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SYNTHESIS, ANTIMICROBIAL AND ANTHELMINTIC EVALUATION OF NOVEL QUINAZOLINONYL CHALCONES

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ABSTRACT

The objective of the present study was synthesis, physical and spectral characterization, *in vitro* antimicrobial and anthelmintic evaluation of a series of some novel quinazolinonyl chalcones as better leads. The titled compounds (3a-r) with IUPAC name {3-phenyl-1-[3'-(un) substituted phenyl-6'-(un) substituted-2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-ones} have been synthesized by Claisen-Schmidt condensation reaction between substituted 1-acetyl-2-thioxoquinazolin-4(3*H*)-ones (2a-r) and aromatic aldehyde (Benzaldehyde). All the synthesized compounds have been confirmed by elemental, IR, ^{1}HNMR and Mass spectral analyses. Further, they were evaluated for *in vitro* antibacterial, antifungal and anthelmintic activities against several pathogenic bacteria, fungi and helminth (*Peritima posthuma)* respectively. Out of 18 newly synthesized quinazolinonyl chalcones, titled compounds 3b, 3f, 3i, 3k, 3l and 3n showed excellent antimicrobial activity against all the selected pathogenic microorganisms. Significant anthelmintic activity was shown by titled compounds 3h, 3i, 3j, 3k, 3l, 3m and 3o in comparison with standard Albendazole. Finally, the titled compounds 3i, 3k and 3l showed significant activity in all the three *in vitro* evaluations and found to be the best among all the synthesized compounds in the series.

Keywords: Anthranilic acid, aromatic amines, 2-thioxo-4(3*H*) quinazolinones, antimicrobial.

INTRODUCTION

To cure microbial infections, various classes of antibiotics showing narrow/broad spectrum activities against various disease causing microbe(s) were developed in the past centuries. But, the present challenge to the existing antibiotics in the market is the antibiotic resistance by majority of disease causing microbes. Upcoming new parasites, bacteria and viruses add more complexity to the lives of human beings on mother earth. Bacteria, fungi are important opportunistic pathogens to humans, which could cause superficial or invasive/systemic infections. Major bacterial and fungal pathogens include genera *like Streptococcus and Staphylococcus; Cryptococcus, Candida* and *Aspergillus*. Now-a-days most of the drug regimens include combinational therapy to many diseases with newer antimicrobial agents and broad spectrum antibiotics. So, exploration of potent antimicrobials to drug resistant microbes is a need of hour.

Chalcones (1, 3-diaryl-2-propen-1-ones) represents a system of two (un) substituted aromatic rings separated by three carbons, of which two are connected by double bond and the third bearing a carbonyl group. Compounds with chalcone system were known to possess wide range of biological activities such as antimicrobial, antiviral, hypoglycemic, anti-inflammatory and anticancer activities[1-6]. Previous reports reveal that presence of reactive α, β-unsaturated keto functional group and hydroxyl group in the chalcone system was responsible for its anti-oxidant activity[7]. Besides chalcones, quinazolinone congeners were also reported to possess diverse biological actions ranging from antimicrobial to antitubercular activities[8-15]. Previous studies have focused on the synthesis and evaluation of simple quinazolinone derivatives by substitution at different positions of quinazolinone ring. It is also observed that introduction of an aryl/heteroaryl/alkyl group at 2nd and 3rd positions of quinazolinone ring is beneficial to chemotherapeutic activity[16]. So far, only scanty work have been done in synthesis of substituted compounds with 3-aryl-2-thioxo quinazolin-4-(3*H*) ones as a lead. Therefore, the objective of

the present study was to synthesize 1-substituted thioxoquinazolinone chalcones followed by their physical and spectral characterization, *in vitro* antimicrobial and anthelmintic evaluations.

EXPERIMENTAL

Materials

Anthranilic acid for synthesis is of analytical grade and procured from Sigma Aldrich Ltd. Chemicals like Hydroxyl Amine HCl ($NH_2OH.HCl$), Aniline, *p*-chloro aniline, *p*-bromo aniline, *m*-chloro aniline, *p*-fluoro aniline and *p*-methyl aniline were procured from Fischer Scientific Ltd. All other chemicals used for synthetic purpose were of reagent grade and procured from S D Fine Chemical Ltd. and Loba chemicals Ltd.

Methods

Step-1: Synthesis of 3-(un) substituted phenyl-6-(un) substituted-2-thioxo-4(3*H*)-quinazolinones (1a-r) [17]

A mixture of carbon disulfide (30mM) and the appropriate aromatic amines (12mM) was added drop wise to the refluxed mixture of anthranilic acid (10mM) and potassium hydroxide (12mM) in methanol (10 ml). The mixture was heated under reflux for 3 hours and the solid produced was dissolved in potassium hydroxide solution (10%, 10 ml), filtered and then conc. HCl was added to the filtrate. The white precipitate obtained was filtered, washed with water and dried. The crude product obtained was recrystallized from absolute alcohol.

Step-2: Synthesis of 1-acetyl-3-(un) substituted phenyl-6-(un) substituted-2-thioxo-4(3*H*)-quinazolinones (2a-r) [18]

Each Step-1 compound (1a-r) at concentration of 0.01M was taken in a 100 ml RBF, refluxed gently in 10 ml of acetic anhydride containing 2-5 drops of Conc. Sulphuric Acid for 10-15 minutes. After cooling, the reaction mixture was poured into cold water and stirred until the gum converts into solid. The reaction mixture was boiled for about 10-15 minutes to decompose the excess acetic anhydride. The hot solution was allowed to cool and filtered and finally the crude product obtained was recrystallized from absolute alcohol.

