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"MICROWAVE ASSISTED Mg(OTf)2.SiO2 CATALYSED SYNTHESIS OF SOME HETEROCYCLIC SULFONATE AND SULFONAMIDE BEARING QUINOLINE MOTIF"

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ABSTRACT

An efficient green route for the synthesis of quinoline sulfonates by reaction of 8-Quinoline sulfonyl chloride (QSC) with Phenol/Benzyl Alcohol/Alcohol while sulfonamides by reaction of Quinoline sulfonyl chloride (QSC) with Aniline/Benzylamine/Amines has been developed under microwave irradiation using $Mg(OTf)_2.SiO_2$ as a heterogeneous catalyst. Characterization of prepared molecules was carried out with the help of analytical techniques including MP, MS, ¹H-NMR etc.

KEYWORDS: Microwave, Quinoline, Sulfonamide, Sulfonates, Mg(OTf)₂.SiO₂

1. INTRODUCTION

Molecules containing sulfonamide distinctively heterocyclic moieties bearing sulfonyl derivatives such as sulfonamide (Sulfa drugs) have been greatly attracted by pharmacist or academic researchers due to their versatile biological applications. In last few decades most of the literature had open up with moieties, scaffolds or nuclei possessing small sulfonamides or sulfonamide functional groups. Particularly Quinoline nuclei possessing functional groups like sulfonamides exhibit their diversified therapeutic importance such as antibacterial^{[1],} anti-carbonic anhydrase^[III,V], diuretic^[V], hypoglycemic^{[VII}, anti-thyroid^[VII], Anticancer , leukemia, thyroid cancer^[VIII, VX], (**Figure-1**).

In the same way quinoline sulfonates are also important class of organic chemistry and as equally potent as Quinoline sulfonamides. Quinoline sulfonates itself as an active motif possessing variety of biological activities such as papillomavirus microbicidal^[X] anti-HIV-1^[XI], antineoplastic ^[XII] and anticancer activity ^[XIII, XIV]. In addition, various sulfonates derivatives of quinoline exhibit interesting pharmacological activities ^[XV].

By keeping these facts in mind, we focused on the synthesis of some quinoline- sulfonamides and quinoline- sulfonates derivatives by reacting quinoline sulfonyl chloride (3) with Phenol/Alcohol/Benzyl alcohol and Aniline/Amines/Benzylamine respectively to results moderate to good yields under microwave irradiation.

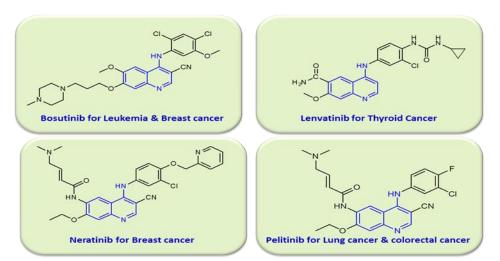
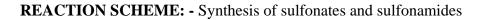
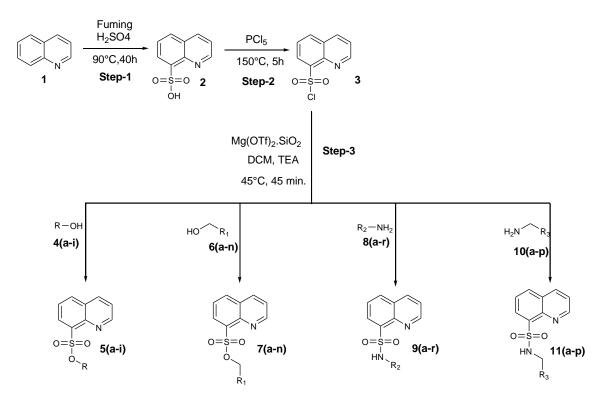
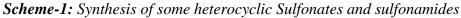
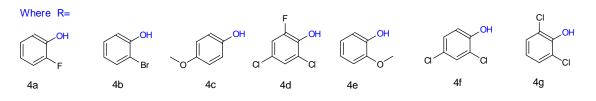


