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Artigo

EFFICIENT SYNTHESIS OF SULFONAMIDE DERIVATIVES ON SOLID SUPPORTS CATALYZED USING SOLVENT-FREE AND MICROWAVE-ASSISTED METHODS

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In this work we report the synthesis of sulfonamide derivatives using a conventional procedure and with solid supports, such as silica gel, florisil, alumina, 4Å molecular sieves, montmorillonite KSF, and montmorillonite K10 using solvent-free and microwave-assisted methods. Our results show that solid supports have a catalytic activity in the formation of sulfonamide derivatives. We found that florisil, montmorillonite KSF, and K10 could be used as inexpensive alternative catalysts that are easily separated from the reaction media. Additionally, solvent-free and microwave-assisted methods were more efficient in reducing reaction time and in increasing yield.

Keywords: synthesis; sulfonamide; solid supports.

INTRODUCTION

Sulfonamides are groups of compounds consisting of SO_2-NH functional groups that have biological importance as antibacterial agents.[1,2] They has have also been shown to exhibit antifungal,[3] antineoplasic,[4] and antiviral[5] activity, considering this class of compounds a "privileged structure" in medicinal chemistry.[6]

Because of the importance of sulfonamide derivatives in the pharmaceutical industry, synthetic methods under various reaction conditions have been previously reported;[7-13] however, these processes suffer from one or more restrictions, such as low product yield. Recently, the use of solid supports, such as florisil,[14] molecular sieves,[15] and alumina,[16] in various chemical syntheses has been documented. Some solid supports with catalytic activity, such as montmorillonite KSF and K10 have been widely used as reusable catalysts.[17-19]

Our objective in this study was the synthesis of new sulfonamides derivatives using a conventional procedure and solid supports (silica gel, florisil, alumina, 4Å molecular sieves, montmorillonite KSF, and montmorillonite K10) with solvent-free and microwave-assisted methods as an alternative strategy for synthesizing new agents with potential antitumor, antidiabetic, and antibacterial biological activity.

RESULTS AND DISCUSSION

In the search for new compounds with potential biological activity as antitumorals, antidiabetics and antibacterials, our research group has carried out the synthesis of various sulfonamide derivatives through the nucleophilic attack of an amine derivative with sulfonyl chloride using dichloromethane, triethylamine and dimethylaminopyridine stirred at room temperature (conventional procedure); however, the yield obtained has been low (Table 1).

As an alternative strategy in the synthesis of sulfonamide derivatives, in the first step we tried a solvent-free method, using 500 mg of solid supports (florisil, silica gel, alumina, 4Å molecular sieves, montmorillonite KSF and K10) that have been reported with catalytic activity, which help enhance the yields. With this strategy we obtained the compounds previously synthesized using the conventional procedure, but with increased yields and a decreased reaction time (Table 1). In the reaction system starting with aniline and benzenesulfonyl chloride (entry 1) without the addition of solid supports monitoring by thin layer chromatography at different times for 24 h, the reaction did not proceed, but when a solid support (florisil) was added, and monitoring the reaction at 5, 15 and 30 min for 1, 12 and 24 h, we found that the optimal time of reaction was 1 h and that lengthening the reaction time did not increase the reaction yield (95%).

This same reaction was tested on silica gel, alumina, 4Å molecular sieves, montmorillonite KSF, and K10 and we obtained similar yields (85, 80, 90, 85, and 90%, respectively). Analyzing the influence of electron-withdrawing and electron-donating groups on aniline, we determined that electron-withdrawing groups reduced the reaction yield and in several cases the desired product was not obtained. Additionally, the same behavior occurred if the amino group was not directly attached to an aromatic ring (entry 7), if it joined a group, to allow its resonance and prevent nucleophilic attack of amine to sulfonyl chloride (entry 5 and 7). Furthermore, the presence of electron-withdrawing and electron-donating groups in benzenesulfonyl chloride derivatives also affects the yield of the reaction. This behavior may be due to the overlap of the reagent on the solid support, which results in a decrease of molecular interactions between reagents to form the desired product.

