 2H), 7.89 (d, J = 8.4 Hz, 2H), 8.34 (d, J = 9.2 Hz, 1H), 8.48 (d. J = 2.2 Hz, 1H), 8.76 (s, 1H), 8.86 (s, 1H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 21.09, 113.6, 119.4, 124.3, 125.5, 127.4, 130.5, 133.0, 141.8, 143.4, 144.3, 146.7. Anal.Calcd for $C_{14}H_{11}N_3O_4S$: C, 52.99; H, 3.49; N, 13.24; S, 10.10. Found: C, 52.97; H, 3.48; N, 13.25; S, 10.11%.

1-(4-Chlorophenylsulfonyl)-5-nitro-1*H*-indazole, 4b: Light cream coloured powder. Yield 80%.m.p.197-199°C. R_f - 0.58 (DCM:Hexane:: 7:3); ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 7.45 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.4 Hz, 2H), 8.34 (d, J = 9.2 Hz, 1H), 8.48 (d, J = 2.4 Hz, 1H), 8.86 (s, 1H), 8.87 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 113.4, 119.7, 124.8, 125.4, 127.6, 130.8, 133.5, 141.9, 143.6, 144.5, 146.7. Anal.Calcd for $C_{13}H_8ClN_3O_4S$: C, 46.23; H, 2.39; N, 12.44; Cl, 10.50; S, 9.49. Found: C, 46.24; H, 2.37; N, 12.43; Cl, 10.48; S, 9.48%.

5-Nitro-1-(4-nitrophenylsulfonyl)-1*H*-indazole, 4c: Off white coloured powder. Yield 78%.m.p.200-201°C. R_f - 0.56 (DCM:Hexane:: 7:3); ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 7.44 (d, J = 8.0 Hz, 2H), 7.88 (d, J = 8.4 Hz, 2H), 8.34 (d, J = 9.2 Hz, 1H), 8.50 (d, J = 2.2 Hz, 1H), 8.76 (s, 1H), 8.86 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 113.5, 119.4, 124.5, 125.4, 127.4, 130.5, 133.2, 141.7, 143.4, 144.5, 146.6. Anal.Calcd for $C_{13}H_8N_4O_6S$ C, 44.84; H, 2.33; N, 16.05; S, 9.20. Found: C, 44.85; H, 2.34; N, 16.06; S, 9.22%.

N-(6-Ethoxybenzothiazol-2-yl)-4-methylbenzenesulfonamide, 5a: Light yellow powder. Yield 90%.m.p.222-224°C. R_f - 0.55 (DCM:Hexane :: 5:5); ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm}: 1.42 (t, J = 6.8 Hz, 3H), 2.37 (s, 3H,), 3.92-3.98 (q, J = 6.8 Hz, 2H), 6.72-6.74 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.8 Hz, 2H), 8.25 (d, J = 8.8Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 14.8, 21.8, 63.4, 105.6, 113.1, 118.3, 123.8, 127.3, 142.9, 148.3, 151.5, 153.6, 155.9, 164.7. Anal.Calcd for $C_{16}H_{16}N_2O_3S_2$: C, 55.15; H, 4.63; N, 8.04; S, 18.40%. Found: C, 55.13; H, 4.62; N, 8.03; S, 18.39%.

4-Chloro-N-(6-ethoxybenzothiazol-2-yl)benzenesulfonamide, 5b: Lemon Yellow powder. Yield 86%. m.p.235-236°C. R_f - 0.58 (DCM:Hexane

:: 5:5); ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 1.41 (t, J = 6.8 Hz, 3H), 4.02 (q, J = 6.8 Hz, 2H), 6.75 (d, J = 8.4 Hz,1H), 7.18 (d, J = 2.4 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.8 Hz, 2H), 8.26 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 14.7, 63.5, 105.8, 113.2, 118.3, 123.4, 127.7, 142.9, 148.3, 151.4, 152.7, 155.8, 165.8. Anal.Calcd for $C_{15}H_{13}ClN_2O_3S_2$: C, 48.84; H, 3.55; N, 7.59; Cl, 9.61; S, 17.39%. Found: C, 48.83; H, 3.54; N, 7.57; Cl, 9.62; S, 17.38%.

