"ULTRASOUND ASSISTED CE(OTF)$_3$.SIO$_2$ CATALYZED SYNTHESIS OF SULFONAMIDE LINKED UP WITH QUINOLINE NUCLEI."

Mahesh More[1], Anil Solunke[2], Sandip Agare[3], Tanuja Kadre[4*]

ABSTRACT

Quinoline, aryl-3,4-dihydropyrimidin-2(1*H*)-one (DHPMs) and 2-substituted quinazolin-4(3*H*)-ones, cephalosporin and 4-chloro-7-azaindole are of the most sought heterocycles for the development of new drug candidates. These rings can be traced in a number of well established, commercially available drugs. Wide array of pharmacological applications exhibited by these derivatives have made them obligatory anchors for the development of novel therapeutic agents. The current article herein highlights the synthesis of some miscellaneous quinoline derivatives with 2-substituted quinazolin-4(3*H*)-ones, aryl-3,4-dihydropyrimidin-2(1*H*)-one (DHPMs), cephalosporin and 4-chloro-7-azaindole linked-up with sulfonyl bridge. A series of diversified quinoline sulfonyl chloride devatives i.e. quinoline sulfonamides with 2-substituted quinazolin-4(3*H*)-ones, aryl-3,4-dihydropyrimidin-2(1*H*)-one (DHPMs), cephalosporin and 4-chloro-7-azaindole are synthesized and characterized using physical as well as spectroscopic techniques.

Keywords: Quinoline sulfonamide, Aryl-3, 4-dihydropyrimidin-2(1H)-one, 2-Substituted Quinazolin-4(3H)-ones, Sulfonamides, Cephalosporin

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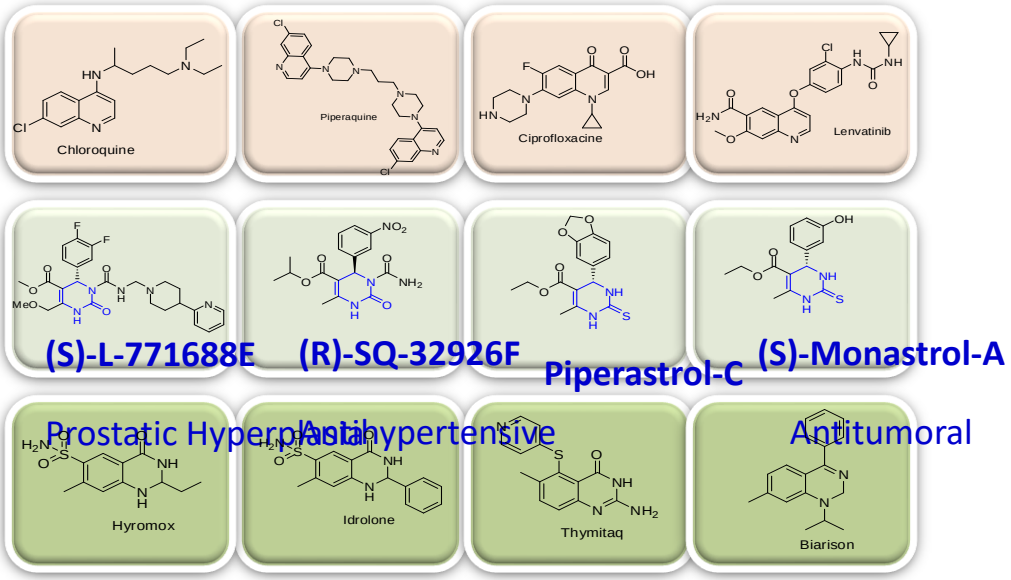
1. INTRODUCTION

Ultrasound synthesis is a most useful method which is being used in green chemistry approach to accelerate rate of organic reactions. Ultrasound is useful techniques over conventional methods which offer excellent yields, lesser reaction time, high selectivity and minimal side product formation and simple purification procedures. Sulfonamides are important functional group and present in a number of drug molecules, acknowledged as sulfa drugs. Any compound bearing -SO2NHR group in their structure is referred to as sulfonamide. Sulfonamides have gained a great deal of consideration due to their assorted biological behavior in pharmaceutical as well as in agricultural areas. Sulfonamide is used extensively to enhance the activity of organic compounds during development.