The use of domestic microwave-assisted synthesis reactions has been reported in previous articles,[20,21] so we also decided to use this method as a third alternative for carrying out sulfonamide derivative synthesis in order to efficiently determine its yield. Analyzing the results of the microwave-assisted versus the solvent-free method (entry 1) we found that the yields obtained are similar on all solid supports, although the microwave method shortens the reaction time to a total of 5 min.

CONCLUSION

We discovered that the reaction system of an amine and sul-

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Table 1. Reaction systems and total yields in the conventional procedure, solvent-free and microwave-assisted methods on the solid support tested

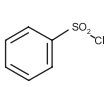
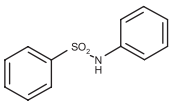
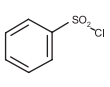
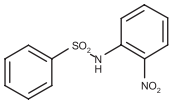
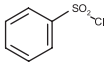
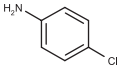
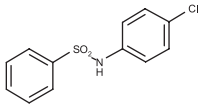
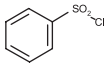
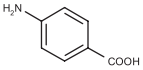
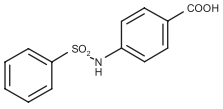
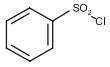
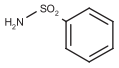
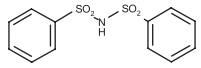
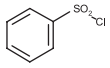
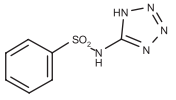
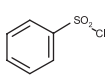
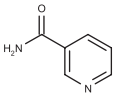
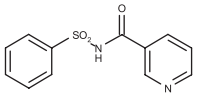
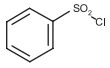
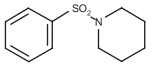
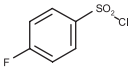
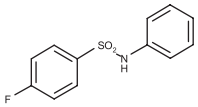
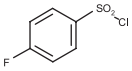
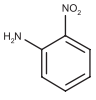
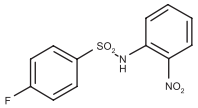
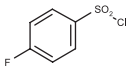
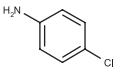
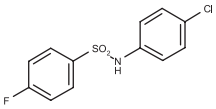
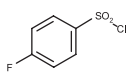
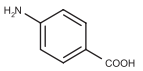
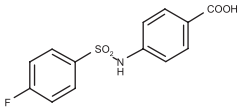
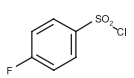
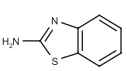
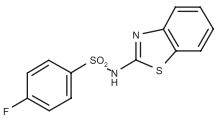
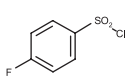
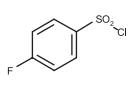
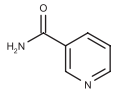
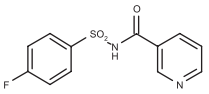
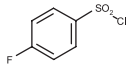
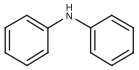
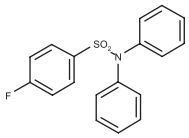
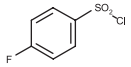
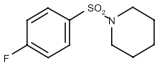
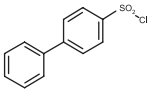
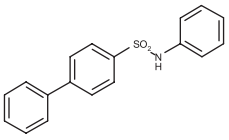
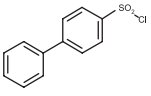
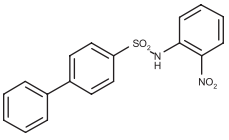
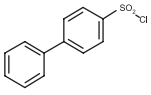
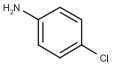
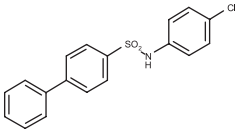
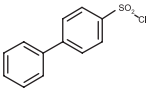
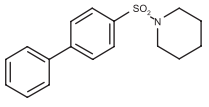
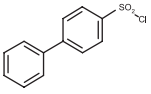
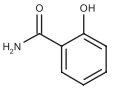
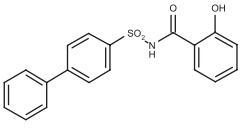
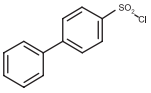
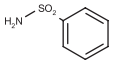
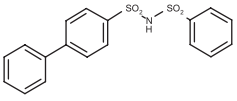
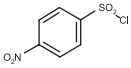
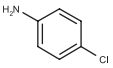
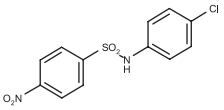
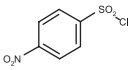
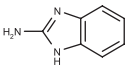
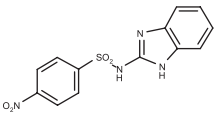
Entry	Sulfonyl chloride	Amine derivative	Product	CP (%)	SF (%)						MA (%)					
					F	S	A	MS	KSF	K10	F	S	A	MS	KSF	K10
1				30	95	85	80	90	85	90	90	80	80	80	90	90
2				15	10	10	NR	NR	NR	NR	45	60	35	40	35	10
3				25	75	80	80	85	90	80	85	90	90	75	80	80
4				10	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
5				NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
6				NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
7				NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
8				75	90	90	70	95	95	50	95	90	85	95	95	80
9				20	75	75	70	90	80	85	80	95	90	75	85	80
10				10	NR	NR	NR	NR	NR	5	5	60	5	10	NR	5
11				20	95	95	90	70	90	95	95	95	90	95	95	95
12				10	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
13				15	90	85	80	70	85	60	95	90	95	80	90	80
14				NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
15				NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 1. continuation

