Synthesis, biological investigations, QSAR and DFT analysis of sulfonamide chalcones as potential: antimicrobial, antifungal and antimalarial agents

Lakshman R. Meena*, Vinay S. Sharma, Pawan Swarnkar
Department of Chemistry, Faculty of Basic and Applied Science, Madhav University, Rajasthan, India
E-mail address: laxmanmeena6686@gmail.com

ABSTRACT

Various aromatic aldehydes condense with aryl ketone (N-(4-(phenylsulfonamido)phenyl)acetamide) in presence of aqueous alkali NaOH to form α, β-unsaturated ketone (N-(4-(N-phenyl sulfamoyl)phenyl)cinnamamide derivatives or sulfonamide chalcone derivatives). We were synthesized novel sulfonamides chalcones synthesized through Claisen-Schmidt condensation of aromatic aldehydes and sulfonamide containing acetanilide. All the synthesized compounds were characterized using Mass, FTIR, NMR (¹H & ¹³C) spectra analysis. The synthesized sulfonamide chalcone hybrids were screened antimicrobial activity, antifungal and antimalarial activity.

Keywords: Claisen-Schmidt condensation, α-β-unsaturated ketone, antimicrobial, antifungal, antimalarial, sulfonamide hybrids
GRAPHICAL ABSTRACT

1. INTRODUCTION

Synthetic sulfonamide chalcones are unique chemical structure, wide biological properties, relieve of synthesis, and described presenting a wide range of potential pharmacological activities [1], including antioxidant [2], anti-inflammatory [3], antiulcer [4], antioxidant [5], antimicrobial [6], anti-malarial [7], anticancer [8-10] and antiviral [11, 12]. Chalcones were availed for their multifarious biological activities and there are a number of reviews that have dealt with the pharmacological and chemical bases of the biological activities noticed under the effect of chalcones. Sulfonamide chalcones as chemotherapeutic agents have effective and potent biological activities [13, 14] that also have a versatile advantage in the synthesis of bioactive scaffolds, such as pyrazoles, isocazoles, cyanopyridines, and pyrididine-2-thiens [15, 16]. Cyclohexanone which exhibits significant biological activities as an anticancer agent [17] and pheromones [18-20]. Chalcones are precursors for flavonoids compounds, where two aromatic rings with α,β-unsaturated ketones i.e. 1,3-diphenyl-2-propene-1-one derivatives are fused [21].

Generally, chalcones that occur naturally have methoxy (-OCH₃) or hydroxyl (-OH) groups on aromatic rings [22]. Chalcones moiety design is one of the most important nanovic basis for novel and interesting atomic drugs. Synthetic and naturally occurring chalcones with methoxy groups are quite interesting molecules for their excellent medicinal and biological properties [23]. Some of the various derivatives of sulfonamide chalcones are currently being evaluated through clinical practitioners under current conditions that are being used as anticancer drugs, which would be more effective and less effective than available pharmacological agents [24]. Due to the medicinal and biological potential of the sulfonamide and chalcones skeletons, they felt the need for growth and hence fused to preserve or enhance the medicinal potential. Compounds that have relatively similar structure with sulfonamide (RSO₂NH-) such as sulfonate, thiosulfonyl and sulfamate also exhibit excellent activity as synthetic drugs like sulfonamide.

They are exhibited broad spectrum of pharmacological and biological properties such as antibacterial [25, 26], anticancer [27], anti-inflammatory [28], diuretic [29], anti-histaminic [30], anti-diabetic, anti-protozoal [31], antifungal etc. Gerhard Domagk’s discover the first azo
dye which is named prontosil to be the first effective chemotherapeutic agent and it was converted to sulphanilamide which indicates effective antibacterial activity [32]. A large number of sulfonamide chalcones derivatives have recently been reported to show substantial antitumor activity, both in vitro and in vivo. Their biochemical properties of sulfonamide containing SO\textsubscript{2} and NH\textsubscript{2} polar groups are coordination to metal ions in various, metal enzyme. Establishment of special hydrogen bonds that regenerate tetrahedral transition states of various enzymatic reactions and the possibility of lipophilic interactions through aryl groups [33, 34].

Malaria is a dangerous infectious disease of humans, especially in the trade-wind littoral climate of the world where temperature is less than 28 °C, every year about 275 million new infected cases and death rate reaching 2 million annually, which is more infectious especially in children in Africa [35]. Malaria is a parasitic disease mainly found in four species in India such as \textit{Plasmodium vivax}, \textit{Plasmodium malaria}, \textit{Plasmodium falciparum}, and \textit{Plasmodium ovale}. \textit{P. vivax} causes 7.5 million malaria cases per year. South-East Asia has the highest number of malaria cases (53%). Thus, there is a convincing, persuasive, undeniable and urgent need for novel antimalarial, which differ from existing diseases and are more effective and prevalent [36]. Quinine and Chloroquine which have proven effective in preventing hemozoin formation within the parasitic food vacuole [37].