Quinoline, 3,4-dihydropyrimidin-2(1*H*)-one (3, 4-DHPMs) and 2-substituted quinazolin-4(3*H*)-ones are most important N-heterocyclic motifs. These nuclei's are extensively present in numerous natural products and shows their therapeutic applications against variety of diseases. Quinoline shows biological activities such as antimalarial (quinine, quinidine, chloroquine, mefloquine, amodiaquine etc), antibacterial (fluoroquinolones such as ciprofloxacin, sparfloxacin), antifungal-antiprotozoal (Clioquinol), anthelmintic (oxamniquine), local anesthetic (dibucaine), antiasthmatic (montelukast), anticancer (camptothecin, irinotecan, topotecan), antipsychotic (Aripiprazole, brexpiprazole), antiglaucoma (carti-olol) and cardiotonic (vesnarinone) [1-3].
Quinazolinones shows wide range of their antibacterial, antifungal (4-9), anti-inflammatory (10, 11), antimalarial (12), anti-HIV (13), antiviral (13, 14), antituberculosis (4, 15).

Molecules containing3,4-DHPMs shows their biological importance in pharmaceuticals are as such antiviral, antibacterial, antihypertensive, antitumor, antimalarial, anticancer, antimicrobial activities [16], [17], [18] etc. Some of marketed drug containing these motif are represented in

following figure-1.



Graphical Abstract: Figure-1: Marketed Drug containing sulfonamide group with DHPMs, Quinazolinones and Quinoline motif

2. RESULTS AND DISCUSSION

Quinoline sulfonyl chloride (QSC) (2) (21.96 mmol) was reacted with equimolar amines such as (3,4-DHPMs) (21.96 mmol) (3a-i) or substituted cephalosporin (21.96 mmol) (5a-d) or 2-substituted quinazolin-4(3*H*)-ones (21.96 mmol) (7a-k) or 4-chloro-7-azaindole (21.96 mmol) or ammonia (21.96 mmol) or methylamine (21.96 mmol) or hydrazine hydrate (21.96 mmol), in dry THF in the presence of triethylamine (43.92 mmol) as a base and 5 mole% Ce(OTf)3.SiO2 as a catalyst under ultrasound irradiation at 55°C for 45 min. to obtain corresponding sulfonamides (4a-i) or (6a-d) or (8a-k) or (9) or (10) or (11) or (12) respectively (Scheme 1).
The progress of the reaction was monitored by TLC using Dichloromethane: MeOH (8:2) as a mobile phase. After completion of reaction catalyst was filtered out and solvent from ML was removed under vacuum to obtain the crude product. The

resulting crude products were purified by Ethanol re-crystallization method.

For reaction optimization purpose QSC (2) and 4-chloro-7-azaindole used as a standard substrate along with TEA and Ce(OTf)$_3$.SiO$_2$ as a catalyst in THF (5.0 rel vol). **Table-1, Entry-1** represents lower yield in absence of catalyst. Entry 2-12 indicates requirement of mole % of catalyst, time and temperature respectively. Out of which **(Entry-10, Table-1)** observed as an excellent reaction condition with respect to yield, time and temperature.

After concluding reaction condition, selected amine substrates were evaluated by optimized reaction condition to obtain desired sulfonamides are summarized in **Table 2.** The catalyst was recovered and recycled with standard optimized reaction condition using QSC (2) and 4-chloro-7-azaindole along with TEA and catalyst in THF (5.0 rel vol) used as a reference substrates described in Table-3. Entry-1-3 in Table-3, offered comparative yield while it decreases from next cycle i.e. from cycle 4 and 5.

Scheme-1: Ultrasound assisted Ce(OTf)$_3$.SiO$_2$ catalyzed synthesis of sulfonamides