Entry	Sulfonyl chloride	Amine derivative	Product	CP (%)	SF (%)						MA (%)					
					F	S	A	MS	KSF	K10	F	S	A	MS	KSF	K10
16				NR	5	5	5	NR	5	5	25	5	10	20	5	5
17				10	10	50	NR	20	20	20	10	60	10	30	20	20
18				50	60	70	55	60	80	80	80	70	65	70	90	90
19				30	95	85	80	90	85	90	90	80	80	80	90	90
20				10	10	10	NR	NR	NR	NR	45	60	35	40	35	10
21				50	NR	NR	NR	85	85	90	85	95	90	5	5	5
22				30	90	80	70	90	95	95	95	90	80	90	95	95
23				50	20	20	18	25	NR	NR	NR	25	15	15	NR	NR
24				40	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
25				40	NR	NR	NR	80	80	NR	65	90	80	60	90	90
26				50	NR	NR	NR	NR	95	NR	NR	50	70	80	70	50

CP - Conventional procedure; SF - Solvent-free; MA - Microwave-assisted; F - Florisil; S - Silica gel; A - Alumina; MS - Molecular sieves 4A; KSF - Montmorillonite KSF; K10 - Montmorillonite K10; NR- No Reaction.

fonyl chloride derivative on solid supports, with solvent-free and microwave-assisted methods, was more efficient than a conventional procedure in reducing reaction time and increasing product yield. These results also demonstrated that florisil, montmorillonite KSF, and K10 are available and inexpensive and can be used as new alternative catalysts in this kind of reaction systems and that they are easily separated from the reaction media.

EXPERIMENTAL

General experimental procedure for the synthesis of sulfonamide derivatives

Conventional procedure

Sulfonyl chloride (1.1 equiv.), amine derivative (1 equiv.), trie-

thylamine (3 equiv.) and dimethylaminopyridine (catalytic amount) were added to a 50 mL round-bottomed flask and dissolved in dichloromethane (30 mL). The contents were then stirred for 24-48 h at room temperature. Progress of the reaction was monitored by thin layer chromatography. Afterwards, the compound obtained was filtering, dryness and purified by column chromatography using dichloromethane:methanol (95:5) as an eluent or recrystalized with methanol/hexane (2:1).

Solvent-free

Sulfonyl chloride (1.1 equiv.), amine derivative (1 equiv.) and 500 mg of solid support were added to a 50 mL round-bottomed flask and dissolved in dichloromethane (30 mL). The solvent was then evaporated under reduced pressure and dried in a vacuum pump. Progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, we add dichloromethane and the catalyst was removed by filtration and the crude compound was dryness and purified by column chromatography using dichloromethane:methanol (95:5) as an eluent or recrystalized with methanol/hexane (2:1).