Sulfonamide chalcones derivatives are promoting compounds which developing novel drugs can be used as CNS (Central Nervous System Disease) disorder [38]. According to E.G.’s National Malarial Control Program (2019), the incidence of \textit{P. falciparum} malaria (within 2 to 14 years age group) was 12.5%. According to the WHO report 2018, 99.7% of malaria infections have been reported by \textit{P. falciparum} in the African region, 50% in Southeast Asia, 71% in the Eastern Mediterranean region and 65% in the Western Pacific region [39]. Pregnant women are more likely to develop falciparum malaria in the second and third trimesters of pregnancy, due to the incidence of fatal death and premature labour due to malaria infection.

In present research work, a sequence of sulfonamide chalcone derivatives (2a-2m) were synthesis and investigated for their anti-microbial, anti-fungal and anti- malarial activity.

2. EXPERIMENTAL SECTION

All solvents and reagents which are used in experimental process were analytical grade and purchased from Sigma Aldrich. Melting points were measured with 350 deg. C melting point. The progress of reaction on pre-coated TLC plates was investigated and spots were visualized using UV light. Pre-coated TLC plates and UV light were used to investigate of process of the reactions. Chemical shifts are given in ppm (parts per million). The design and synthesized compounds were described with spectral analysis of mass, FTIR, NMR (\textsuperscript{1}H & \textsuperscript{13}C).

IR (Infrared) Spectra were recorded using the Shimadzu FT-IR spectrophotometer. Mass spectra of given compounds were determined with GCMS-QP1000 EX spectrometer. \textsuperscript{1}H spectrum was taken at 500 MHz and \textsuperscript{13}C spectrum was taken with Bruker DMX spectrometer at 100 MHz in dimethylsulphoxide (DMSO-d\textsubscript{6}). Analytical thin layer chromatography (TLC) plate (Silica gel 60 F254, Merck) was used to test the purity of the products, monitored the reaction which also used UV light and iodine chamber. Here the abbreviation are as follows: s (singlet); d (doublet) and m (multiplet). The synthesis route of the reaction is given in Scheme 1 with library derivatives are shown in Table 1 respectively.
Synthesis of N-(4-(phenylsulfonamido)phenyl)acetamide (1) [40]

N-(4-aminophenyl)acetamide (0.01mol) was dissolved in minimum amount of pyridine and add 20 ml of MeOH and benzenesulfonylchloride (0.01 mol). After it the reaction mixture was kept refluxing at 6hr and after completed the reaction, reaction mixture were then quenched in 100 gm ice bath and obtained solid was wash with 50ml dilute hydrochloric acid and dry it. Orange power, yield 82%, Mp: 120-121 °C; IR (KBr, ν cm⁻¹): 3423.4, 3338.2 (NH), 1638.17 (amide C=O), 1318.18 (S=O); ¹H-NMR (500 MHz, CDCl₃), δ (ppm): 9.82 (s, 1H, SO₂NH), 8.32 (S, 1H, CO-NH), 7.68 (d, 1H, CH=HC), 6.80 (d, 1H, CH=HC), 7.51-7.53 (d, 4H, Ar-H), 6.80 (d, 1H, CH=CH), 6.79-6.81 (s, 4H, Ar-H), 6.52-6.54 (d, 10H, Ar-H), 3.65 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 160.07 (amide C=O), 115.42, 114.18, 108.33 (Ar-C, First aromatic ring), 125.33, 123.51, 121.80 (Ar-C, First aromatic ring), 56.06(O-CH₃), 56.07(O-CH₃) ppm, Anal. Calcd. For C₁₄H₁₄N₂O₃S (290.57).

Synthesis of sulfonamide chalcone derivatives (2a-2j) [41]

In two neck flask dissolved 0.01 mole of N-(4-(phenylsulfonamido)phenyl)acetamide (1) and 0.01 mol of aromatic aldehydes substitute in 20 ml EtOH. After 10 min. add aqueous solution of NaOH (2 equ., 2 mol) as a drop-wise with constant stirring. The reaction mixture were kept reflux at 8 hr and the reaction was monitoring by thin layer chromatography in 1:2 (ethyl acetate : hexane). After the completed of reaction, reaction mixture were quenched in 100 gm ice bath. The resulting obtained solid was filter and recrystallized using ethanol.