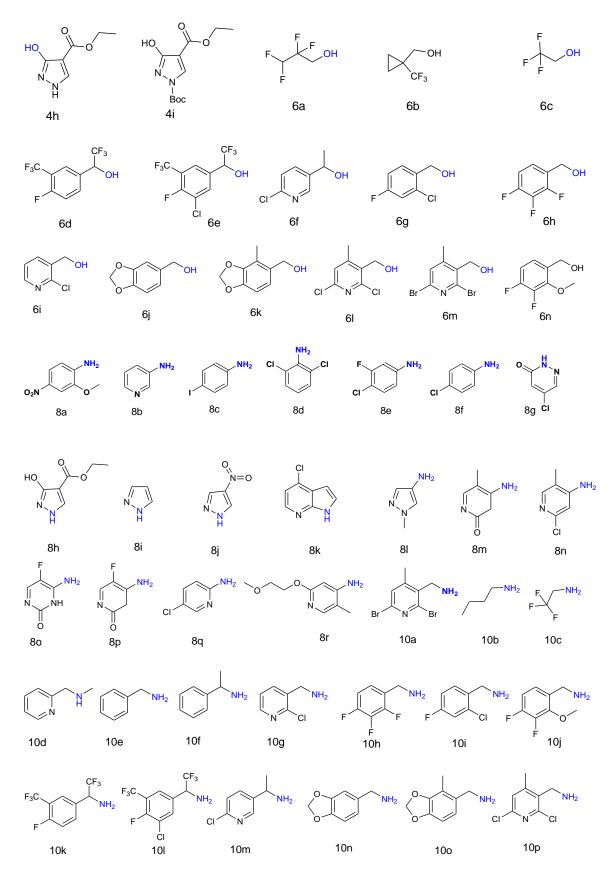
Figure-1: Structures of Organic molecules shows their application against cancer cell











2. **RESULTS AND DISCUSSION**

As a comprehensive attempt to synthesize QSC-Sulfonates, we had reported here a simplified process under microwave irradiation using $Mg(OTf)_2.SiO_2$ with efficient isolation techniques to obtain desired targets with moderate to good yield. Synthesis of substituted QSC-sulfonates from QSC (3), substituted R (Phenol/Benzyl alcohol/Alcohol), TEA and $Mg(OTf)_2.SiO_2$ in Dichloroethane as a solvent.

Initially QSC (3), 2-Fluoro Phenol, TEA and Mg(OTf)₂.SiO₂ were selected as reference substrates, for optimization of reaction condition. Different time, temperature and mole % of Mg(OTf)₂.SiO₂ were screened as described in **Table-1**. As a result of optimization studies it is observed that, less yield obtained in absence of Mg(OTf)₂.SiO₂ catalyst (**Entry-1, Table-1**). To determine the minimum requirement of catalyst for reaction, we screened mole percents of catalyst such as 20, 10, 5, 8 and 2 (**Entry-2-6, Table-1**) and observed that 5 mole % Mg(OTf)₂.SiO₂ is optimum requirement of reaction to get good result. During investigation of reaction time (**Entry-7-9, Table-1**); it is found that, 45 min. is sufficient time for completion of reaction. We also investigated reaction temperature (**Entry-10-12, Table-1**); and observed that at lower temperature yields are obtained less due to incomplete conversion of reaction while at higher temperature yield was comparatively low. The catalyst was recovered and recycled with standard optimized reaction condition using QSC (3), 2-Fluoro Phenol, TEA and Mg(OTf)₂.SiO₂ as a reference substrates summarized in **Table-3**. Comparative yields were obtained by using recycled catalyst up to three cycles (**Entries-1-3, Table-3**), while yield drop observed from next cycle i.e. from cycle 4 onwards.

To further extend the scope of Mg(OTf)₂.SiO₂ catalyst, a range of QSC- sulfonates and QSCsulfonamides were prepared under the optimized reaction conditions by changing the substrate from simple aryl group to substituted Phenol, Benzyl alcohol, Alcohol, Aniline, Amines, and Benzylamine. The detailed results were summarized in **Table -2**.