Microwave-assisted

Sulfonyl chloride (1.1 equiv.), amine derivative (1 equiv.) and 500 mg of solid support were added to a 50 mL round-bottomed flask and dissolved in dichloromethane (30 mL). The solvent was then evaporated under reduced pressure and exposed to a domestic microwave oven, Samsung MW 1446WC, 1000 W for three reaction times of 5 min or more. After completion of the reaction, we add dichloromethane and the catalyst was removed by filtration and the crude compound was dryness and purified by column chromatography using dichloromethane/methanol (95:5) as an eluent or recrystalized with methanol/hexane (2:1).

All obtained compounds were structurally confirmed by IR and ^{1}H-NMR spectra.

Entry 1: N-phenyl-benzenesulfonamide

IR (KBr) υ cm^{-1}: 3220 (N-H), 1190 and 1075 (SO_2-N), 700 (S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.20-7.24 (m, 5H: NH-C_6H_5); 7.50- 7.55 (m, 5H: C_6H_5-SO_2); 7.67 (s, 1H: NH).

Entry 2: N-(2-nitro-phenyl)-benzenesulfonamide

IR (KBr) υ cm^{-1}: 3315 (N-H), 1167 and 1083 (SO_2-N), 725 (S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.60 (t, 1H: C_6H_5-SO_2); 7.63 (d, 2H: C_6H_5-SO_2); 7.71 (d, 2H: C_6H_5-SO_2); 7.78 (s, 1H: NH); 7. 84 (d, 2H: C_6H_5-NO_2); 7.88 (d, 1H: C_6H_5-NO_2); 8.05 (d, 1H: C_6H_5-NO_2).

Entry 3: N-(4-chloro-phenyl)-benzenesulfonamide

IR (KBr) υ cm^{-1}: 3240 (N-H), 1340 and 1180 (SO_2-N), 900 (C-Cl), 738 (f: S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.23 (d, 2H: C_6H_4-Cl); 7.31 (t, 2H: C_6H_4-Cl); 7.36 (d, 1H: C_6H_5-SO_2); 7.48 (d, 2H: C_6H_5-SO_2); 7.59 (d, 2H: C_6H_4-Cl); 7.71 (s, 1H: NH).

Entry 4: 4-(phenyl-sulfonylamino)-benzoic acid

IR (KBr) υ cm^{-1}: 3327 (N-H), 1643 (C=O), 1319 and 1168 (SO_2-N), 750 (S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.13 (t, 1H: C_6H_4-SO_2); 7.24 (d, 2H: C_6H_5-SO_2); 7.27 (d, 2H: C_6H_5-SO_2); 7.44 (d, 2H: C_6H_4-COOH); 7.49 (d, 2H: C_6H_4-COOH); 7.61 (s, 1H: NH).

Entry 5: N-(phenylsulfonyl)-benzenesulfonamide

No obtained.

Entry 6: N-(1H-tetraazol)-benzenesulfonamide

No obtained.

Entry 7: N-(phenylsulfonyl)-nicotinamide

No obtained.

Entry 8: 1-(phenylsulfonyl)-piperidine

IR (KBr) υ cm^{-1}: 2893 (C-H), 1160 (SO_2-N), 727 (S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.35 (m, 4H: $C_5H_{10}N$); 2.91 (m: 4H: $C_5H_{10}N$); 3.19 (d, 2H: $C_5H_{10}N$); 7.26 (t, 1H: C_6H_5-SO_2); 7.31 (d, 2H: C_6H_5-SO_2); 7.35 (d, 2H: C_6H_5-SO_2).

Entry 9: 4-fluoro-N-(phenyl)-benzenesulfonamide

IR (KBr) υ cm^{-1}: 3232 (N-H), 1181 and 1065 (SO_2-N), 734 (S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.25-7.29 (m, 5H: NH-C_6H_5); 7.48- 7.53 (m, 4H: F-C_6H_4-SO_2); 7.63 (s, 1H: NH).