(E)-3-(3-methoxy-4-phenoxyphenyl)-N-(4-(phenylsulfamoyl)phenyl)acrylamide (2a) Orange power, yield 60%, Mp: 177-178 °C; IR (KBr, ν cm⁻¹): 3426.4, 3334.6 (NH), 1630.7 (amide C=O), 1507.4 (C=C), 1320.8 (S=O); ¹H-NMR (500 MHz, CDCl₃), δ (ppm): 9.80 (s, 1H, SO₂NH), 8.40 (S, 1H, CO-NH), 7.87 (d, 1H, CH=HC), 7.76-7.78 (d, 4H, Ar-H), 7.56-7.53 (s, 3H, Ar-H), 7.48-7.10 (d, 10H, Ar-H), 6.78 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 160.0 (amide C=O), 150.0 (C=C), 138.80, 135.90, 134.03 (Ar-C, First aromatic ring), 133.04, 131.54, 129.03 (Ar-C, First aromatic ring) ppm; Anal. Calcd. For C₂₈H₂₄N₂O₅S (500.57).

N-(4-(phenylsulfamoyl)phenyl)cinnamamide (2b) Plum power, yield 68%, Mp: 179-180 °C; IR (KBr, ν cm⁻¹): 4246.3, 3432.5 (NH), 1628.6 (amide C=O), 1578.1 (C=C), 1324.9 (S=O), cm⁻¹; ¹H-NMR (500 MHz, CDCl₃), δ (ppm): 9.78 (s, 1H, SO₂NH), 8.40 (S, 1H, CO-NH), 7.87 (d, 1H, CH=HC), 7.76-7.78 (d, 4H, Ar-H), 7.56-7.53 (s, 4H, Ar-H), 7.48-7.10 (d, 10H, Ar-H), 6.78 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 160.0 (amide C=O), 150.0 (C=C), 138.80, 135.90, 134.03 (Ar-C, First aromatic ring), 133.04, 131.54, 129.03 (Ar-C, First aromatic ring) ppm; Anal. Calcd. For C₂₁H₁₈N₂O₃S (378.45).

(E)-3-(2-hydroxyphenyl)-N-(4-(phenylsulfamoyl)phenyl)acrylamide (2c) Orange power, yield 71%, Mp: 119-120 °C; IR (KBr, ν cm⁻¹): 3426.3, 3333.4 (NH), 1618.3 (amide C=O), 1506.7 (C=C), 1321.3 (S=O), cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) δ (ppm): 13.08 (OH), 9.60 (s, 1H, SO₂NH), 8.56 (S, 1H, CO-NH), 7.79 (d, 1H, CH=HC), 7.77 (d, 1H, CH=HC), 7.67-7.68 (d, 4H, Ar-H), 7.40-7.48 (s, 4H, Ar-H), 7.13-7.18 (d, 10H, Ar-H), 6.80 (s, 3H); ¹³C NMR (100MHz, CDCl₃) δ (ppm): 162.10 (amide C=O), 148.25 (C=C), 140.80, 138.06, 137.80
(Ar-C, First aromatic ring), 135.40, 132.74, 129.36 (Ar-C, First aromatic ring) ppm; Anal. Calcd. For C$_{21}$H$_{18}$N$_2$O$_3$S (394.45).

(E)-3-(4-fluorophenyl)-N-(4-(N-phenylsulfaamoyl)phenyl)acrylamide (2d)

Purple power, yield 58%, Mp: 279-280 °C; IR (KBr, ν cm$^{-1}$): 3423.3, 3333.9 (NH), 1604.7 (amide C=O), 1508.3 (C=C), 1157.6 (S=O), cm$^{-1}$; $^1$H-NMR (500 MHz, CDCl$_3$), δ (ppm): 8.37 (s, 1H, SO$_2$NH), 8.33 (S, 1H, CO-NH), 7.82 (d, 1H, CH=HC), 7.80 (d, 1H, CH=HC), 7.55-7.51 (d, 4H, Ar-H), 7.45-7.40 (s, 4H, Ar-H), 7.1-7.05 (d, 10H, Ar-H), 6.29 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$), δ (ppm): 160.30 (amide C=O), 153.65 (C=C), 150.80, 149.66, 138.10 (Ar-C, First aromatic ring), 140.80, 136.44, 130.60 (Ar-C, First aromatic ring) ppm; Anal. Calcd. For C$_{21}$H$_{17}$FN$_2$O$_3$S (396.44).