N-(6-Ethoxybenzothiazol-2-yl)-4-nitrobenzenesulfonamide, 5c: Dark yellow powder. Yield 88%.m.p.242-243°C. R_f - 0.55 (DCM:Hexane :: 5:5); ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 1.32 (t, J = 6.8 Hz, 3H), 3.98-4.04 (q, J = 6.8 Hz, 2H), 6.72-6.76 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.8 Hz, 2H), 8.26 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 14.8, 63.5, 105.6, 113.4, 118.2, 123.8, 127.4, 142.9, 148.4, 151.4, 153.8, 155.8, 164.9. Anal.Calcd for $C_{15}H_{13}N_3O_5S_2$: C, 47.48; H, 3.45; N, 11.08; S, 16.90. Found: C, 47.46; H, 3.46; N, 11.07; S, 16.88%.

4-Methyl-N-(thiazol-2-yl)benzenesulfonamide, 6a: Mustard coloured viscous solid. Yield 85%.R_f - 0.56 (EtOAc:Hexane :: 3:7); ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 2.88 (s, 3H), 4.02 (s, 1H), 6.86 (d, J = 4.5 Hz, 1H), 7.28 (d, J = 4.6 Hz, 1H), 7.63 (d, J = 8.6 Hz; 2H), 7.80 (d, J = 4.7 Hz; 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 21.6, 113.9, 128.4, 130.4, 136.5, 137.2, 137.9, 172.5. Anal.Calcd for $C_{10}H_{10}N_2O_2S_2$: C, 47.23; H, 3.96; N, 11.01; S, 25.22. Found: C, 47.25; H, 3.98; N, 11.02; S, 25.24%.

4-Chloro-N-(thiazol-2-yl)benzenesulfonamide, 6b: Light brown viscous solid. Yield 82%.R_f - 0.55(EtOAc:Hexane :: 3:7); ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 4.05 (s, 1H), 6.86 (d, J = 4.5 Hz, 1H), 7.29 (d, J = 4.6 Hz, 1H), 7.66 (d, J = 8.6 Hz, 2H), 7.83 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 112.5, 128.9, 129.4, 137.3, 137.7, 138.0, 171.8. Anal.Calcd for $C_9H_7ClN_2O_2S_2$: C, 39.34; H, 2.57; N, 10.20; Cl, 12.90; S, 23.34. Found: C, 39.36; H, 2.56; N, 10.21; Cl, 12.92; S, 23.35%.

5,6-Dibromo-2-chloro-1-tosyl-1*H*-benzimidazole, 7a: Dirty white viscous oil. Yield 89%.R_f - 0.60 (DCM:Hexane :: 8:2); ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 2.38 (s, 3H), 7.23 (d, J = 6 Hz, 2H), 7.48 (d, J = 3.2 Hz, 1H), 7.84 (s, 1H), 8.19 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 21.5, 120.6, 121.5, 128.5, 130.5, 132.6, 134.5, 139.7, 140.5, 141.9. Anal.Calcd for $C_{14}H_9Br_2ClN_2O_2S$: C, 36.20; H, 1.95; N, 6.03; Cl, 7.63; Br, 34.40; S, 6.90. Found: C, 36.19; H, 1.97; N, 6.02; Cl, 7.65; Br, 34.38; S, 6.92%.

5,6-Dibromo-2-chloro-1-(4-nitrophenylsulfonyl)-1*H*-benzimidazole, 7c: Dull white viscous oil. Yield 81%.R_f - 0.55 (DCM:Hexane :: 8:2); ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 7.22 (d, J = 6 Hz, 2H), 7.51 (d, J = 3.2 Hz, 2H), 7.85 (s, 1H), 8.20 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_{ppm} 120.6, 120.8, 129.5, 129.9, 132.2, 135.9, 139.5, 140.2, 141.7. Anal.Calcd for $C_{13}H_6Br_2ClN_3O_4S$: C, 31.51; H, 1.22; N, 8.48; Cl, 7.15; Br, 32.25; S, 6.47. Found: C, 31.48; H, 1.21; N, 8.46; Cl, 7.12; Br, 32.28; S, 6.49%.