Step-3: Synthesis of 3-phenyl-1-[3'-(un) substituted phenyl-6'- (un) substituted-2'-thioxo-4' (3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3a-r) [19]

A mixture of 1-acetyl-3-(un)substitutedphenyl-6-(un) substituted-2-thioxo-4(3*H*)-quinazolinones (2a-r) (0.01M) and benzaldehyde (0.01M) was refluxed with absolute ethanol (50ml) containing 2% NaOH for 8-12 hrs. Reaction mixture was concentrated and then diluted with ice cold water after bringing it to room temperature. The solid thus obtained was filtered, recrystallized from absolute ethanol to get the compounds 3a-r. The titled compounds were synthesized according to Scheme-1.

Characterization

Melting point of the synthesized compounds was determined by an open-end capillary tube method using electrically heated melting point apparatus. The respective values were expressed in ^{o}C and were uncorrected. Reaction progress and compounds purity was ascertained by thin layer chromatography (TLC). The elemental analyses were performed using Carlo Erba-1108 elemental analyzer. The structures of the synthesized compounds were elucidated by Perkin Elmer 1600 series FT-IR using KBr-Pellet method, ^{1}H FT-NMR (BRUCKER MX 400 MHz) analysis using TMS as internal standard. The mass spectrum of the compounds was recorded on Agilent 1100 series LC-MS.

In vitro antimicrobial and anthelmintic activity

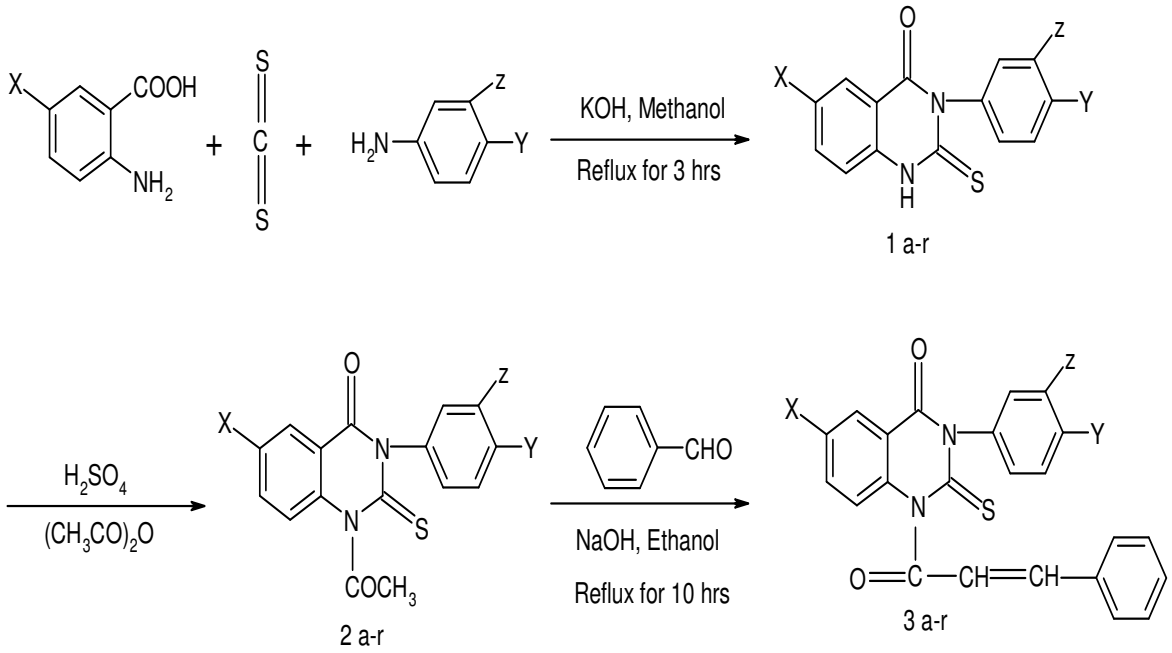
Preparation of Sterile Drug Discs

Whatman filter paper discs (grade-1) of 5 mm diameter were used for studies. They were autoclaved at standard conditions (121°C, 15lb pressure for 15 min) for sterilization. All test compounds were dissolved

in 10% DMSO in methanol. The sterilized discs were impregnated with different synthesized compounds to obtain concentrations 200 µg/disc, 400 µg/disc and 600 µg/disc.

Antibacterial activity

The synthesized compounds 3a-r were screened for their *in vitro* antibacterial activity against Non-pathogenic bacteria like *Bacillus subtilis MTCC 441, Bacillus cereus MTCC 430* and pathogenic bacteria *like Staphylococcus aureus MTCC 737, Staphylococcus epidermidis MTCC 3086(gram positive), Pseudomonas aeruginosa MTCC 1035* and *Escherichia coli MTCC 1687(gram negative)* by paper disc diffusion method[20]. The zone of inhibition was measured in mm after incubation at 37±1°C for 18-24 hrs using digital antibiotic zone reader. The activity of the test compounds was compared with standard Ciprofloxacin at 100 µg/disc concentration.