(E)-N-(4-(N-phenylsulfamoyl)phenyl)-3-(pyridin-4-yl)acrylamide (2c)

Dark brown power, yield 69%, Mp: 79-80 °C; IR (KBr, ν cm$^{-1}$): 3423.3, 3333.9 (NH), 1604.7 (amide C=O), 1508.3 (C=C), 1157.6 (S=O), cm$^{-1}$; $^1$H-NMR (500 MHz, CDCl$_3$), δ (ppm): 8.71 (s, 1H, SO$_2$NH), 7.26 (S, 1H, CO-NH), 7.68 (d, 1H, CH=HC), 7.66(d,1H,CH=HC), 7.41-7.44 (d, 4H, Ar-H), 6.79-6.82 (s, 4H, Ar-H), 6.52-6.55 (d, 10H, Ar-H), 6.15(s,3H); $^{13}$C NMR (100 MHz, CDCl$_3$), δ (ppm): 162.62 (amide C=O), 155.20 (C=C), 165.05, 160.13, 152.10 (Ar-C, First aromatic ring), 144.80, 136.02, 133.56 (Ar-C, First aromatic ring) ppm; Anal. Calcd. For C$_{20}$H$_{17}$N$_3$O$_3$S (379.43).

(E)-3-(4-hydroxy-3-methoxyphenyl)-N-(4-(N-phenylsulfaamoyl)phenyl)acrylamide (2f)

Yellow power, yield 62%, Mp: 179-180 ºC; IR (KBr, ν cm$^{-1}$): 3426.5, 3334.3 (NH), 3261.5 (OH), 1629.2 (amide C=O), 1505.0 (C=C), 1393.10 (S=O), cm$^{-1}$; $^1$H-NMR (500 MHz , CDCl$_3$), δ (ppm): 9.83 (OH), 8.28 (s, 1H, SO$_2$NH), 7.26 (S, 1H, CO-NH), 7.76 (d, 1H, CH=HC), 7.67 (d, 1H, CH=HC), 7.51-7.57 (d, 4H, Ar-H), 7.45-7.40 (s, 4H, Ar-H), 6.97-7.08 (d, 10H, Ar-H), 6.28 (s, 3H), 3.65 (O-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$), δ (ppm): 160.21 (amide C=O), 156.10 (C=C), 162.05, 157.33, 154.60 (Ar-C, First aromatic ring), 145.10, 146.55, 151.16 (Ar-C, First aromatic ring) ppm; Anal. Calcd. For C$_{22}$H$_{20}$N$_2$O$_3$S (424.47).

(E)-4-(2-methoxy-4-(3-oxo-3-((4-(N-phenylsulfaamoyl)phenyl)amino)prop-1-en-1-yl)phenoxy)benzenesulfonyl chloride (2g)

Yellow power, yield 70%, Mp: 159-160 ºC; IR (KBr, ν cm$^{-1}$): 3425.5, 3330.9 (NH), 1628.6 (amide C=O), 1505.8 (C=C), 1158.6 (S=O), cm$^{-1}$; $^1$H-NMR (500 MHz , CDCl$_3$), δ (ppm): 7.68 (s, 1H, SO$_2$NH), 7.67 (S, 1H, CO-NH), 6.81 (d, 1H, CH=HC), 6.79 (d, 1H, CH=HC), 7.51-7.53 (d, 4H, Ar-H), 7.40-7.44 (s, 4H, Ar-H), 6.52-6.53 (d, 10H, Ar-H), 6.16 (s, 3H), 3.65 (O-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$), δ (ppm): 162.41 (amide C=O), 160.11 (C=C), 158.60, 155.02, 150.56 (Ar-C, First aromatic ring), 144.44, 142.21, 140.11 (Ar-C, First aromatic ring), 54.87 (O-CH$_3$) ppm; Anal. Calcd. For C$_{28}$H$_{23}$ClN$_2$O$_3$S$_2$ (599.07).

(E)-3-(3-methoxy-4-(2-phenoxyethoxy)phenyl)-N-(4-(Nphenylsulfaamoyl)phenyl)acrylamide (2h)