Antibacterial Activity

All compounds were screened for their *in vitro* antibacterial activity across some selected strains of two gram +ve bacteria, *viz*. *Bacillus subtilis*, *Staphylococcus pyrogenes* and two gram −ve bacteria *viz*., *Pseudomonas vulgaris*, *Pseudomonas mirabilis* for assessing the minimum inhibitory concentration (MIC, μg/mL) using micro dilution susceptibility test[25]. Popular marketable antibiotics-chloramphenicol and sulfamethoxazole in DMSO were used as classic or standard pharmaceuticals for reference and the conclusions are summarized in Table III and Figure 1. Investigation of antibacterial screening acknowledged that compounds **2c, 4c, 5c, 6a-b, 7a** and **7c** exhibited significant antibacterial activity (MIC: 6.2-3.1 μg/mL) across entire set of tested microorganism and some moieties displayed even better activity compared to reference drugs. General pattern of antibacterial screening results of compounds **1-7** and derivatives with standard antibiotics has been represented in Figure 1 which chased the progression of activity across approved bacterial strains as: **7** (5,6-dibromo-2-Cl-benzimidazole) >**6** (2-amino-thiazole) >**4** (5-NO_2-Indazole) >**2** (2-Cl-1*H*-Benzimidazole) ≈ **5** (2-amino-6-ethoxy-benzothiazole) >**1** (1-*H*-Benzimidazole) ≈ **3** (1-*H*-Indazole).

Structure Activity Relationship (SAR) study (Figure 2) demonstrated that sulfonamides possessing –NO_2 moiety exhibited greater antibacterial activity due to the existence of polar substituents since it offered greater opportunity for the formation of hydrogen bonds. Substituents at 5, 6 position of heterocyclic ring **7a** and **7c**, affected the antibacterial activity significantly showing exceptional inhibition arrangement among whole strains. Table III illustrated

Table III — Antibacterial results of *N*-heterocyclic sulfonamides (compounds **1-7**and derivatives) across gram +ve and gram –ve bacterial strains (MIC in µg/mL) and cytotoxicity results

Compd	MIC				Cytotoxicity: CC_{50} µg/mL	
	Gram +ve strain		Gram –ve strain		HEL	HeLa
	B. subtilis	*S. pyrogenes*	*P. vulgaris*	*P. mirabilis*		
1a	50	50	12.5	12.5	ND	ND
1b	25	12.5	6.2	12.5	ND	ND
2a	12.5	12.5	12.5	12.5	>100	100
2b	12.5	12.5	6.2	6.2	100	>100
2c	6.2	6.2	3.1	3.1	>100	>100
3a	25	25	12.5	12.5	ND	ND
3b	25	25	6.2	12.5	ND	ND
3c	12.5	12.5	3.1	6.2	ND	ND
4a	12.5	12.5	6.2	12.5	4	4
4b	12.5	12.5	3.1	6.2	20	100
4c	6.2	6.2	3.1	3.1	100	>100
5a	25	12.5	12.5	12.5	>100	>100
5b	12.5	12.5	3.1	6.2	>100	>100
5c	6.2	6.2	3.1	6.2	>100	>100
6a	6.2	6.2	3.1	3.1	>100	>100
6b	3.1	6.2	3.1	3.1	100	>100
7a	6.2	6.2	3.1	6.2	>100	>100
7c	3.1	3.1	3.1	3.1	>100	>100
Chloramphenicol	6.2	6.2	6.2	6.2	–	–
Sulfamethoxazole	6.2	6.2	3.1	3.1	–	–

MIC-Minimum Inhibitory Concentration in µg/mL; CC_{50} = 50% cytotoxicity concentration