Entry	Mg(OTf) ₂ .SiO ₂ (Mole %)	Time (min.)	Temperature °C	Yield (%)
1.	-	480	45	38
2.	20	45	45	80
3.	10	45	45	86
4.	5.0	45	45	93
5.	8.0	45	45	93
6.	2.0	45	45	84
7.	5.0	45	45	93
8.	5.0	30	45	62

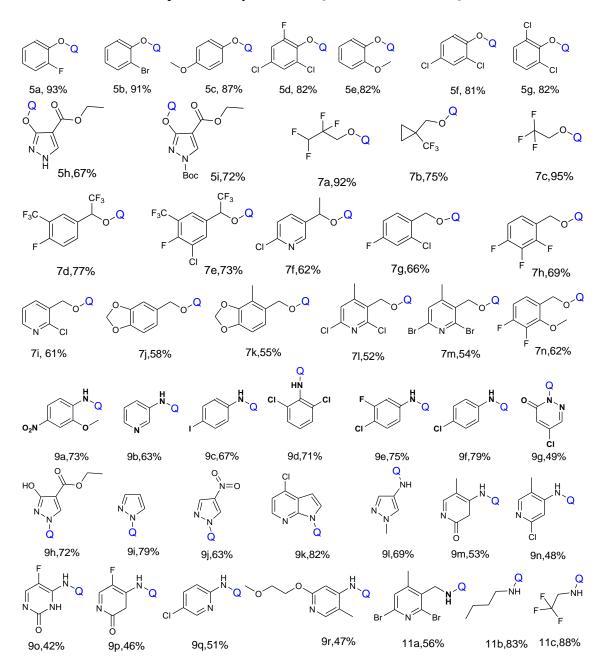
Table-1: Optimization of reaction conditions for the synthesis of QSC-Sulfonates.

9.	5.0	90	45	55
10.	5.0	45	60	91
11.	5.0	45	90	85
12.	5.0	45	30	82

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* Reaction conditions: 3 (1.0), R-OH (1.0), TEA (2.0), Mg(OTf)₂.SiO₂ (5.0 mole %) and solvent EDC (5.0 rel vol.) was maintained at 45°C for 45.0 min under Microwave irradiation.

Table-2: Substitution pattern of Synthesized QSC-Sulfonates and QSC- Sulfonamides



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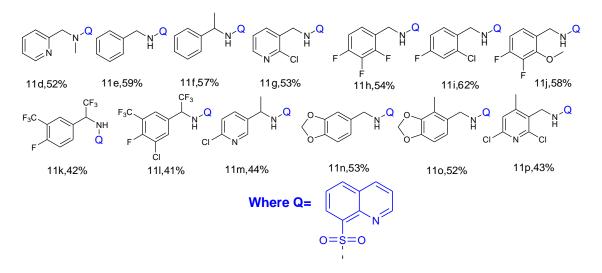


 Table-3 Recycle study of catalyst recovered from spent

Entry	Mg(OTf) ₂ .SiO ₂ (5.0 Mole %)	Time (min.)	Temperature °C	Yield (%)
1	Cycle-1	45	45	91
2	Cycle-2	45	45	91
3	Cycle-3	45	45	91
4	Cycle-4	45	45	87
5	Cycle-5	45	45	79

3. EXPERIMENTAL SECTION

All Solvents, chemicals and reagents were purchased from resources like Sigma-Aldrich, finar and Spectrochem etc utilized as such from the suppliers. Wherever necessary, anhydrous solvents were used. Thin layer chromatography (TLC) analysis was done by utilizing Merk silica gel 60 F254 aluminum plates and visualized under UV light. Melting points were obtained by using (SMP 30) apparatus. The ¹H-NMR spectra were recorded using CDCl₃ or DMSO-d₆ as a solvent on Bruker 300 MHz instrument using TMS as the internal standard. Isolated compounds are purified using re-crystallization technique. Synthesized products were reported and identified by melting points, MASS and 1H-NMR values with reported values.

3.1 Preparation of silica supported magnesium trifluoromethanesulfonate.

The silica supported magnesium trifluoromethanesulfonate was prepared by mixing Silica gel (45.0 g, Merck grade (60-120 and 100–200 mesh) with a solution of magnesium trifluoromethanesulfonate (5.0 g) in distilled water (30mL). The resulting mixture was stirred for 60 min to for absorption of magnesium trifluoromethanesulfonate on the surface of silica gel. After complete absorption, water removed by vacuum distillation on rotary evaporator. The isolated solid powder was dried at 120°C for 5 h under reduced vacuum.