Scheme-1: Synthesis of Novel Quinazolinonyl Chalcones

Antifungal activity

The synthesized compounds 3a-r were screened for their *in vitro* antifungal activity against various pathogenic fungi like *Aspergillus niger MTCC 2638, Aspergillus foetidus MTCC 2737*, *Candida albicans MTCC 301* and *Candida glabrata MTCC 3019* and non pathogenic fungi *Saccharomyces cerevisiae MTCC 170* by paper disc diffusion method[20]. The zone of inhibition was measured in mm after incubation at 25±1°C for 72 hrs using digital antibiotic zone reader. The zone of inhibition was measured in mm and activity was compared with standard Fluconazole at 100 µg/disc concentration.

Anthelmintic activity

The synthesized compounds were tested for their *in vitro* anthelmintic activity according to the method described by Ghosh et al. with slight modification[21]. Adult Indian earth worm *Peritima posthuma* of nearly equal size (9±1.5 cm) was selected for present study because of its anatomical and physiological resemblance with the intestinal parasites of human beings. The synthesized compounds were prepared in 1% DMF in normal saline to obtain 1mg/ml concentration which was taken in each petri dish (4inches). Paralytic and lethal time taken for individual worms was observed taking 2hr time period as the maximum time for parasite response to compound. Paralysis was said to occur when the worms did not revive even

in normal saline. Lethal time was concluded or ascertained when worms lose their motility with a faded body color. Standard used for comparing the anthelmintic activity was Albendazole at 10mg/ml concentration.

Statistical Analysis

All the results were expressed as mean ± SEM. Statistical analyses were performed using one-way ANOVA followed by a *post hoc Newman-keuls multiple comparison test*. In all cases, $p < 0.05$ was considered as significant.

RESULTS AND DISCUSSION

Reaction of anthranilic acid and its derivatives with aromatic amines (aniline, *p*-chloro aniline, *p*-bromo aniline, *m*-chloro aniline, *p*-fluoro aniline and *p*-methyl aniline) and carbon disulfide in the presence of potassium hydroxide in methanol under reflux for 3hr afforded the corresponding 3-(un)substitutedphenyl-6-(un)substituted-2-thioxo-4(3*H*)-quinazolinones 1a-r. Absorption bands in the range 3210-3445 cm^{-1} and 1505-1590 cm^{-1} in the IR spectrum of the synthesized compounds (1a-r) indicated the presence of N-H and a thioureide group (N-C=S) in the system. Strong absorption band in the range of 1600-1690 cm^{-1} and a medium band at 1100-1290 cm^{-1} were also observed due to C=O stretching and C=S stretching respectively[22]. The absence of any band in the region 2600-2550 cm^{-1} (characteristic of a thiol group) indicated that the compound exists in the solid state in the thione form. The ^{1}HNMR spectrum of 2-thioxo-quinazolin-4(3*H*)-one in DMSO-d_6 showed a singlet of 1H intensity at δ13 ppm for the proton attached to the nitrogen at position 1, and a complex multiplet of 14 protons between δ6.0-8.8 ppm[22]. All the above results correlate and confirm the formation of thioxoquinazolinone ring system in respective compounds.

When above synthesized first step compounds were treated with acetic anhydride, acetyl group was introduced at 1st position of the quinazolinone nucleus and resulted in compounds 2a-r. The disappearance of a peak corresponding to NH in between δ9.7ppm to δ13.0ppm and appearance of peak at δ1.72ppm due to the protons of acetyl group confirms acetyl group introduction.

Claisen Schmidt condensation of 2a-r with benzaldehyde in alcoholic alkali gave corresponding quinazolinonyl chalcones 3a-r. IR spectrum of the quinazolinonyl chalcones showed a peak at 1670cm^{-1} because of presence of α, β-unsaturated keto functional group[23]. Appearance of doublets in the range of δ 6.7-6.9ppm and 7.44-7.56, disappearance of singlet corresponds to 3 protons of the N- acetyl group confirmed the 2-propen-1-one moiety of the titled (3a-r) compounds[24].

All the physical characterization data of compounds 3a-r were tabulated and were summarized in table-1. The spectral data of all respective chalcone derivatives is given below-

3-Phenyl-1-[3'-phenyl-2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3a): Amorphous cream solid. IR-(KBr, $V_{max,}$ cm^{-1}): 1678.52(-CO-CH=CH-), 1600.12(-CH=CH-), 3146.53(-CH of propene), 1516.87(-CH=CH- of aromatic ring), 3213.63(Ar-CH-), 1211.32(C=S). ^{1}H-NMR (δ ppm): 6.87(1H, d, -CO-CH=), 7.51(1H, d, -CH-Ar), 7.06-8.32(14H, m, Ar-H). MS (m/z): 384.09.

3-Phenyl-1-[3'-(4"-chlorophenyl)-2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3b): Amorphous yellow solid. IR-(KBr, $V_{max,}$ cm^{-1}): 1696.67(-CO-CH=CH-), 1615.19(-CH=CH-), 3016.62(-CH of propene), 1545.91(-CH=CH- of aromatic ring), 3166.84(Ar-CH-), 1232.51(C=S). ^{1}H-NMR (δ ppm): 6.81(1H, d, -CO-CH=), 7.52(1H, d, -CH-Ar), 7.16-8.26(13H, m, Ar-H). MS (m/z): 418.05.