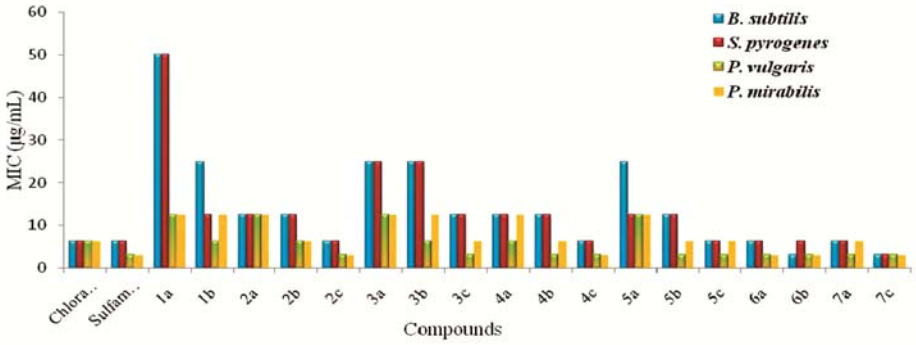


Figure 1 — Correlation of antibacterial results (MIC in µg/mL) of *N*-heterocyclic sulfonamides**1-7**and derivatives with reference antibiotic (Chloramphenicol and Sulfamethoxazole)

that entire derivatives with electron withdrawing substituents (-NO_2, -Cl, -Br) exhibited undoubtedly greater antibacterial efficacy as a result of higher electronic effect compared to electron donating substituent (-CH_3) displaying reasonable activity. Moreover, the antibacterial results of sulfonamide derivatives were decided by the nature of heterocyclic ring. Conclusively, empirical results exposed the sequence of antibacterial activity of *N*-heterocyclic derivatives across various bacterial strain in the following order *P. vulgaris* > *P. mirabilis* > *S. pyrogenes* ≈ *B. subtilis*.

Out of 18, twelve molecules were also subjected to cytotoxicity testing against HEL (human embryonic lung cells) and HeLa (human epithelial cells) cell lines using MTT assay[26,27] and data are summarized in Table III. Results revealed that all molecules were seen as less fatal except compound **4a** against HEL and HeLa cell lines and **4b** against HEL cell line used in cytotoxicity assay.

To elucidate theoretically the antibacterial mechanism of these sulfonamide analogues, all molecules were subjected to molecular docking using Discovery Studio 2.5 software in order to explore the

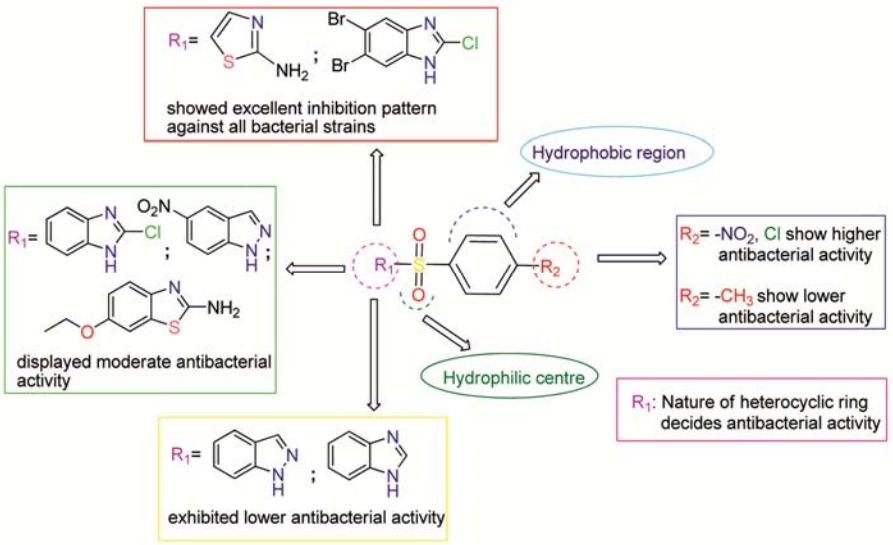


Figure 2 — SAR illustration of arylsulfonamide analogues based on antibacterial results