3.2 General procedure for the preparation of 8-Quinoline Sulfonic Acid (2) ^[XVI, XVII].

The titled compound prepared as per reported literature process [16, 17]. 8-Quinoline Sulfonic Acid: To a ice cooled Fuming Sulfuric Acid (30%, 123 ml, 2.08 rel vol), Quinoline (59.0 ml) was slowly added dropwise below 90°C (addition exothermic). The resulting reaction mass was heated at 90°C and maintained for 40 hours, Reaction progress monitored by TLC (Visualized under UV light). After completion of reaction, Reaction mass cooled to room temperature and poured onto crushed ice 500 g. White solid precipitated out under stirring was filtered out under vacuum , washed with plenty of water and dried under vacuum at 60°C to obtain 67.0 g pure white colored solid (Yield-54%) .The colorless prisms which crystallized out on cooling were filtered, washed with water, and dried; yield 67 g. (54%) of the practically pure 8-sulfonic acid. The synthesized product confirmed by Melting point (summarized in Table-2) and ¹H-NMR data with reference standards. ¹H NMR (400 MHz, CDCl3) δ : 15.46 (s, 1H), 9.85-9.88(d, 1H), 9.33-9.35(d, 1H), 8.42-8.45(d, 1H), 8.20-8.26(m, 2H), 8.08-8.19(m, 1H).

3.3 General procedure for the preparation of 8-Quinoline Sulfonyl Chloride (QSC) (3)^[XVIII, XIX, XX].

Different methodologies were utilized for the synthesis of 8-Quinoline Sulfonyl Chloride and compound verified with melting point and ¹H-NMR.

Method-A: The titled compound prepared as per reported literature $process^{[XVIII]}$ using PCl₅: A Mixture of Quinoline-8-sulphonic acid (2) (40 g, 1.0 eq.) and phosphorus pentachloride (50 g, 1.1 eq.) were heated at 145-150°C and maintained for 5 h. The progress of the reaction monitored on TLC. After completion of reaction, reaction mass cooled and poured onto crushed ice (200 g, 5.0 rel wt.), under vigorous stirring. The yellow precipitate was filtered off, sucked well and dried to obtain QSC (3) (47.2 g), m.p. 124-126°C (Reported- 122°C).

Method-B: Alternative process for the synthesis of 8-Quinoline Sulfonyl Chloride as per reported literature process^[XIX] using Thionyl chloride: To a stirred solution of Quinoline sulfonic acid (10.0 g, 47.8 mmol), in thionyl chloride (40ml, 4.0 rel vol), 1ml DMF added dropwise, then reaction mass warm up to 85°C and maintained for completion 3 hours. Progress of the reaction monitored by TLC (Visualized under UV light 254nm). After completion of reaction, Reaction mass cooled to room temperature, added Dichloromethane, stirred for 30 min, layers were separated. MDC layer concentrated under vacuum to get residue. This residue was crystallized using Ethyl acetate to obtain QSC (3) 9.0 g white solid yield: 84.3%, m.p. 123-124°C (Reported-122°C).

Method-C: Alternative process for the synthesis of 8-Quinoline Sulfonyl Chloride as per reported literature process ^[XX] from Quinoline: - 7.0 g quinoline was slowly added to a precooled chlorosulphonic acid (25 ml, 3.57 rel vol) in 1-2h duration (Addition exothermic). The reaction mass heated to 140°C and maintained for a further 40 hr. after completion of reaction (reaction progress checked on TLC), reaction mass cooled to ambient temperature. The reaction mixture was then poured onto crushed ice (150 g) under vigorous stirring. The resulting reaction mass extracted with Methyl tert. butyl ether. The MTBE layer decolorized with activated carbon treatment and evaporated to get thick slurry. This slurry diluted with n-Heptane, stirred and filtered out. The white crystalline QSC was dried under vacuum to obtain QSC (3) 3.0 g yield (24%), m.p. 125-126°C (Reported- 122°C), ¹H NMR (400 MHz, CDCl3) δ : 9.26-9.28(dd, 1H), 8.56-8.59(dd, 1H), 8.34-8.37(dd, 1H), 8.24-8.27(dd, 1H), 7.65-7.76(m, 2H).