Dark Orange power, yield 70%, Mp: 264-265 ºC; IR (KBr, ν cm$^{-1}$): 3267.2, 3417.3 (NH), 1597.9 (C=C), 1338 (S=O), 1683.1 (amide C=O) cm$^{-1}$; $^1$H-NMR (500 MHz , CDCl$_3$), δ (ppm): 9.86 (s, 1H, SO$_2$NH), 8.30 (S, 1H, CO-NH), 7.75 (d, 1H, Alkene), 7.53 (t, 1H), 7.41-7.46 (m, 2H), 7.08-7.31 (m, 4H), 7.06-7.08 (m, 2H), 6.93-7.01 (m, 7H), 4.47 (t, 2H), 4.40 (t, 2H), 3.92
(E)-3-(2-chlorophenyl)-N-(4-(N-phenylsulfamoyl)phenyl)acrylamide (2i)
Dark brown power, yield 66%, Mp: 131-132 °C; IR (KBr, ν cm⁻¹): 3238.3, 3132.6 (NH), 1620.6 (amide C=O), 1503.2 (C=C), 1330.4 (S=O), cm⁻¹; ¹H-NMR (500 MHz, CDCl₃), δ (ppm): 8.86 (s, 1H, SO₂NH), 8.57 (S, 1H, CO-NH), 8.20 (d, 1H, CH=HC), 8.18 (d, 1H, CH=HC), 7.78-7.76 (d, 4H, Ar-H), 7.42-7.47 (d, 4H, Ar-H), 7.09-7.16 (d, 10H, Ar-H), 6.55 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 164.77 (amide C=O), 156.0 (C=C), 125.13, 121.51, 119.60 (Ar-C, First aromatic ring), 118.42, 117.12, 111.30 (Ar-C, First aromatic ring), 58.44 (O-CH₃), 56.07 (O-CH₃) ppm; Anal. Calcd. For C₃₉H₂₈N₂O₆S (544.62).

(E)-3-(4-methoxyphenyl)-N-(4-(N-phenylsulfamoyl)phenyl)acrylamide (2j)
Gray power, yield 63%, Mp: 137-138 °C; IR (KBr, ν cm⁻¹): 3425.6, 3334.4 (NH), 1604.8 (amide C=O), 1508.3 (C=C), 1159.2 (S=O), cm⁻¹; ¹H-NMR (500 MHz, CDCl₃), δ (ppm): 8.32 (s, 1H, SO₂NH), 8.11 (S, 1H, CO-NH), 7.82 (d, 1H, CH=HC), 7.75 (d, 1H, CH=HC), 7.54-7.51 (d, 4H, Ar-H), 7.45-7.40 (d, 4H, Ar-H), 7.07-7.06 (d, 10H, Ar-H), 3.87 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 166.50 (amide C=O), 156.90 (C=C), 136.84, 134.50, 133.41 (Ar-C, First aromatic ring), 130.22, 128.24, 124.23 (Ar-C, First aromatic ring) ppm; Anal. Calcd. For C₂₁H₁₉ClN₂O₅S (412.89).

(E)-3-(4-hydroxyphenyl)-N-(4-(N-phenylsulfamoyl)phenyl)acrylamide (2k)
Orange power, yield 71%, Mp: 159-160 °C; IR (KBr, ν cm⁻¹): 3425.7, 3334.0 (NH), 3264.6 (OH), 1631.3 (amide C=O), 1507.1 (C=C), 1320.9 (S=O), cm⁻¹; ¹H-NMR (500 MHz, CDCl₃), δ (ppm): 9.87 (s, 1H, SO₂NH), 8.30 (S, 1H, CO-NH), 7.80 (d, 1H, CH=HC), 7.68 (d, 1H, CH=HC), 7.54-7.51 (d, 4H, Ar-H), 7.44-7.40 (s, 4H, Ar-H), 6.81-6.80 (d, 10H, Ar-H), 6.18 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 145.27 (amide C=O), 141.58 (C=C), 132.72, 128.82, 127.30 (Ar-C, First aromatic ring), 116.44, 115.42 (Ar-C, First aromatic ring); Anal. Calcd. For C₂₁H₁₈N₂O₅S (394.45).

(E)-3-(3,4-dimethoxyphenyl)-N-(4-(N-phenylsulfamoyl)phenyl)acrylamide (2l)
Dark brown power, yield 76%, Mp: 129-130 °C; IR (KBr, ν cm⁻¹): 3439.8, 3415.2 (NH), 1624.2 (amide C=O), 1579.4 (C=C), 1329.0 (S=O), cm⁻¹; ¹H-NMR (500 MHz, CDCl₃), δ (ppm): 8.31 (s, 1H, SO₂NH), 7.54 (S, 1H, CO-NH), 7.76 (d, 1H, CH=HC), 7.57 (d, 1H, CH=HC), 7.42-7.45 (d, 4H, Ar-H), 7.26-7.29 (s, 4H, Ar-H), 6.91-6.93 (d, 10H, Ar-H), 6.71 (s, 3H), 3.96 (O-CH₃); ¹³C NMR (100 MHz, CDCl₃): δ = 165.24 (amide C=O), 143.18 (C=C), 132.72, 130.12, 127.31 (Ar-C, First aromatic ring), 120.14, 116.42 (Ar-C, First aromatic ring), 55.12 (O-CH₃); Anal. Calcd. For C₂₄H₂₃N₂O₆S (438.50).