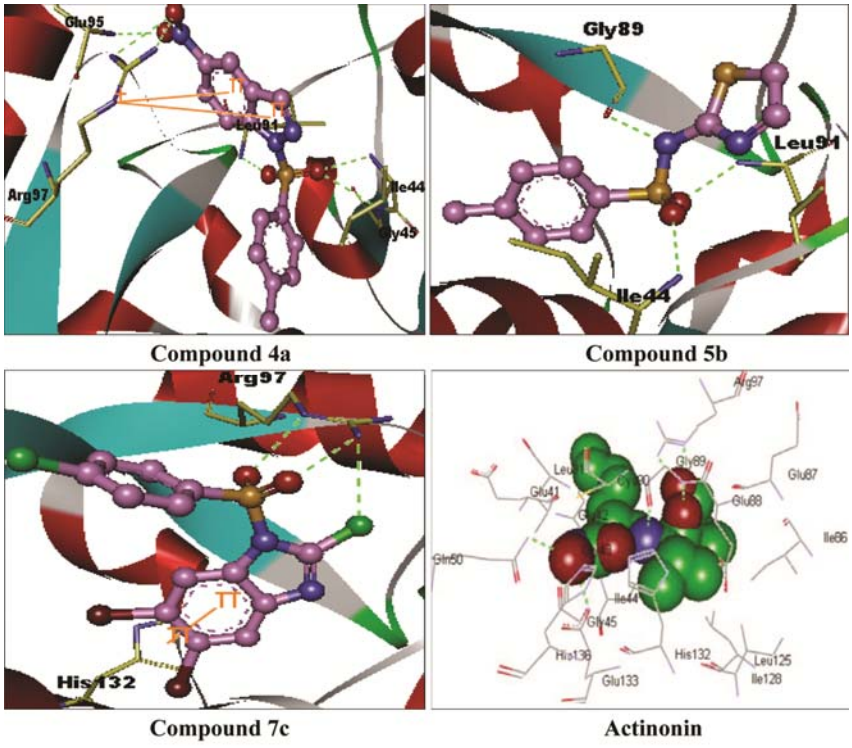


Figure 3 — Docked orientation of compounds **4a**, **5b**, **7c** and reference antibiotic actinoninin the active site of PDF receptor (hydrogen bond shown in green dashed line and pie interaction shown by solid orange line)

binding pattern with peptide deformylase enzyme recovered from protein data bank (PDB ID-1G2A), as docking receptor[28,29]. All compounds exhibited higher binding free energy, (ΔG) ranging between −6.59 and −8.60 kcal ⁄ mol as compared to reference antibiotic actinonin (−5.98 kcal/mol) and chloramphenicol (−6.58 kcal/mol), which could give reasonable explanation for their good antibacterial activity. Recent investigation revealed that greater value of ΔG was correlated with greater affinity, which corresponded to reduced EC_{50}value[30]. Binding mode of compounds **4a**, **5b**, **7c** and **Ref** (**actinonin**)is shown in Figure 3. From scoring functions it can be inferred that molecules possessing nitro group

Table IV — Scoring functions and docking interaction of sulfonamides**1-7(a-c)** with PDF receptor in ligand-receptor docked complexes