3.4 General procedure for the synthesis of sulfonates derivatives of QSC (3) (5a-i) and (7a-n)

A solution of QSC (3) (1.0 eq.), Substituted Phenol/Benzyl alcohol/Alcohol (1.0eq), Mg(OTf)₂.SiO₂ (5.0 mole%) and triethylamine (2.0eq) in Dichloroethane (EDC) (5.0 rel. vol) was irradiated under microwave at 45°C for 45 min. Progression of reaction monitored on TLC. After completion of reaction, the resulting mass was cooled to ambient temperature, and diluted

with EDC. The heterogeneous solid catalyst was removed by filtration, washed with plenty of EDC. Then the filtrate was concentrated under vacuum to obtain crude product. The isolated crude product was re-crystallized from ethanol to afford a pure solid of substituted QSC-sulfonates in moderate to good yields. The physical and spectroscopic data of compounds (5a-i) and (7a-n) are given below.

Spectral data of some synthesized sulfonates:

2-fluorophenyl quinoline-8-sulfonate (5a): Yield-93%, [M+H] =304, ¹H NMR (400 MHz, CDCl3) δ: 9.11-9.12(d, 1H), 8.43-8.66(d, 3H), 7.68-7.86(m, 3H), 7.21-7.34(m, 2H), 6.96-6.98(d, 1H).

4-methoxyphenyl quinoline-8-sulfonate (5c): Yield-91%, [M+H] =316, ¹H NMR (400 MHz, CDCl3) δ: 9.23(d, 1H), 8.30-8.65(d, 3H), 7.72-7.84(m, 2H), 7.69-7.87(d, 4H), 3.66(s, 3H).

2,4-dichloro-6-fluorophenyl quinoline-8-sulfonate (5d): Yield-82%, ¹H NMR (400 MHz, CDCl3) δ: 9.14-9.16(d, 1H), 8.45(d, 1H), 8.31-8.35(d, 1H), 8.17-8.20(d, 1H), 7.61-7.71(m, 2H), 7.21-7.22(d, 1H), 7.04-7.08(d, 1H).

2,4-dichlorophenyl quinoline-8-sulfonate (5f): Yield-81%, [M+H] =353,355, ¹H NMR (400 MHz, CDCl3) δ: 9.10-9.12(d, 1H), 8.44-8.66(d, 3H), 7.75-7.86(m, 3H), 7.41-7.43(d, 1H), 7.11-7.14(d, 1H).

Ethyl 4-(quinolin-8-ylsulfonyloxy)-1H-pyrazole-3-carboxylate (5h): Yield-67%, [M+H]=348, ¹H NMR (400 MHz, CDCl3) δ: 11.64 (s, 1H), 9.32-9.40(d, 1H), 8.56-8.72(dd, 2H), 8.34-8.37(d, 1H), 8.24-8.27(d, 1H), 7.65-7.76(dd, 2H), 4.16-4.23(q, 2H), 1.22-1.27(t, 3H). **1-tert-butyl 3-ethyl 4-(quinolin-8-ylsulfonyloxy)-1H-pyrazole-1,3-dicarboxylate (5i):** Yield-72%, [M+H]=448,348, ¹H NMR (400 MHz, CDCl3) δ: 9.14-9.16(dd, 1H), 8.56-8.59(dd, 1H), 8.49(s,1H), 8.28-8.31(dd, 1H), 8.16-8.20(dd,1H), 7.67-7.72(t, 1H), 7.57-7.61(dd, 1H), 4.11-4.18(q, 2H), 1.58-1.63(s, 9H), 1.30-1.34(t, 3H).

1,1,2,2-tetrafluoroethyl quinoline-8-sulfonate (7a): Yield-92%, [M+H]=324, ¹H NMR (400 MHz, CDCl3) δ: 9.14-9.16(d, 1H), 8.46-8.65(d, 3H), 7.77-7.87(m, 2H), 6.40-6.78(m, 1H).

(1-(trifluoromethyl)cyclopropyl)methyl quinoline-8-sulfonate (7b): Yield-75%, [M+H]=332.

2,2,2-trifluoroethyl quinoline-8-sulfonate (7c): Yield-95%, [M+H]=292, ¹H NMR (400 MHz, CDCl3) & 9.11(d, 1H), 8.56-8.59(d, 1H), 8.34-8.31(d, 1H), 8.17-8.20(d, 1H), 7.60-7.74(m, 2H), 5.01-5.09(q, 2H).