(E)-3-(8-methoxy-3-phenyl-3,4-dihydro-2H-benzo[e][1,3]oxazin-6-yl)-N-(4-(N-phenylsulfamoyl)phenyl)acrylamide (2m)
Brown power, yield 69%, Mp: 329-330 °C; IR (KBr, ν cm⁻¹): 3700, 2926.3 (NH), 1613.3 (amide C=O), 1508.5 (C=C), 1226.8 (S=O), cm⁻¹; ¹H-NMR (500 MHz, CDCl₃), δ (ppm): 7.16 (s, 1H, SO₂NH), 7.05 (S, 1H, CO-NH), 4.50 (d, 1H, CH=HC), 4.33 (d, 1H, CH=HC), 6.68-6.60 (d, 4H, Ar-H), 7.26-7.29 (s, 4H, Ar-H), 4.70-4.18 (d, 10H, Ar-H), 3.33 (s, 3H), 4.18 (O-CH₃),
2.96 (O-CH₂); $^{13}$C NMR (100 MHz, CDCl₃), δ (ppm): 166.34 (amide C=O), 141.48 (C=C), 138.72, 136.42, 130.31 (Ar-C, First aromatic ring), 126.42, 122.32 (Ar-C, First aromatic ring), 57.12 (O-CH₃), Anal. Calcd. For C₃₀H₂₇N₃O₅S (541.62).

Reaction Scheme

Scheme 1. (a) Pyridine, MeOH, Reflux, 6h; (b) MeOH, 20% NaOH, Reflux, 8h.
Table 1. Library derivatives of sulphonamide derivatives.

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<th>Comp. Id</th>
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2. 1. Biological evaluation

*In vitro antibacterial screening*

The antibacterial activity of the target sulfonamide chalcone compounds (2a–2m) were compared with standard drugs of “Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin” and their results are represented in Table 2 and graphical represented in Figure 1(a). Agar well-diffusion method was used to determine the antibacterial activity. As designate in Table 1, mostly sulfonamide chalcones were describe potent antibacterial activity against. Bacterial strains; *E. coli, P. aeruginosa, S. aureus, S. pyogenus*. Compounds 2e, 2l and 2j are higher potential against *P. aeruginosa* (MTCC-1688), *E. coli* (MTCC-443) and *S. aureus* (MTCC-96) respectively while compounds 2a, 2k and 2m are also higher potential against *S. pyogenus* (MTCC-442). Above all six compounds i.e. 2e, 2l, 2j, 2a, 2k and 2m are higher potential which MIC (minimal inhibition concentration) value is 50 mg/ml. While seven compounds 2b, 2d, 2f, 2k, 2m, 2c, 2g were found to be intermediate antimicrobial activity which MIC value is 62.5 mg/ml. These results along antimicrobial activity with the MIC values are shown in Table 1 while a graphical representation of the same data is given in Figure 1. The sulfonamide chalcones having the 2a, 2l, 2j, 2m (methoxy group), 2e (pyridine moiety), 2k (–OH group)
showed the higher antimicrobial activity (MIC value are 50 mg/ml). Whereas sulfonamide chalcones with the 2b, 2d (fluoro group), 2f (both –OCH₃ and -OH group), 2k and 2c (hydroxyl group), 2m and 2g (–OCH₃ group) were found to be intermediate in activity.

**In vitro antifungal activity**

The antifungal activity of the target sulfonamide chalcone compounds (2a–2m) and their results are represented in Table 1 and graphical represented in Figure 1(b). In vitro antifungal activity of all the newly synthesized sulfonamide chalcone compounds were tested against three fungal strains such as *C. albicans*, *A. niger* and *A. clavatus* following agar diffusion method using standard drugs of Nystatin and Greseofulvin. Mostly all the compounds exhibited significant potential as fungicides. It was evaluated that mostly compounds have been higher potential aganist *C. albicans*. Compounds 2a, 2g, 2j and 2l are exhibit higher potential against *C. albicans* which MIC value is found to be 250 mg/ml, while compounds 2b, 2c, 2d, 2e, 2f, 2h, 2i, 2k and 2m are exhibit intermediate antifungal activity which MIC value is found to be 500 mg/ml. It was also found that mostly compounds are lowered antifungal activity against *A. clavatus*. The sulfonamide chalcones having the methoxy group (2a, 2g, 2j & 2l) showed the greatest antifungal activity (MIC value is 250 mg/ml).