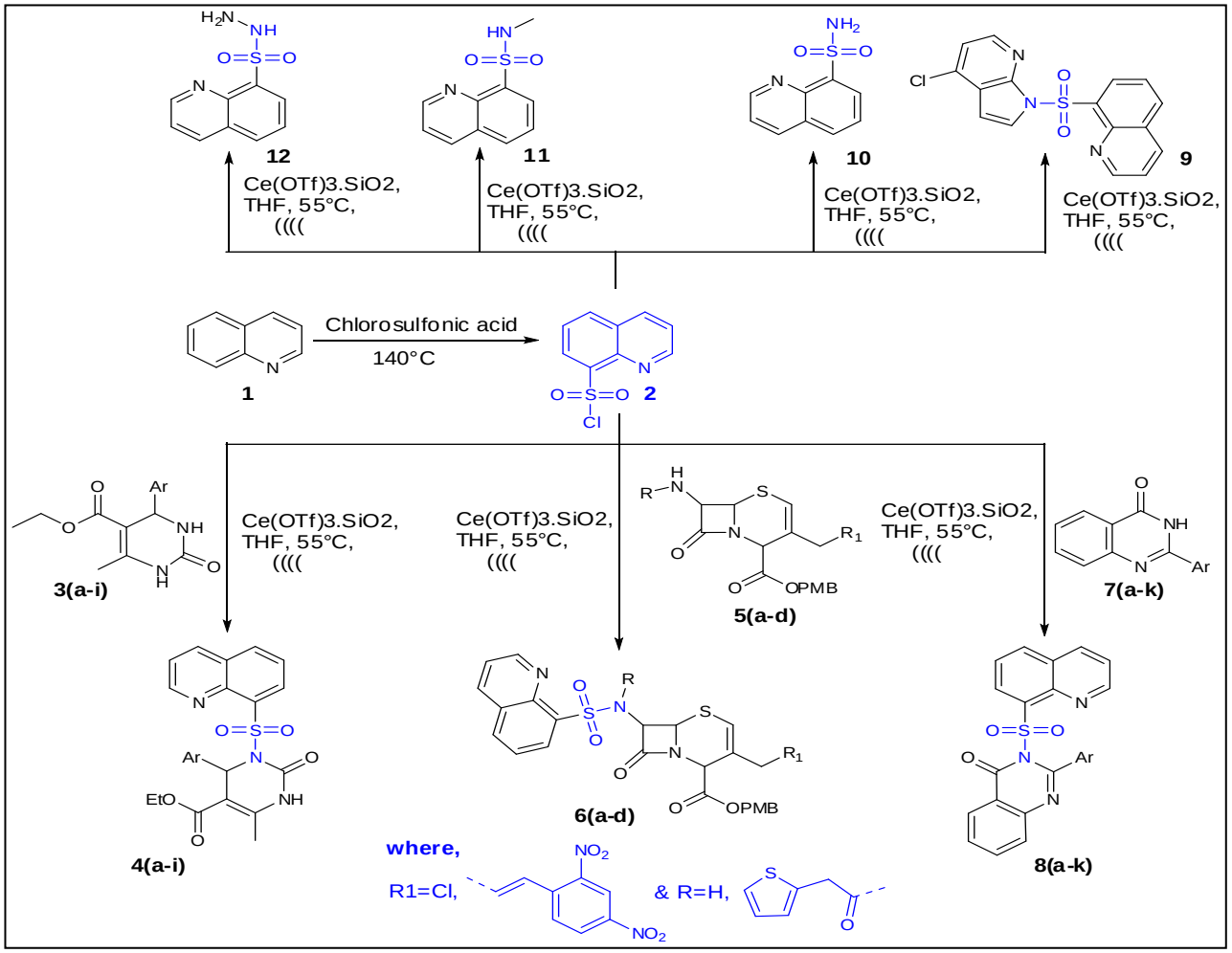


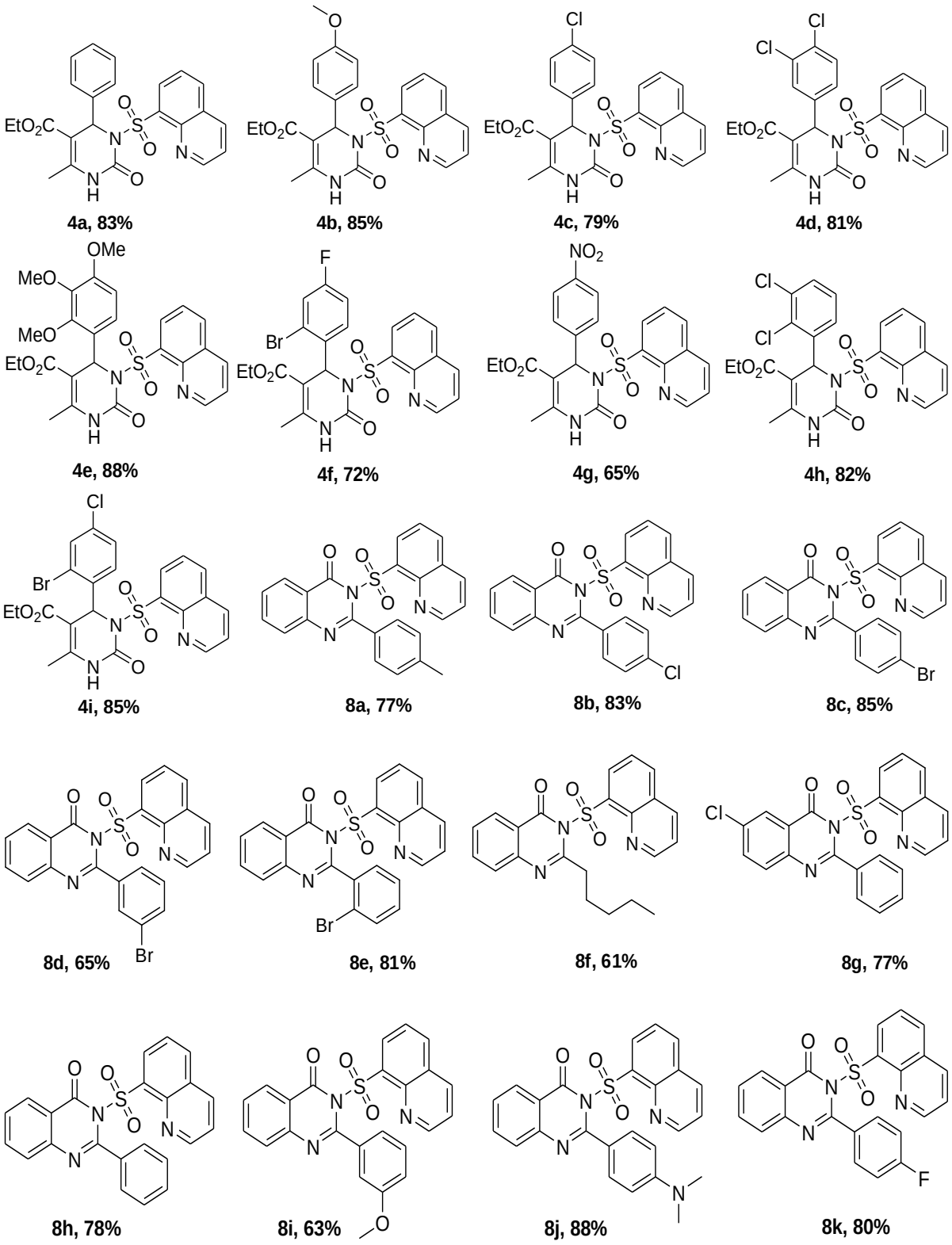
Table-1: Optimization of reaction conditions for the synthesis of Sulfonamide

Entry	Ce(OTf)$_3$.SiO$_2$ (Mole %)	Time (min.)	Temperature °C	Yield (%)
1.	-	120	55	38
2.	20	120	55	70
3.	15	120	55	73
4.	10	120	55	67
5.	5	120	55	59
6.	2	120	55	64
7.	5	90	55	79
8.	5	60	55	72
9.	5	30	55	75
10.	**5**	**45**	**55**	**90**

11.	5	45	70	67
12.	5	45	100	57

* **Reaction conditions:** QSC (21.96 mmol), Amine (21.96 mmol), TEA (43.92 mmol), catalyst (1.09 mmol, 5 mol %), was maintained at 55°C for 45 min., in THF as a solvent (5.0 rel vol) under ultrasound irradiation.

Table-2 Exploration of reaction conditions on a selected amine substrates to afford products.