3-Phenyl-1-[3'-(4"-bromophenyl)-2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3c): Amorphous brown solid. IR-(KBr, $V_{max,}$ cm^{-1}): 1713.64(-CO-CH=CH-), 1618.93(-CH=CH-), 3003.27(-CH of propene), 1556.39(-CH=CH- of aromatic ring), 3184.25(Ar-CH-), 1204.67(C=S). ^{1}H-NMR (δ ppm): 6.83(1H, d, -CO-CH=), 7.48 (1H, d, -CH-Ar), 7.23-8.65(13H, m, Ar-H). MS (m/z): 462.00

3-Phenyl-1-[3'-(3"-chlorophenyl)-l-2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3d):
Amorphous grey solid. IR-(KBr, $V_{max,}$ cm^{-1}): 1677.72(-CO-CH=CH-), 1648.16(-CH=CH-), 3026.72(-CH of propene), 1545.61(-CH=CH- of aromatic ring), 3296.812(Ar-CH-), 1201.26(C=S). ^{1}H-NMR (δ ppm): 6.80(1H, d, -CO-CH=), 7.46(1H, d, -CH-Ar), 7.20-8.31(13H, m, Ar-H). MS (m/z): 418.05.

3-Phenyl-1-[3'-(4"-fluorophenyl)-phenyl-2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3e):
Amorphous yellow solid. IR-(KBr, $V_{max,}$ cm^{-1}): 1656.80(-CO-CH=CH-), 1610.46(-CH=CH-), 3080.16(-CH of propene), 1520.32(-CH=CH- of aromatic ring), 3108.62(Ar-CH-), 1230.63(C=S). ^{1}H-NMR (δ ppm): 6.88(1H, d, -CO-CH=), 7.52(1H, d, -CH-Ar), 7.05-8.54(13H, m, Ar-H). MS (m/z): 402.08.

3-Phenyl-1-[3'-(4"-toluidinyl)-2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3f):
Amorphous brown solid. IR-(KBr, $V_{max,}$ cm^{-1}): 1726.35(-CO-CH=CH-), 1649.19(-CH=CH-), 3028.34(-CH of propene), 1514.17(-CH=CH- of aromatic ring), 3136.36(Ar-CH-), 1271.13(C=S). ^{1}H-NMR (δ ppm): 6.90(1H, d, -CO-CH=), 7.53(1H, d, -CH-Ar), 7.18-8.18(13H, m, Ar-H), 2.14 (3H, s, $-CH_3$). MS (m/z): 398.10.

3-Phenyl-1-[6'-bromo-3'-phenyl-2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3g):
Amorphous brown solid. IR-(KBr, $V_{max,}$ cm^{-1}): 1689.61(-CO-CH=CH-), 1601.53(-CH=CH-), 3158.73(-CH of propene), 1509.81(-CH=CH- of aromatic ring), 3253.28(Ar-CH-), 1206.57(C=S). ^{1}H-NMR (δ ppm): 6.82(1H, d, -CO-CH=), 7.44(1H, d, -CH-Ar), 6.96-7.98(13H, m, Ar-H). MS (m/z): 462.00.

3-Phenyl-1-[6'-bromo -3'-(4"-chlorophenyl)- 2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3h):
Amorphous brown solid. IR-(KBr, $V_{max,}$ cm^{-1}): 1669.55(-CO-CH=CH-), 1608.69(-CH=CH-), 3304.17(-CH of propene), 1537.32(-CH=CH- of aromatic ring), 3194.23(Ar-CH-), 1261.49(C=S). ^{1}H-NMR (δ ppm): 6.83(1H, d, -CO-CH=), 7.49(1H, d, -CH-Ar), 7.03-7.99(12H, m, Ar-H). MS (m/z): 495.96.

3-Phenyl-1-[6'-bromo -3'-(4"-bromophenyl)- 2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3i):
Amorphous brown solid. IR-(KBr, $V_{max,}$ cm-1): 1674.12(-CO-CH=CH-), 1605.15(-CH=CH-), 3136.60(-CH of propene), 1565.84(-CH=CH- of aromatic ring), 3270.41(Ar-CH-), 1224.80(C=S). ^{1}H-NMR (δ ppm): 6.84(1H, d, -CO-CH=), 7.46(1H, d, -CH-Ar), 7.21-8.65(12H, m, Ar-H). MS (m/z): 541.91.

3-Phenyl-1-[6'-bromo -3'-(3"-chlorophenyl)- 2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3j):
Amorphous brown solid. IR-(KBr, $V_{max,}$ cm^{-1}): 1663.17(-CO-CH=CH-), 1620.01(-CH=CH-), 3061.20(-CH of propene), 1553.92(-CH=CH- of aromatic ring), 3175.51(Ar-CH-), 1243.50(C=S) ^{1}H-NMR (δ ppm): 6.80(1H, d, -CO-CH=), 7.49(1H, d, -CH-Ar), 7.14-8.05(12H, m, Ar-H). MS (m/z):495.96.

3-Phenyl-1-[6'-bromo -3'-(4"-fluorophenyl)- 2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3k):
Amorphous brown solid. IR-(KBr, $V_{max,}$ cm^{-1}): 1666.60(-CO-CH=CH-), 1619.16(-CH=CH-), 3065.18(-CH of propene), 1501.51(-CH=CH- of aromatic ring), 3201.99(Ar-CH-), 1208.32(C=S). ^{1}H-NMR (δ ppm): 6.87(1H, d, -CO-CH=), 7.55(1H, d, -CH-Ar), 7.18-8.46(12H, m, Ar-H). MS (m/z): 479.99.