2,2,2-trifluoro-1-(4-fluoro-3-(trifluoromethyl)phenyl)ethyl quinoline-8-sulfonate (7d): Yield-77%, [M+H]=454, ¹H NMR (400 MHz, CDCl3) δ : 9.32-9.40(dd, 2H), 8.44-8.47(d, 2H), 8.19-8.21(d, 1H), 7.98-8.03(d, 1H), 7.15-7.17(m, 3H), 7.07(s, 1H).

1-(3-chloro-4-fluoro-5-(trifluoromethyl)phenyl)-2,2,2-trifluoroethyl quinoline-8sulfonate (7e): Yield-77%, [M+H]=488, ¹H NMR (400 MHz, CDCl3) δ: 9.99(d, 2H), 8.99(d, 1H), 8.23-8.43(dd, 2H), 7.99-8.01(d, 1H), 7.45-7.60(m, 2H).

1-(6-chloropyridin-3-yl)ethyl quinoline-8-sulfonate (7f): Yield-62%, [M+H]=488, ¹H NMR (400 MHz, CDCl3) δ: 8.97(d, 1H), 8.21-8.49(m, 3H), 7.95-7.97(d, 1H), 7.51-7.78(m, 4H), 3.35-3.38(q, 1H), 3.22-3.29(d, 3H).

3.5 General procedure for the synthesis of sulfonamide derivatives of QSC (3) (9a-r) and (11a-p)

A solution of QSC (3) (1.0 eq.), Substituted Aniline/Benzylamine/Amines (1.0eq), $Mg(OTf)_2.SiO_2$ (5.0 mole%) and triethylamine (2.0eq) in Dichloroethane was irradiated under microwave at 45°C for 30-45 min. Progression of reaction monitored on TLC. After completion of reaction, the resulting mass was cooled to ambient temperature, and diluted with EDC. The heterogeneous solid catalyst was removed by filtration, washed with plenty of EDC. Then the

filtrate was concentrated under vacuum to obtain crude product. The isolated crude product was re-crystallized from ethanol to afford a pure solid of substituted QSC-sulfonamides in moderate to good yields. The physical and spectroscopic data of compounds (9a-r) and (11a-p) are given below.

Spectral data of some synthesized sulfonamides:

N-(2-methoxy-4-nitrophenyl)quinoline-8-sulfonamide (9a): Yield-73%, [M+H]=361.

N-(pyridin-3-yl)quinoline-8-sulfonamide (9b): Yield-63%, [M+H]=286, ¹H NMR (400 MHz, CDCl₃) δ : 10.41(s, 1H), 9.13(s, 1H), 8.09-8.54(d, 5H), 7.72(d, 2H), 7.45-7.47(d, 1H) 7.15(d, 1H).

N-(4-iodophenyl)quinoline-8-sulfonamide (**9c):** Yield-67%, [M+H]=411, ¹H NMR (400 MHz, CDCl₃) δ: 10.30(s, 1H), 9.11-9.13(d, 1H), 8.27-8.54(dd, 3H), 7.70-7.75(m, 2H), 7.41-7.44(d, 2H) 6.87-6.89(d, 2H).

N-(2,6-dichlorophenyl)quinoline-8-sulfonamide (**9d**): Yield-71%, [M+H]=354,356, ¹H NMR (400 MHz, CDCl₃) δ: 10.11(s, 1H), 9.30-9.39(dd, 2H), 8.43-8.46(d, 2H), 8.15-8.18(t, 1H), 7.97-7.99(t, 1H), 7.71-7.76(m, 1H), 7.41-7.44(m, 1H), 7.29-7.32(m, 1H).

N-(4-chloro-3-fluorophenyl)quinoline-8-sulfonamide (9e): Yield-75%, ¹H NMR (400 MHz, CDCl₃) δ: 10.15(s, 1H), 9.33-9.40(dd, 2H), 8.44-8.47(d, 2H), 8.17-8.22(d, 1H), 7.98-8.03(d, 1H), 7.10-7.16(t, 1H), 6.38-6.50(m, 2H).

N-(4-chlorophenyl)quinoline-8-sulfonamide (**9f**): Yield-79%, [M+H]=319, ¹H NMR (400 MHz, CDCl₃) δ: 10.30(s, 1H), 9.12-9.14(d, 1H), 8.27-8.54(dd, 3H), 7.69-7.75(dd, 2H), 7.04-7.17(dd, 4H).