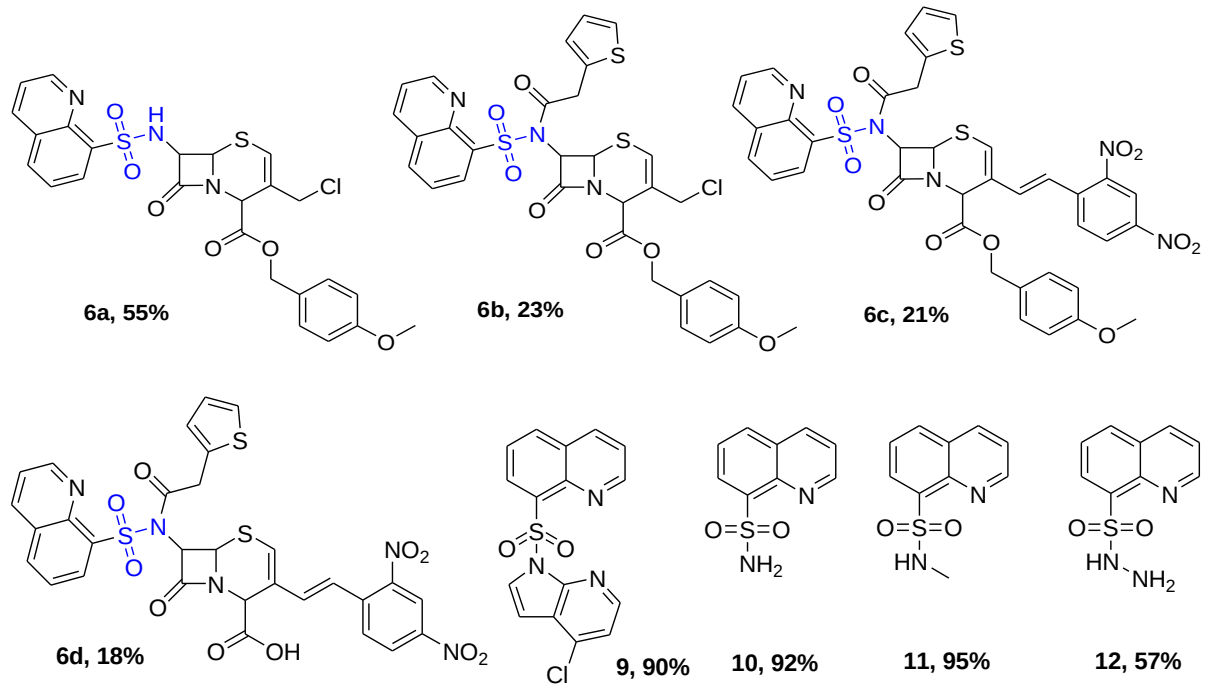


Table-3 Recycle of catalyst recovered from spent

Entry	Ce(OTf)$_3$.SiO$_2$ (cycles)	Time (min.)	Temperature °C	Yield (%)
1	Cycle-1	45	55	88
2	Cycle-2	45	55	88
3	Cycle-3	45	55	87
4	Cycle-4	45	55	83
5	Cycle-5	45	55	77

3. EXPERIMENTAL SECTION

All chemicals and reagents were purchased from commercial resources like Avra, Spectrochem and finar etc and utilized directly without purification. Reaction progress was monitored on TLC plate of silica-gel and visualized under UV light. Melting points were obtained by using Lab-India MR. Vis+ apparatus. The ^{1}H-NMR spectra were determined using 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 comparing with melting points and 1H-NMR values with reported values.

3.1Preparation of silica supported Cerium Trifluoromethanesulfonate.

The silica supported Ceriumtrifluoromethan-esulfonate was prepared by mixing Silica gel (45.0 g, Merck grade 60, 100–200 mesh) with a solution of Cerium trifluoromethanesulfonate (5.0 g) in distilled water (30mL). The resulting mixture was stirred for 60 min to for absorption of Cerium 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.

3.2General procedure for the preparation of Quinoline sulfonyl chloride (QSC) (2)

Synthesis of 8-Quinoline Sulfonyl Chloride as per reported literature process [19] from Quinoline: - 50.0 g quinoline was slowly added to a pre-cooled chlorosulphonic acid (637.2 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 (1071 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) 21.4 g yield (24%), m.p.126°C (Reported- 122°C). ^{1}H-NMR (CDCl3,

300 MHz):d (ppm): 9.26-9.28 (s,1H), 8.56-8.59 (dd,1H), 8.34-8.37 (dd,1H), 8.24-8.27 (dd,1H), 7.65-7.26 (m, 2H).

3.3General procedure for the preparation of 3,4-DHPMs (3a-i) [20]