3-Phenyl-1-[6'-bromo -3'-(4"-toluidinyl)- 2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3l):
Amorphous brown solid. IR-(KBr, $V_{max,}$ cm^{-1}): 1666.55(-CO-CH=CH-), 1627.97(-CH=CH-), 3030.27(-CH of propene), 1512.24(-CH=CH- of aromatic ring), 3190.37(Ar-CH-), 1251.84(C=S). ^{1}H-NMR (δ ppm): 6.86(1H, d, -CO-CH=), 7.56(1H, d, -CH-Ar), 7.18-8.06(12H, m, Ar-H), 2.33(3H, s, $-CH_3$). MS (m/z): 476.01.

3-Phenyl-1-[6'-iodo -3'-phenyl-2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1'-one (3m):
Amorphous black solid. IR-(KBr, $V_{max,}$ cm^{-1}): 1676.76(-CO-CH=CH-), 1607.42(-CH=CH-), 3056.38(-CH of propene), 1536.61(-CH=CH- of aromatic ring), 3321.73(Ar-CH-), 1203.917(C=S). ^{1}H-NMR (δ ppm): 6.83(1H, d, -CO-CH=), 7.42(1H, d, -CH-Ar), 6.95-8.10(13H, m, Ar-H). MS (m/z): 509.98.

3-Phenyl-1-[6'-iodo -3'-(4"-chlorophenyl)- 2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3n):
Amorphous black solid. IR-(KBr, $V_{max,}$ cm^{-1}): 1687.71(-CO-CH=CH-), 1653.05(-CH=CH-), 3042.13(-CH of propene), 1525.74(-CH=CH- of aromatic ring), 3201.91(Ar-CH-), 1217.12(C=S). ^{1}H-NMR (δ ppm): 6.84(1H, d, -CO-CH=), 7.46(1H, d, -CH-Ar), 7.05-8.16 (12H, m, Ar-H). MS (m/z): 543.95.

3-Phenyl-1-[6'-iodo -3'-(4"-bromophenyl)-2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3o):
Amorphous light green solid. IR-(KBr, $V_{max,}$ cm^{-1}): 1661.50(-CO-CH=CH-), 1607.42(-CH=CH-), 3029.58(-CH of propene), 1515.30(-CH=CH- of aromatic ring), 3236.95(Ar-CH-), 1211.89(C=S). ^{1}H-NMR (δ ppm): 6.85(1H, d, -CO-CH=), 7.51(1H, d, -CH-Ar), 7.24-8.57(12H, m, Ar-H). MS (m/z): 587.90.

3-Phenyl-1-[6'-iodo -3'-(3"-chlorophenyl)-2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3p):
Amorphous black solid. IR-(KBr, $V_{max,}$ cm^{-1}): 1716.35(-CO-CH=CH-), 1663.40(-CH=CH-), 3059.37(-CH of propene), 1484.15(-CH=CH- of aromatic ring), 3236.66(Ar-CH-), 1209.41(C=S). ^{1}H-NMR (δ ppm): 6.78(1H, d, -CO-CH=), 7.42(1H, d, -CH-Ar), 7.00-8.16(12H, m, Ar-H). MS (m/z): 543.95.

3-Phenyl-1-[6'-iodo -3'-(4"-fluorophenyl)-2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3q):
Amorphous grey solid. IR-(KBr, $V_{max,}$ cm-1): 1667.59(-CO-CH=CH-), 1610.45(-CH=CH-), 3106.65(-CH of propene), 1507.07(-CH=CH- of aromatic ring), 3237.30(Ar-CH-), 1264.28(C=S). ^{1}H-NMR (δ ppm): 6.79(1H, d, -CO-CH=), 7.48(1H, d, -CH-Ar), 6.95-8.56(12H, m, Ar-H). MS (m/z): 527.98.

3-Phenyl-1-[6'-iodo-3'-(4"-toluidinyl)-2'-thioxo-4'(3'*H*)-quinazolinon-1'-yl]-2-propen-1-one (3r):
Amorphous brown solid. IR- (KBr, $V_{max,}$ cm^{-1}): 1660.47(-CO-CH=CH-), 1649.19(-CH=CH-), 3023.69(-CH of propene), 1508.70(-CH=CH- of aromatic ring), 3136.36(Ar-CH-), 1208.76(C=S). ^{1}H-NMR (δ ppm): 6.86(1H, d, -CO-CH=), 7.53(1H, d, -CH-Ar), 7.14-8.21(12H, m, Ar-H), 2.26 (3H, s, $-CH_3$). MS (m/z): 524.00.

Table-1: Physical Characterization data of the Synthesized Chalcones

Compd.	X	Y	Z	Mol. Formula & Mol. Wt.	MP (°C)	% Yield	Elemental Analysis (%): Calcd. (Found)		
							C	H	N
3a	H	H	H	$C_{23}H_{16}N_2OS$ (384)	130	26.7	71.87 (70.18)	4.16 (4.02)	7.29 (6.83)
3b	H	Cl	H	$C_{23}H_{15}N_2O_2SCl$ (418.45)	190	40.6	65.95 (63.56)	3.58 (3.06)	6.69 (5.45)
3c	H	Br	H	$C_{23}H_{15}N_2O_2SBr$ (463)	192	21.7	59.26 (59.02)	3.24 (3.08)	6.04 (5.91)
3d	H	H	Cl	$C_{23}H_{15}N_2O_2SCl$ (418.45)	250	50.1	65.95 (64.53)	3.58 (3.22)	6.69 (6.42)
3e	H	F	H	$C_{23}H_{15}N_2O_2SF$ (402)	149	65.0	68.65 (66.47)	3.73 (3.51)	6.96 (5.87)
3f	H	CH_3	H	$C_{24}H_{18}N_2O_2S$ (398)	166	67.3	69.34 (70.15)	4.52 (4.12)	7.03 (6.83)
3g	Br	H	H	$C_{23}H_{15}N_2O_2SBr$ (463)	148	56.5	59.62 (56.48)	3.24 (3.18)	6.04 (5.92)