5-chloro-2-(quinolin-8-ylsulfonyl)pyridazin-3(2H)-one (9g): Yield-49%, [M+H]=319, ¹H NMR (400 MHz, CDCl₃) δ: 8.55-8.59(d, 1H), 8.30-8.33(dd, 2H), 7.99-8.00(d, 1H), 7.71-7.79(m, 2H), 7.15-7.19(dd, 2H).

Ethyl 3-hydroxy-1-(quinolin-8-ylsulfonyl)-1H-pyrazole-4-carboxylate (9h): Yield-72%, [M+H] = 348, ¹H NMR (400 MHz, CDCl₃) δ : 11.05-11.06(s, 1H), 9.03-9.05(d, 1H), 8.39-8.47(d, 1H), 8.11-8.14(dd, 1H), 7.80-7.84(d, 1H), 7.47-87.51(d, 1H), 7.01-7.30(m, 2H), 4.13-4.20(q, 2H), 1.25-1.29(t, 3H).

8-(1H-pyrazol-1-ylsulfonyl)quinoline (9i): Yield-79%, ¹H NMR (400 MHz, CDCl₃) δ: 9.32-9.40(dd, 2H), 8.44-8.47(d, 2H), 8.19-8.21(m, 1H), 8.17(m, 1H), 7.98-8.03(m, 2H), 7.15-7.17(m, 1H).

8-(4-nitro-1H-pyrazol-1-ylsulfonyl)quinoline (9j): Yield-63%, ¹H NMR (400 MHz, CDCl₃) δ: 9.32-9.40(dd, 2H), 8.44-8.47(d, 2H), 8.19-8.21(m, 1H), 8.17(m, 1H), 7.98-8.03(m, 1H), 7.15-7.17(m, 1H).

N-butylquinoline-8-sulfonamide (11b): Yield-83%, ¹H NMR (400 MHz, CDCl₃) δ: 9.08(d, 1H), 8.55-8.59(d, 1H), 8.30-8.32(dd, 2H), 7.71-7.79(dd, 2H), 7.15-7.19(t, 1H), 2.74-2.81(t, 2H), 1.08-1.29(m, 4H), 0.64-0.69(t, 3H).

N-methyl-N-(pyridin-2-ylmethyl)quinoline-8-sulfonamide (11d): Yield-52%, ¹H NMR (400 MHz, CDCl₃) δ: 9.06-9.08(d, 1H), 8.99-9.01(d, 1H), 8.56-8.58(d, 2H), 7.99-8.02(m, 3H), 7.71-7.80(m, 2H), 7.04(s, 1H), 2.41(s, 3H), 2.35(s, 2H).

N-benzylquinoline-8-sulfonamide (**11e**): Yield-59%, ¹H NMR (400 MHz, CDCl₃) δ: 9.06-9.08(d, 1H), 8.93-8.95(s, 1H), 8.41-8.44(d, 1H), 8.23-8.26(d, 1H), 8.01-8.05(d, 1H), 7.62-7.65(dd, 1H), 7.50-7.60(dd, 1H), 7.06-7.11(m, 5H), 4.10(d, 2H).

3.6 Recovery of Catalyst

The separated catalyst after reaction completion was washed with plenty of ethyl acetate, dried under vacuum tray dryer at 120°C for 5 h and reused for next reaction cycle under optimized reaction conditions (**Table-1, Entry-7**).

4. CONCLUSION

An efficient, mild, and green methodology has been developed for the synthesis of substituted sulfonamides and sulfonates bearing quinoline nuclei under microwave irradiation .using Mg(OTf)₂.SiO₂ the heterogeneous catalyst. The catalyst could be reused after a simple work-up and used several times without noticeable reduction in the catalytic activity. Moderate to good yields, relatively short reaction times, simple operation and easy work-up are some advantages of this protocol. This improved reaction condition allows the preparation of a wide variety of substituted sulfonamides and sulfonates in moderate to good yields and excellent purity under mild reaction conditions. We believe the applicability of Mg(OTf)₂.SiO₂ with the mentioned advantages makes our method superior among other reported methods to synthesize substituted sulfonamides and sulfonates.

5. ACKNOWLEDGEMENT

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