Entry 10: 4-fluoro-N-(2-nitro-phenyl)-benzenesulfonamide

IR (KBr) υ cm^{-1}: 3311 (N-H), 1193 and 1153 (SO_2-N), 747 (S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.65 (d, 2H: F-C_6H_4-SO_2); 7.73 (d, 2H: F-C_6H_4-SO_2); 7.79 (s, 1H: NH); 7.84 (t, 1H: C_6H_4-NO_2); 7. 89 (d, 2H: C_6H_4-NO_2); 7.94 (d, 1H: C_6H_4-NO_2).

Entry 11: 4-fluoro-N-(4-chloro-phenyl)-benzenesulfonamide

IR (KBr) υ cm^{-1}: 3249 (N-H), 1335 and 1186 (SO_2-N), 915 (C-F), 754 (S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.26 (d, 2H: C_6H_4-Cl); 7.38 (d, 2H: C_6H_4-Cl); 7.51 (d, 2H: F-C_6H_4-SO_2); 7.57 (d, 2H: F-C_6H_4-SO_2); 7.67 (s, 1H: NH).

Entry 12: 4-(4-fluoro-phenyl-sulfonylamino)-benzoic acid

IR (KBr) υ cm^{-1}: 3320 (N-H), 1650 (C=O), 1324 and 1170 (SO_2-N), 944 (C-F), 763 (f: S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.52 (d, 2H: F-C_6H_4-SO_2); 7.58 (d, 2H: F-C_6H_4-SO_2); 7.78 (s, 1H: NH); 7.87 (d, 2H: C_6H_4-COOH); 7.90 (d, 2H: C_6H_4-COOH).

Entry 13: 4-fluoro-N-(1,3-benzothiazol-2-yl)-benzenesulfonamide

IR (KBr) υ cm^{-1}: 3310 (N-H), 1169 and 1094 (SO_2-N), 743 (S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.40 (d, 2H: NH_2-C_7H_4); 7.53 (d, 2H: NH_2-C_7H_4); 7.66 (s, 1H: NH); 7.70 (d, 2H: F-C_6H_4-SO_2); 7.75 (d, 2H: F-C_6H_4-SO_2).

Entry 14: 4-fluoro-N-(phenylsulfonyl)-benzenesulfonamide

No obtained.

Entry 15: 4-fluoro-N-(1H-tetraazol)-benzenesulfonamide

No obtained.

Entry 16: N-(4-fluoro-phenylsulfonyl)-nicotinamide

IR (KBr) υ cm^{-1}: 3245 (N-H), 1165 and 1086 (SO_2-N), 755 (S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.53 (d, 2H: F-C_6H_4-SO_2); 7.58 (m, 2H: F-C_6H_4-SO_2); 7.65 (t, 1H: CO-C_5H_4N); 7.87 (m, 3H: CO-C_5H_4N); 8.52 (s, 1H: NH).

Entry 17: 4-fluoro-N,N-diphenyl-benzenesulfonamide

IR (KBr) υ cm^{-1}: 1178 and 1062 (SO_2-N), 733 (S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.22-7.36 [m, 10H: NH-(C_6H_5)$_2$]; 7.47- 7.53 (m, 4H: F-C_6H_4-SO_2).

Entry 18: 1-(4-fluoro-phenylsulfonyl)-piperidine

IR (KBr) υ cm^{-1}: 2993 (C-H), 1167 (SO_2-N), 708 (S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.30 (m, 4H: $C_5H_{10}N$); 2.93 (m: 4H: $C_5H_{10}N$); 3.17 (d, 2H: $C_5H_{10}N$); 7.53 (d, 2H: F-C_6H_4-SO_2); 7.65 (d, 2H: F-C_6H_4-SO_2).

Entry 19: N-phenyl-biphenyl-4-sulfonamide

IR (KBr) υ cm^{-1}: 3260 (N-H), 1188 and 1067 (SO_2-N), 730

(S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.10-7.14 (m, 5H: C_6H_5-C_6H_4); 7.21-7.25 (m, 4H: C_6H_5-C_6H_4); 7.34 (m, 3H: NH-C_6H_5); 7.41 (d, 2H: NH-C_6H_5); 7.65 (s, 1H: NH).