**Table 2.** Antimicrobial, antifungal & antimalarial activity of synthesized comp. (2a-2m).

<table>
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<th>Sr. No.</th>
<th>Comp.</th>
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<th>Antifungal activity (mg/ml)</th>
<th>Antimalarial activity (µg/ml)</th>
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<tr>
<td>Chloramphenicol</td>
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<tr>
<td>Ciprofloxacin</td>
<td>25 25 50 50</td>
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<tr>
<td>Greseofulvin</td>
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<tr>
<td>Chloroquine</td>
<td>- - - - 0.268</td>
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*Figure 1. (a) Shows the antibacterial activity of various sulfonamide chalcone derivatives (2a-2m) on the OY axis and compares them to four standards drugs; G = Gentamycin, A = Ampicillin, Ch = Chloramphenicol and C = Ciprofloxacin with MIC value 50 gm /ml; (b) shows the antifungal activity of various sulfonamide chalcone derivatives (2a-2m) on the OY axis and is compared to standard drugs; N = Nystatin and Gr = Greseofulvin with MIC value is 250 gm/ml.*

**Antimalarial activity**

Thirteen analogs of sulfonamides chalcone derivatives were tested for their Antimalarial activity against *P. falciparum* parasites in Table 1 and the graphical represented in Figure 2. Antimalarial activity of about thirteen sulfonamide chalcones were evaluated and it was found
that. Four compounds (2a, 2e, 2j and 2k) showed better antimalarial activity which Mean IC50 ($P. falciparum$, µg/ml) value is 0.83, 0.37, 0.54 and 0.61 respectively. While other compounds showed lower antimalarial activity which Mean IC50 ($P. falciparum$, µg/ml) value is greater than one. As a reference drugs Quinine and Chloroquine were used. Compounds containing alkoxy group (2a, 2e, and 2j) in romantic ring exhibit biologically high potency. We have also found that the presence of a hydroxyl substitution group (2k) in the romantic ring increases antimalarial activity. All these results offer many new possibilities as well as further improvements in the antimalarial performance of sulfonamide chalcone derivatives. In this study antibacterial, antifungal and antimalarial were developed by us using convenient chemistry and low production cost which is necessary to develop them as therapeutic agents. We will make direct efforts to find even more powerful antibacterials, antifungals and antimalarials in the future.

![Antimalarial activity graph](image)

**Figure 2.** Shows the antimalarial activity of various sulfonamide chalcone derivatives (2a-2m) on the OY axis as well as a comparison of standard drugs; Q = Quinine and CQ = Chloroquine.

2. 2. Quantitative Structure–activity relationships (QSAR) and DFT based chemical descriptors

Generally Sulfonamide anti-bacterial attributes are directly similarity to the inhibition of the enzymes dihydroporate synthase (DHPS). Antibacterial sulfonamides efficient as competitive inhibitors (CI) of the enzyme dihydroporate synthesize in bacteria, which catalyzed the translation of PABA (para-aminobenzoic acid) to diabetes. Sulfonamides and para-aminobenzoic acid (PABA) are structural analogs of each other so they act as competitive resistor in Microbes cells. Microorganisms require para-aminobenzoic acid (PABA) to form dihydrofolic acid, a precursor to folic acid. Due to the similarity of sulfonamide to PABA, it fulfills the function of PABA. The synthesis of purine and pyrimidine by folic acid is essential for nucleic acid synthesis and absence of folate cell will be unable to further divination. Therefore sulfonamides exhibit bacteriostatic properties efficiently compared to the bactericidal effect. Structure–activity relationship (SAR) studies of antimicrobial active sulfonamide chalcone derivatives were carried out and $E_{HOMO}$ & $E_{LUMO}$ are represented in **Figure 3 (2e)**. It was found that most of sulfonamide chaconne which have a methoxy group, and pyridine
moiety are more potential against antibacterial activity. While the -OH, -F, -Cl and both group are attach to aromatic ring (–OH and –OCH₃) case the activity of compounds is reduced. Structure–activity relationship (SAR) studies of antifungal active compounds were carried out of different sulfonamide chalcone derivatives. It was found that sulfonamide chalcone which have methoxy group (2a, 2g, 2j and 2l) are higher potential due to the electro-donating properties.

Figure 3. The molecular orbital and energy for E_{HOMO} and E_{LUMO} comp. (2e)

While the hydroxy group is attached to aromatic ring is showed intermediate active of all three types of tested fungus. The higher negatively energy value of HOMO due to presence of nitro hetero atom (2e). Quantitative Structure–activity relationship (QSAR) studies of antimalarial compounds were carried out separately on the different sulfonamide chalcone derivatives. It was found that most of sulfonamides chalcone which have a methoxy group, hydroxyl and pyridine moiety is more potential against antimalarial activity.

While the hydroxy group is also attached to the methoxy group on the same ring, in which case the activity of compounds is reduced. DFT calculation is given an idea about the reactivity and selectivity of the synthesized compounds.

Here we are calculated the E_{LUMO} (eV), E_{HOMO} (eV), energy gap (eV), electro negativity, Chemical potential (µ), hardness (η), and softness (σ). The hardness (η), and softness (σ) evaluate both the reactivity and stability.