A mixture of benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), and urea (3 mmol) was heated at 100-105 °C. After some time (~1h) product started to precipitate out and after complete precipitation (reaction progress monitored on TLC) the resulting solid was diluted with cold water, filtered under vacuum and dried at 45°C under vacuum to give the crude product which was purified by Ethanol re-crystallization method to obtain pure product **(3a).** (Yield-92%), Mp: 204–207 °C; MS: 261 (M+H); ^{1}H-NMR (DMSO-d6, 300 MHz):d (ppm): 10.33 (s, 1H, NH), 9.65-9.66 (s, 1H, NH), 7.22-7.35 (m, 5H, Ar-H), 5.16-5.18 (s, 1H, CH), 3.97-4.04 (q, 2H, OCH_2CH_3), 2.29 (s, 3H, CH_3), 1.08-1.12 (t, 3H, OCH_2CH_3).

Above procedure is followed for the preparation of all remaining desired 3,4-DHPMs **(3b-i)**. All the products are reported earlier and are identified by comparison of their Melting Point and 1H-NMR, spectral data with those reported.

3.4General procedure for the preparation of Quinazolin-4(3*H*)-ones (7a-k) [21]

Benzaldehyde (1.0eq) reacted with 2-Aminobenzamide (1.0eq) in dimethyl carbonate at reflux in presence of 5 mol% of CeCl3 under air for 8 h to obtain 2-substituted quinazolinones **(7a)** in good yields. (Yield-92%), Mp: 223–225 °C; 1H-NMR (300 MHz, CDCl3): δ 7.53 (t, 2H, J= 7.1 Hz), 7.72-7.87 (m, 5H), 8.10-8.16 (m, 2H), 12.58 (s, 1H).

Above procedure is followed for the preparation of all remaining desired Quinazolin-4(3H)-ones **(7b-k).**

All the products are reported earlier and are identified by comparison of their Melting Point and 1H-NMR, spectral data with those reported.

3.5General procedure for the preparation of substituted cephalosporin (6a-d) [22]

Cephalosporin intermediates or substituted cephalosporin i.e. 5(a-d) was prepared as per reported procedures of literature [22] and used for the preparation of corresponding sulfonamides. All the substituted cephalosporin intermediates are reported earlier and are identified by comparison of their 1H-NMR spectral data with those reported.

3.6General procedure for the preparation of Sulfonamides of 3,4-DHPMs- (4a-i)

Quinoline sulfonyl chloride (QSC) (2) (21.96 mmol) was reacted with 5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (21.96 mmol) in dry THF in the presence of triethylamine (43.92 mmol) as a base and 5 mole% $Ce(OTf)_3.SiO_2$ as a catalyst under ultrasound irradiation at 55°C for 2h. The progress of the reaction was monitored by TLC using Dichloromethane: MeOH (8:2) as a mobile phase. After completion of reaction catalyst was filtered out and solvent from ML was removed under vacuum to obtain the crude product. The resulting crude products were purified by Ethanol re-crystallization method,

to obtain corresponding sulfonamides **(4a)** with yield-83%. Mp: 308–310°C; ^{1}H-NMR (DMSO-d6, 300 MHz):d (ppm): 10.33 (s,1H), 9.33-9.41 (m, 2H), 8.44-8.47 (dd, 2H), 7.99-8.04 (dd,2H), 7.20-7.35 (m, 5H), 5.16-5.18 (s, 1H), 3.97-4.06 (q,2H),2.39 (s,3H),1.03-1.12 (t, 3H).,

Above procedure is followed for the preparation of all remaining desired 3,4-DHPMs-Sulfonamides

(4b-i). Yield, physical and spectroscopic (^{1}H-NMR) data of some selected compounds:-

4(b): Yield-85%. Mp: 323–326°C; 1H-NMR (DMSO-d6, 300 MHz):d (ppm): 9.32-9.40 (dd,2H), 9.14 (s, 1H), 8.44-8.46 (d,2H), 8.17-8.21 (dd,1H), 7.98-8.03 (dd,1H), 6.88-7.66 (d, 2H), 6.86 (d, 2H), 5.08-5.09 (s, 1H), 3.94-4.01 (q, 2H, OCH2CH3), 3.71 (s, 3H), 2.23 (s, 3H), 1.08-1.12 (t, 3H).