3h	Br	Cl	H	$C_{23}H_{14}N_2O_2SBrCl$ (497.35)	152	47.3	55.49 (54.82)	2.81 (2.14)	5.62 (5.02)
3i	Br	Br	H	$C_{23}H_{14}N_2O_2SBr_2$ (542)	216	40.1	50.94 (49.16)	2.58 (2.28)	5.16 (5.07)
3j	Br	H	Cl	$C_{23}H_{14}N_2O_2SBrCl$ (497.35)	250	56.7	55.49 (52.63)	2.81 (2.17)	5.62 (5.05)
3k	Br	F	H	$C_{23}H_{14}N_2O_2SBrF$ (481)	122	61.7	57.39 (55.84)	2.91 (2.13)	5.82 (4.96)
3l	Br	CH_3	H	$C_{24}H_{17}N_2O_2SBr$ (477)	154	71.6	60.39 (60.01))	3.56 (3.48)	5.87 (5.18)
3m	I	H	H	$C_{23}H_{15}N_2O_2SI$ (510)	180	58.9	54.13 (52.65)	2.94 (2.52)	5.49 (4.47)
3n	I	Cl	H	$C_{23}H_{14}N_2O_2SICl$ (544.35)	196	26.8	50.70 (49.85)	2.57 (2.18)	5.14 (5.00)
3o	I	Br	H	$C_{23}H_{14}N_2O_2SIBr$ (589)	216	66.7	46.87 (45.12)	2.37 (2.23)	4.75 (3.96)
3p	I	H	Cl	$C_{23}H_{14}N_2O_2SICl$ (544.35)	270	69.2	50.70 (49.84)	2.57 (2.36)	5.14 (4.93)
3q	I	F	H	$C_{23}H_{14}N_2O_2SIF$ (528)	140	56.2	52.28 (50.18)	2.65 (2.15)	5.30 (5.18)
3r	I	CH_3	H	$C_{24}H_{17}N_2O_2SI$ (524)	190	80.4	54.97 (53.86)	3.24 (3.06)	5.34 (4.72)

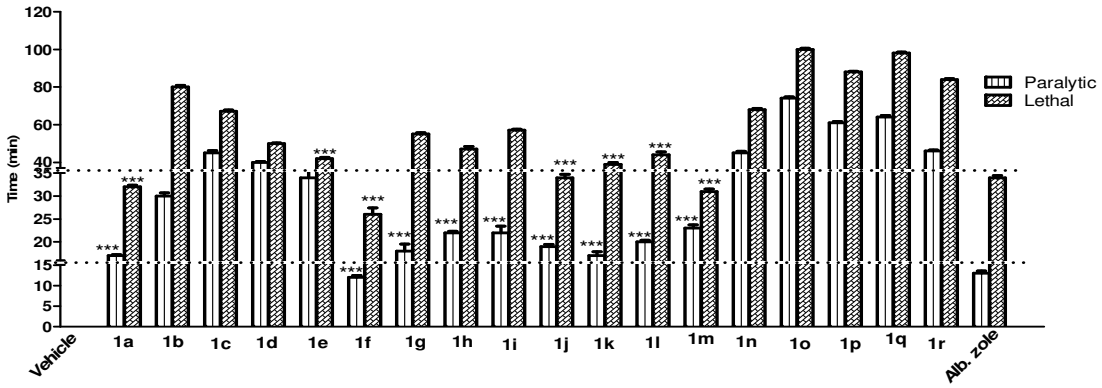


Fig.-1: Anthelmintic activity of Compounds 1a-r. Results are expressed as Mean ± SEM (n=6). ***P < 0.05 compared to lethal and paralytic time (min) of Albendazole.

In vitro antimicrobial activity

Antimicrobial activity results of all synthesized quinazolinones and quinazolinonyl chalcones were given in table 2 and table 3. The results revealed that quinazolinonyl chalcones 3a-r exhibited better antimicrobial activity than the corresponding quinazolinones 1a-r. Antimicrobial data of various synthesized compounds was divided into active types (less, weak, moderate and high) basing upon inhibition zone data (table 4 and table 5). Especially compounds 3b, 3f, 3i, 3k, 3l and 3n showed better antimicrobial activity against all the selected microorganisms while the remaining compounds have shown moderate antimicrobial activity. The significant activity was might be due to α, β-unsaturated

keto functional group and the substituent's at the quinazolinone nucleus. The order of activity for the compounds is 3g-3l>3a-f>3m-r.