Compd	ΔG	EC_{50}	No. of H-B/ Amino acid in H-B	No. of π-B/ Amino acid in π-B
1a	−6.81	2.29×10^{-5}	3/ Ile44, Gly89, Leu91	π^+ 1/ Arg97
1b	−6.94	2.08×10^{-5}	3/ Ile44, Gly89, Leu91	π-π 1/ His132, π^+ 1/ Arg97
2a	−7.19	3.71×10^{-5}	2/ Ile44, Gly89	π^+ 1/ Arg97
2b	−7.27	4.78×10^{-5}	2/ Ile44, Gly89	π^+ 1/ Arg97
2c	−7.68	1.23×10^{-5}	5/ Ile44,Gly89,Arg97,Arg97,Glu95	π^+ 1/ Arg97
3a	−7.52	1.54×10^{-5}	4/ Ile44,Leu91,Leu91,Cys90	π^+ 1/ Arg97
3b	−7.66	1.86×10^{-5}	2/ Ile44,Ileu91	π-π 1/ His132, π^+ 1/ Arg97
3c	−7.72	1.00×10^{-5}	4/ Ile44,Arg97,Arg97, Leu91	π-π 1/ His132, π^+ 1/ Arg97
4a	−7.16	2.23×10^{-5}	6/ Ile44,Gly45,Glu95,Arg97,Arg97, Leu91	π^+ 2/ Arg97, Arg97
4b	−8.09	3.49×10^{-6}	5/ Ile44,Glu95,Arg97,Arg97,Leu91	π-π 1/ His132 , π^+ 1/ Arg97
4c	−8.15	1.95×10^{-5}	5/ Ile44,Glu95,Arg97,Arg97,Leu91	π-π 1/ His132, π^+ 1/ Arg97
5a	−6.59	2.08×10^{-5}	2/ Ile44,Gly89	π-π 1/ His132, π^+ 2/ Arg97, Arg97
5b	−6.68	2.45×10^{-5}	4/Ile44,Gly45,Glu95,Leu91	π-π 1/ His132, π^+ 2/ Arg97, Arg97
5c	−7.42	1.35×10^{-4}	2/ Cys90,Arg97	π-π 2/ His132, His132
6a	−8.60	3.12×10^{-5}	3/Ile44,Leu91,Gly89	π-π 1/ His132, π^+ 1/ Arg97
6b	−8.00	2.57×10^{-5}	3/ Ile44,Gly45,Leu91	π-π 1/ His132, π^+ 1/ Arg97
7a	−7.39	2.45×10^{-5}	4/Gly89 ,Arg97,Arg97,Arg97	π-π 2/ His132, His132
7c	−7.48	2.95×10^{-5}	3/ Arg97,Arg97,Arg97	1/His132
Actinonin	−5.98	1.82×10^{-4}	7/Gly50,Arg97,Arg97,Gly45,Gly89,Glu133	–
Chloramphenicol	−6.55	3.63×10^{-5}	5/ Arg97,Arg97,Gly45,Glu133,Gly89	–

ΔG -predicted binding free energy (kcal/ mol), Predicted EC_{50}-predicted 50% effective concentration required to inhibit bacterial replication (μM).

stabilizes the protein-ligand complex additionally. Docking interactions revealed that all molecules formed two-to-seven H-bonds with amino acid residues Ile44, Gly89, Leu91, Arg97, Glu95, Cys90, Leu91, Gly45, Glu133 and one-to-three π -π and π^- + interactions through Arg97 and His132 amino acid residues that was not experimentally found in standard drugs. Docking results (Table IV) recommended that every compound showed comparable binding pattern with reference antibiotics within active site of PDF receptor protein.

Conclusion

It is concluded that DMAP has been found to be a remarkably potent catalyst as compared to TEA and pyridine so as to synthesize new series of *N*-heteroarylsulfonamides **1-7** (**a/b/c**).The optimized method resulted in higher yield of the products with shorter reaction time and comparatively under milder condition. All compounds exhibited promising *in silico* results that were in collaboration with exceptionally good *in vitro* antibacterial bioactivity. Antibacterial results revealed that all compounds exhibited excellent efficiency against *P. vulgaris*, symbolic potency against *P. mirabilis* and satisfactory to valuable activity against *S. pyrogenes* and *B. subtilis* strains. In particular, **2c**, **4c**, **5c**, **6a-b**, **7a** and **7c** emerged as the most active compounds in the series. Molecular docking results were quite fair in understanding the binding interactions of these compounds with PDF enzyme.

All eighteen *N*-heterocyclic sulfonamides synthesized, exhibited excellent inhibition pattern against a broad range of antibacterial strains (including our previous publication and present work), and therefore, one can conclude that these molecules marked towards the progression to highly dominant broad antibacterial drug regimens against bacterial strains.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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Conflict of interest

The authors do not report any conflicts of interest.

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