4(e): Yield-88%. Mp: 346–349°C; 1H-NMR (DMSO-d6, 300 MHz):d (ppm): 9.32-9.40 (dd,2H), 9.11 (s, 1H), 8.44-8.47 (d,2H), 8.17-8.21 (dd,1H), 7.98-8.03 (dd,1H), 6.71-6.81 (dd, 2H), 5.36-5.37 (s, 1H), 3.92-3.94 (q, 2H), 3.81 (s, 3H), 3.74-3.76 (s, 6H), 2.26 (s, 3H), 1.03-1.08 (t, 3H).

4(i): Yield-85%. Mp: 371–374°C; 1H-NMR (DMSO-d6, 300 MHz):d (ppm): 9.13-9.41 (m,3H), 8.44-8.45 (d,2H), 7.77-8.04 (dd,2H), 7.71-7.76 (d,1H), 7.48-7.49 (d, 2H), 7.45-7.49 (d, 1H), 7.33-7.45 (d, 1H), 7.30-7.32 (d, 1H),5.59-5.60 (s,1H), 3.87-3.91 (q, 2H), 2.29 (s, 3H), 0.98-1.03 (t, 3H).

3.7General procedure for the preparation of Sulfonamides of Quinazolin-4(3H)-ones - (8a-k)

Quinoline sulfonyl chloride (QSC) (2) (21.96 mmol) was reacted with 2-(4-Methyl)quinazolin-4(3H)-one (21.96 mmol) in dry THF in the presence of triethylamine (43.92 mmol) as a base and 5 mole% $Ce(OTf)_3.SiO_2$ as a catalyst under

ultrasound irradiation at 55°C for 2h. The progress of the reaction was monitored by TLC using Dichloromethane: MeOH (8:2) as a mobile phase. After completion of reaction catalyst was filtered out and solvent from ML was removed under vacuum to obtain the crude product. The resulting crude products were purified by Ethanol re-crystallization method,
to obtain corresponding sulfonamides **(8a)** with yield-77%. Mp: 317–319°C; 1H-NMR (300 MHz, CDCl3) δ 9.38-9.45 (m, 2H), 8.55-8.65 (d, 2H), 8.08-8.38 (m, 3H), 7.58-7.91 (m, 4H), 7.32-7.46 (m, 3H), 2.55 (s, 3H);
Above similar procedure is followed for the preparation of all remaining desired quinazolinones-Sulfonamides **(8b-k).**

Yield, physical and spectroscopic (^{1}H- NMR) data of some selected compounds:-
(8d): Yield-65%. Mp: 338–341°C; 1H-NMR (400 MHz, DMSO) δ 9.32-9.40 (dd, 2H), 8.44-8.47 (d, 2H), 8.17-8.21 (dd, 1H), 8.03-8.05 (dd, 1H), 7.71-8.01 (m, 3H), 7.41-7.52 (m, 1H), 7.23 – 7.38 (m, 4H).
(8e): Yield-81%. Mp: 353–354°C; 1H-NMR (400 MHz, DMSO) δ 9.32-9.40 (dd,2H), 8.44-8.47 (d,2H), 8.27 (d,1H), 8.17-8.21 (dd,1H), 7.98-8.03 (dd,1H),7.83 (d, 2H), 7.72 (t, 2H), 7.58 – 7.50 (m, 1H), 7.48 (d, 1H), 7.39 (t, 1H).
(8h): Yield-78%. Mp: 313–315°C; 1H-NMR (400 MHz, DMSO) δ 9.08-9.12 (dd,2H), 8.98-9.00 (d,1H), 8.44-8.47 (d,2H), 8.17-8.21 (dd,1H), 7.98-8.03 (dd,1H), 7.59-7.83 (d, 2H), 7.27-7.32 (d, 1H), 7.08 – 7.12 (m, 1H), 7.88-7.98 (m, 4H).