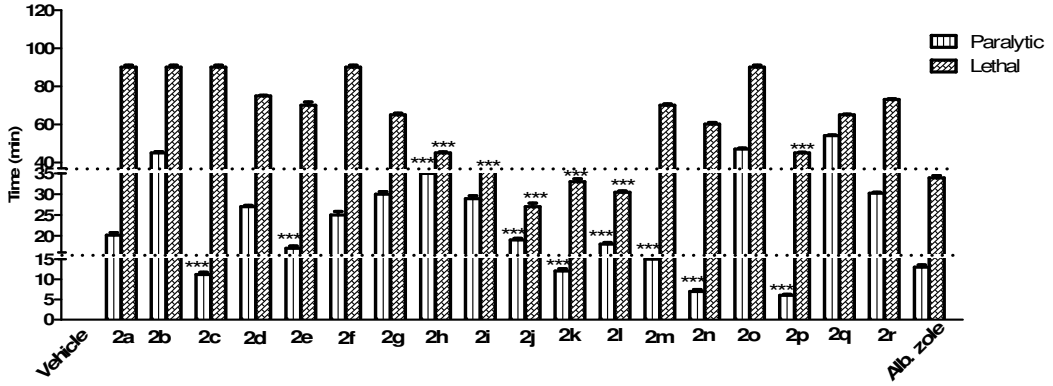


Fig.-2: Anthelmintic activity of compounds 2a-r. Results are expressed as Mean ± SEM (n=6). ***P < 0.05 compared to lethal and paralytic time (min) of Albendazole.

Table-2: Antibacterial activity of Synthesized Compounds

Compd. (600 µg/ml)		Zone of inhibition (mm)											
		B. s		*B. c*		*S. a*		*S. e*		*P. a*		*E. c*	
		1a-r	*3a-r*	*1a-r*	*3a-r*	*1a-r*	*3a-r*	*1a-r*	*3a-r*	*1a-r*	*3a-r*	*1a-r*	*3a-r*
1a	3a	7	13	-	-	-	-	-	6	-	-	8	-
1b	3b	8	9	12	10	11	12	12	13	8	8	9	9
1c	3c	9	9	8	8	6	10	8	7	6	11	8	10
1d	3d	8	-	16	9	9	8	9	8	8	7	-	8
1e	3e	10	13	-	8	6	10	-	-	-	16	-	13
1f	3f	7	11	-	8	-	9	9	10	7	9	9	9
1g	3g	11	12	12	8	9	11	13	-	10	8	11	9
1h	3h	14	-	10	12	16	16	14	-	10	12	11	12
1i	3i	15	9	10	9	10	10	12	8	10	14	11	12
1j	3j	14	15	11	11	11	13	9	-	10	9	10	10
1k	3k	14	12	12	14	13	14	14	11	15	12	13	12
1l	3l	12	12	12	13	13	11	12	10	10	11	12	13
1m	3m	-	8	10	9	-	-	6	10	7	9	8	10
1n	3n	13	11	10	11	15	10	12	8	10	12	10	13
1o	3o	11	9	9	10	-	10	-	-	9	-	9	-
1p	3p	-	14	-	8	9	10	9	13	7	10	8	9
1q	3q	-	14	8	8	-	8	8	-	-	8	-	8
1r	3r	14	8	8	8	8	7	-	-	7	-	8	-
Ciprofloxacin (100 µg/disc)		21		17		20		20		21		20	
10% DMSO in MeOH		-		-		-		-		-		-	

(1) *B.s: Bacillus subtilis, B.c: Bacillus cereus, S.a: Staphylococcus aureus, S.e: Staphylococcus epidermidis, P.s: Pseudomonas aeruginosa, E.c: Escherichia coli*

(2) (-) indicates no zone of inhibition

(3) All the above compounds were divided into various sensitivity types on the basis of respective zone of inhibitions (mm); < 7 mm are Less active, between 8-10 mm are Weakly active, between 11-13 mm are Moderately active, >14 mm are Highly active

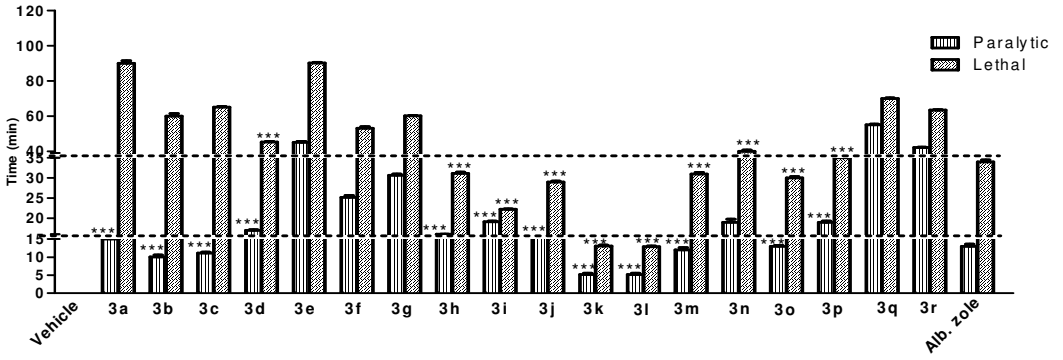


Fig.-3: Anthelmintic activity of compounds 3a-r. Results are expressed as Mean ± SEM (n=6). ***P < 0.05 compared to lethal and paralytic time (min) of Albendazole.