Kohn- Sham density functional theory (DFT) is computed quantum chemical descriptors which were better understand the chemical reaction. DFT used to investigate the electronic structure, nuclear structure and the reaction pathways of particular atoms, molecules and DFT has become useful tool for nuclear spectroscopy [42]. Energetic parameters and Quantum chemical descriptors of comp. (2a-2m) are shown in Table 3.
Table 3. Energetic parameters and Quantum chemical descriptors of comp. (2a-2m)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>$E_{LUMO}$ (eV)</th>
<th>$E_{HOMO}$ (eV)</th>
<th>Egap. (eV)</th>
<th>IP = -$E_{H}$</th>
<th>EA = -$E_{L}$</th>
<th>M</th>
<th>Hardness</th>
<th>Softness</th>
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In DFT, Geometry optimization and energy calculations were achieve of the atom or molecule using the B3LYP functional level [43]. Figure 3 and Table 3 indicated the optimized structures achieved by the B3LYP/6-31G(d) in DMSO solvent phase. Frontier molecular orbital’s (FMO) theory were determines the energy and molecule interaction with other species at the same level of HOMO and LUMO. We apply the energy of the Frontier molecular orbit to calculate many chemical and pharmacological properties. The value of $E_{HOMO}$ refers to the ability of donor molecules to donate electrons, the high value $E_{HOMO}$ refers to the ability of the atom receptor to more easily donate electrons. While the high value of $E_{LUMO}$ is related to the ability of the molecule to readily accept electrons. The lower value of $E_{LUMO}$, indicated the lower the ability to accept electrons. Koopman’s principle is expressed the electron affinity (EA) and ionization energy (IP) of $E_{HOMO}$ and $E_{LUMO}$ orbital energies, according him $IP = -E_{HOMO}$ and $EA = -E_{LUMO}$. The investigation of $E_{HOMO}$ and $E_{LUMO}$ is important due to the indicated the relative order of virtual and occupied orbital provides a reasonably qualitative character of the electronic properties. Both HOMO and LUMO indicate the molecular chemical stability by using donating and accepting the electrons. General, HOMO has an anti-bonding character whereas LUMO show a bonding character between subunits. No direct relationship between HOMO or LUMO energy which designated...
antibacterial activities has been revealed. The energy gap (eV) in between the $E_{\text{HOMO}}$ and $E_{\text{LUMO}}$ is related to compounds stability of the compounds. The higher value of energy gap implies comparatively high stability and low value of energy gap mean low stability of the compounds. Generally, the more stability indicates week chemical reactivity and short energy gap indicates strong chemical reactivity. Another important Pearson theory; Hard–Soft Acid Base (HSAB) was based on the involving the single electron pair of frontier orbitals. Hardness ($\eta$) is an important property of a molecule that accurately measures the amount of a chemical reaction. It is defined as ($\eta$) with $\eta = (E_L - E_H)/2$ which can be correlated with energy gap ($\Delta E_{\text{gap}}$) [44]. Polarization ($\alpha$) is the measurement the capability of a molecule to attract electrons further. A soft molecule has high average polarization efficiency. According to the higher the energy gap in DMSO, the more active the compound will be and the lower its polarization value. Due to the higher energy gap of the compounds (2e) it will be highly antimicrobial active compound.

3. CONCLUSIONS

After the experimental evolution, our result of sulfonamide chalcone compounds (2a-2m) was showed in Table 1. All the compounds were characterized using mass, FT-IR, NMR ($^1$H & $^{13}$C) spectral data. These new derivatives were tested as antimicrobial, antifungal and antimalarial activity.

The synthesized chalcone sulfonamide hybrids were screened antimicrobial activity by broth dilution method. It was founds that six compounds (2a, 2e, 2j, 2k, 2l and 2m) exhibited the most potential antimicrobial activity (which MIC value is 50 mg/ml). Getamycin, ampicillin, chloramphenicol and ciprofloxacin drugs were used as references drugs of antimicrobial activity. Compounds 2a, 2g, 2j and 2l exhibited the better antifungal activity which MIC value is 250 mg/ml against C. albicans (MTCC-227). Greseofulvin and Nystatin were used as antifungal activity as reference drugs. Same ways the antimalarial activity of compounds (2a, 2e, 2j and 2k) are found to be better active which Mean IC50 (P. Falciparum, $\mu$g/ml) value is 0.83, 0.37, 0.54 and 0.61 respectively. Quinine and Chloroquine were used as reference drugs of antimalarial activity.

Acknowledgements

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References


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dibromo-3-aryl-propanoyl)-phenyl]benzenesulfonamide. Der Pharma Chem. 4(3) 2012 1054-1057


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