General procedure for the preparation of substituted cephalosporin -Sulfonamides (6a-d)
Quinoline sulfonyl chloride (QSC) (2) (21.96 mmol) was reacted with cephalosporin 5(a) (21.96 mmol) in dry THF in the presence of triethylamine (43.92 mmol) as a base and 5 mole% Ce(OTf)3.SiO2 as a catalyst under ultrasound irradiation at 55°C for 2h. The progress of the reaction was monitored by TLC using Dichloromethane: MeOH (8:2) as a mobile phase. After completion of reaction catalyst was filtered out and solvent from ML was removed under vacuum to obtain the crude product. The resulting crude products were purified by Ethanol re-crystallization method, to obtain corresponding substituted cephalosporin sulfonamides **(6a)** with yield-55%. Mp: 346–350°C; 1H-NMR (DMSO-d6, 300 MHz):d (ppm): 9.33-9.41 (dd, 2H), 8.45-8.47(s, 1H), 8.44-8.01 (d,2H), 7.16-7.99 (d,2H), 6.92-6.96(d, 2H), 6.91-6.92 (d, 3H), 5.16-5.27 (s,4H), 4.47-4.60 (s,3H), 3.82-3.85 (s,3H).
Above procedure is followed for the preparation of all remaining substituted cephalosporin-Sulfonamides **(6b-d)**
All the products are identified by their Melting Point and 1H-NMR, spectral data.

3.8Preparation of 8-(4-chloro-1*H*-pyrrolo[2,3-b]pyridine-1-sulfonyl)quinoline (9)
Quinoline sulfonyl chloride (QSC) (2) (21.96 mmol) was reacted with 4-chloro-7-azaindole (21.96 mmol) in dry THF in the presence of triethylamine (43.92 mmol) as a base and 5 mole% $Ce(OTf)_3.SiO_2$ as a catalyst under ultrasound irradiation at 55°C for 2h. The progress of the reaction was monitored by TLC using Dichloromethane: MeOH (8:2) as a mobile phase. After completion of reaction catalyst was filtered out and solvent from ML was removed under vacuum to obtain the crude product. The resulting crude products were purified by Ethanol re-crystallization method, to obtain corresponding sulfonamide (9) with yield-90%. Mp: 312–315°C; ^{1}H-NMR (DMSO-d6, 300 MHz):d (ppm): 8.88-8.95 (m, 2H), 8.29-8.33(d, 1H), 8.06-8.16 (m,3H), 7.69-7.74 (t,1H), 7.41-7.45(dd, 1H), 7.06-7.08 (d, 1H), 6.67-6.68 (d,1H).
Above same procedure is followed for the preparation of 10, 11 and 12 Sulfonamides by using corresponding amine source (i.e. ammonia, methylamine and hydrazine hydrate respectively).

Yield, physical and spectroscopic (^{1}H- NMR) data of some selected compounds:-
Quinoline-8-sulfonamide (10): Yield-92%. Mp: 182-185°C; 1H-NMR (DMSO-d6, 300 MHz):d (ppm): 9.07-9.09 (d, 1H), 8.54-8.57(d, 1H), 8.26-8.32 (dd,2H), 7.70-7.78 (dd,2H), 7.27(s, 2H).
N-methylquinoline-8-sulfonamide (11): Yield-92%. Mp: 202-206°C; ^{1}H-NMR (DMSO-d6, 300 MHz):d (ppm): 9.08-9.10 (d, 1H), 8.56-8.60(d, 1H), 8.27-8.38 (dd,2H), 8.03-8.06 (s,1H), 7.71-7.87 (dd,2H), 3.02(s, 3H).
Quinoline-8-sulfonohydrazide (12): Yield-57%. Mp: 229-231°C; ^{1}H-NMR (DMSO-d6, 300 MHz):d (ppm): 9.08-9.10 (d, 1H), 8.56-8.60(d, 1H), 8.27-8.38 (dd,2H), 8.03-8.06 (s,1H), 7.71-7.87 (dd,2H), 4.53(s, 2H).

3.9Recovery of Catalyst
The spent catalyst 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-10).**

4. CONCLUSION

The present work is a green protocol for the synthesis of sulfonamide Linked up with Quinoline Nuclei." in presence of Ce (OTf) 3.SiO2.

The recompense of this method is cheap, ecofriendly, offers good to moderate yields, simple experimental procedures, easy isolation techniques, relatively short reaction times, ability to tolerate a wide variety of substituent's and recovery of catalyst. To optimize the reaction conditions initially all model reaction was performed using (QSC) (2) and 4-chloro-7-azaindole. In general this work leads to a new trend in organic synthesis. We think this will find valuable applications as a suitable alternative for the synthesis of sulfonamides to provide somewhere to fulfill the need of pharmaceuticals/ agrochemicals industry as well as academic research.

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