Entry 20: N-(2-nitro-phenyl)-biphenyl-4-sulfonamide

IR (KBr) υ cm^{-1}: 3322 (N-H), 1159 and 1073 (SO_2-N), 762 (S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.12-7.15 (m, 5H: C_6H_5-C_6H_4); 7.44 (d, 2H: C_6H_5-C_6H_4); 7.51 (m, 2H: C_6H_5-C_6H_4); 7. 60 (d, 2H: NH-C_6H_4-NO_2); 7.65 (s, 1H: NH); 7.74 (d, 2H: NH-C_6H_4-NO_2).

Entry 21: N-(4-chloro-phenyl)-biphenyl-4-sulfonamide

IR (KBr) υ cm^{-1}: 3247 (N-H), 1329 and 1160 (SO_2-N), 905 (C-Cl), 724 (S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.11-7.14 (m, 5H: C_6H_5-C_6H_4); 7.21 (d, 2H: NH-C_6H_4-Cl); 7.31 (d, 2H: NH-C_6H_4-Cl); 7.48 (m, 2H: C_6H_5-C_6H_4); 7.61 (s, 1H: NH); 7.68 (d, 2H: C_6H_5-C_6H_4).

Entry 22: 1-(biphenyl-4-sulfonyl)piperidine

IR (KBr) υ cm^{-1}: 2953 (C-H), 1137 (SO_2-N), 767 (S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.36 (m, 4H: NC_5H_{10}), 2.92 (m: 4H: NC_5H_{10}), 3.19 (d, 2H: NC_5H_{10}); 7.08 (m, 3H: C_6H_5-C_6H_4); 7.14 (d, 2H: C_6H_5-C_6H_4); 7.36 (d, 2H: C_6H_5-C_6H_4); 7.40 (d, 2H: C_6H_5-C_6H_4).

Entry 23: N-(2-hidroxi-phenylcarbonyl)-biphenyl-4-sulfonamide

IR (KBr) υ cm^{-1}: 3490 (N-H), 3300 (OH), 1735 (C=O), 1377 and 1173 (SO_2-N), 692 (S-N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 5.34 (s, 1H: OH); 7.15 (d, 1H: C_6H_4-OH); 7.39 (t, 1H: C_6H_4-OH); 7.48 (m, 2H: C_6H_5-C_6H_4); 7.53 (m, 3H: C_6H_5-C_6H_4); 7.64 (s, 1H: NH); 7.78 (d, 2H: C_6H_4-OH); 7.85 (m, 4H: C_6H_5-C_6H_4).

Entry 24: N-(phenylsulfonyl)-biphenyl-4-sulfonamide

IR (KBr) υ cm^{-1}: 3215 (N-H), 1187 and 1083 (SO_2-N), 718 (S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.27-7.31 (m, 5H: C_6H_5-C_6H_4); 7.57-7.83 (m, 9H: C_6H_5-C_6H_4 and SO_2-C_6H_5); 7.92 (s, 1H: NH).

Entry 25: 4-nitro-N-(4-chloro-phenyl)-benzenesulfonamide

IR (KBr) υ cm^{-1}: 3253 (N-H), 1515 (NO_2), 1172 and 1092 (SO_2-N), 966 (C-Cl), 743 (S-N). ^{1}H-NMR (400 MHz, DMSO-d_6,) δ ppm: 7.52 (d, 2H: C_6H_4-Cl); 7.56 (d, 2H: C_6H_4-Cl); 7.68 (s, 1H: NH); 8.19 (d, 2H: NO_2-C_6H_4-SO_2); 8.21 (d, 2H: NO_2-C_6H_4-SO_2).

Entry 26: 4-nitro-N-(1H-benzimidazol-2-yl)-benzenesulfonamide

IR (KBr) υ cm^{-1}: 3449 (N-H), 3104 (C-H), 1562 (C=N), 1158 (SO_2-N), 671 (S-N). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.24 (s, 1H: NHC_7H_4); 7.50 (m, 4H: NHC_7H_4); 7.70 (d, 2H: F-C_6H_4-SO_2); 7.85 (d, 2H: F-C_6H_4-SO_2); 8.42 (s, 1H: NH).

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