Table-3: Antifungal activity of synthesized chalcone derivatives

Compd. (600 µg/ml)		Zone of Inhibition (mm)									
		C. g		*C. a*		*A. n*		*A. f*		*S. c*	
		1a-r	*3a-r*	*1a-r*	*3a-r*	*1a-r*	*3a-r*	*1a-r*	*3a-r*	*1a-r*	*3a-r*
1a	3a	10	11	-	-	-	11	-	-	-	-
1b	3b	10	12	-	11	9	13	-	8	-	7
1c	3c	10	11	8	-	6	13	-	10	-	9
1d	3d	8	8	8	-	7	10	-	-	-	7
1e	3e	9	9	10	-	9	9	-	-	-	9
1f	3f	7	10	9	9	8	9	10	9	-	12
1g	3g	9	11	8	14	7	10	8	10	9	8
1h	3h	10	8	9	13	10	11	8	-	7	11
1i	3i	13	14	8	15	11	18	10	17	7	9
1j	3j	12	11	8	16	-	-	-	-	10	-
1k	3k	15	18	11	25	10	16	12	13	08	9
1l	3l	16	17	11	17	11	13	10	15	7	14
1m	3m	9	10	-	11	-	-	-	8	-	7
1n	3n	7	11	-	12	-	13	-	12	-	10
1o	3o	13	15	-	10	-	-	-	10	-	-
1p	3p	10	9	-	7	-	-	-	-	-	9
1q	3q	10	12	10	11	11	16	10	12	8	10
1r	3r	14	10	9	9	-	12	-	12	-	11
Fluconazole (100 µg/disc)		21		22		16		16		13	
10% DMSO in MeOH		-		-		-		-		-	

(1.) *C.g: Candida glabrata, C. a: Candida albicans, A. n: Aspergillus niger, A. f: Aspergillus foetidus, S. c: Saccharomyces cerevisiae*

(2.) (-) indicates no zone of inhibition

(3.) All the above compounds were divided into various sensitive types on the basis of respective zone of inhibitions (mm); < 8 mm are Less active, between 9-12 mm are Weakly active, between 13-16 mm are Moderately active, >17 mm are Highly active

Table-4: Comparison of antibacterial activities of synthesized compounds based on various activity types

Comp. ID	Bacteria type											
	B. s		*B. c*		*S. a*		*S. e*		*P. a*		*E. c*	
	1a-r	*3a-r*	*1a-r*	*3a-r*	*1a-r*	*3a-r*	*1a-r*	*3a-r*	*1a-r*	*3a-r*	*1a-r*	*3a-r*
b	++	++	+++	++	+++	+++	+++	+++	++	++	++	++
c	++	++	++	++	+	++	++	++	+	+++	++	++
f		+++		++		++		++		++		++
g	+++		+++		++		+++		++		+++	
h	++++		++		++++		++++		++		+++	
i	++++	+++	++	+++	++	+++	+++	+++	++	++++	+++	+++
j	++++		+++		+++		++		++		++	
k	++++	+++	+++	++++	+++	+++	++++	++++	++++	+++	+++	+++
l	+++	+++	+++	+++	+++	+++	+++	++	++	+++	+++	+++
n	+++	+++	++	+++	++++	++	+++	++	++	+++	++	+++
p		++++		++		++		+++		++		++

(1) For convenience, compounds showing an activity against all the selected organisms were only represented in the above table
(2) + - Less active; ++ - weakly active; +++ - Moderately active; ++++ - Highly active

Table-5: Comparison of antifungal activities of synthesized compounds based on various activity types

Comp. ID	Fungi type									
	C. g		*C. a*		*A. n*		*A. f*		*S. c*	
	1a-r	*3a-r*	*1a-r*	*3a-r*	*1a-r*	*3a-r*	*1a-r*	*3a-r*	*1a-r*	*3a-r*
b		++		++		+++		+		+
f		++		++		++		++		++
g	++	++	+	+++	+	++	+	++	++	++
h	++		++		++		+		+	
i	++++	+++	+	+++	++	++++	++	++++	+	++
k	+++	++++	++	++++	++	++++	++	+++	+	++
l	++++	++++	++	++++	++	+++	++	+++	+	+++
n		++		++		+++		++		++
q	++	++	++	++	++	++++	++	++	+	++

(1) For convenience, compounds showing an activity against all the selected organisms were only represented in the above table
(2) + - Less active; ++ - weakly active; +++ - Moderately active; ++++ - Highly active

In vitro anthelmintic activity

The results of anthelmintic data were represented in Fig. 1, 2 and 3. In first step compounds 1a, 1f, 1j, 1k, 1l, and 1m showed moderate anthelmintic activity. During 2nd step there was no improvement in anthelmintic activity. When 2a-r were condensed with aromatic aldehyde benzaldehyde, owing to the formation of reactive α, β-unsaturated keto functional group, the paralytic and lethal time were reduced significantly. Thus 3a-r showed improved anthelmintic activity than 2a-r and 1a-r respectively. Compounds 3h, 3i, 3j 3k, 3l , 3m and 3o showed extremely significant anthelmintic activity that was comparable to standard Albendazole. Chalcones containing 2-thioxo-4(3*H*)-quinazolinone moiety might contribute to the development of new anthelmintic drugs.

CONCLUSION

In our present work, we have synthesized 18 novel 2-thioxoquinazolinon-1-yl chalcones with two biolabile components which are chalcones and quinazolinones. Compounds possessing bromo (Br) at 6th position and *p*-bromo, *p*-fluoro and *p*-methyl substituted phenyl ring at 3rd position of 2-thioxoquinazolinone nucleus showed better antimicrobial and anthelmintic activities at microgram (µg) concentration levels. Therefore, the present work provides excellent approach for the synthesis of potent antimicrobial and anthelmintic quinazolinonyl chalcones. In future, further studies like establishment of structure activity relationship (SAR, QSAR) might be necessary for better understanding of their mechanism of action. Synthesis of novel pyrazolines, pyrimidines and isoxazoles from the above synthesized thioxoquinazolinon-1-yl chalcones might also lead to new lead with better potency and efficacy.

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