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SYNTHESIS OF NOVEL SERIES OF 2-AMINO-1, 2-DIHYDROISOQUINOLINE-3(4*H*)-ONE DERIVATIVES USED AS ANTIMICROBIAL AND ANTIOXIDANT AGENTS

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ABSTRACT: A facile synthesis of novel 2-amino-1,2-dihydroisoquinoline-3(4*H*)-one and their amide derivatives (**6a-o**) through sydnone intermediate (**3**) was derived from tetrahydroisoquinoline-3-carboxylic acid (**1**) and various substituted phenyl acrylic acid derivatives (**5a-o**) in short reaction time with good yield. The structure of all novel synthesized compounds was established based on Mass, ^{1}H NMR, ^{13}C NMR, IR spectral data and Single crystal X-ray study (**6e**). All the synthesized compounds were evaluated for their antimicrobial and antioxidant activities.

INTRODUCTION: Oxidative metabolism is an essential phenomenon for the survival of cells. The total oxygen intake, about 2-3% oxygen is converted to harmful intermediates that are termed as reactive oxygen species (ROS) which leads to cumulative damage to cellular proteins, DNA, enzymes and membrane lipids.[1 2] Free radicals that lead to cancer,[3] respiratory tract disorders,[4] heart diseases stroke,[5] diabetics,[6] atherosclerosis[7] and intestinal diseases.[8]

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Moreover free radicals directly promote various neurodegenerative diseases [9 10]such as parkinson disease[11] and Alzheimer disease.[12] Recently, resveratrol (3, 5, 4'-trihydroxy-*trans*-stilbene), a natural product derived from grapes, was found to have antioxidative [13, 14, 15] and antimutagenic properties.[16] Microbial resistance also continues to be a growing problem in the treatment of microbial infections. The particular problem is in multidrug resistance for a variety of pathogens such as *Staphylococcus aureus* & *Streptococcus pneumonia* and their control is a matter of great concern. Antimicrobial activity of resveratrol has also been studied against *Staphylococcus aureus*, *Enterococcus faecalis*, *Pseudomona saeruginosa* and *Dermatophytes*. [17] Phenyl acrylic acids also called as stilbene carboxylic acids are contributing a significant role in the medicinal chemistry because of their extensive applications. These

compounds can be prepared by perkin reaction in good yield. Here aromatic aldehydes react with phenyl acetic acid derivatives under basic condition, providing substituted stilbene carboxylic acids with high *E*-selectivity. This type of carboxylic acid groups demonstrate intermolecular hydrogen bonding that leads to dimeric structures. These smaller interactions also enhance the hydrolysis of these compounds that favours the permeation through lipid layer and hence improve the biological activity. [18]

In the literature [19] the title compound **4** have been synthesised from homophthalic acid in five steps. *N*-phenylsydnone has been reported to give phenyl hydrazine on treatment with HCl. [20] [21] Sydnone derived from proline refluxed with propiolic acid in xylene gave the corresponding cyclic hydrazide. [22] These reports revealed that the mechanism of formation of the hydrazine and hydrazide product suggested that **4** could be easily accessed through the sydnone intermediate **3**. In continuation of our work, [23] 2-amino-1, 2-dihydroisoquinoline-3(4*H*)-one **4** and their amide derivatives were listed in **Table 1**. The aim of this study was to evaluate of the 2-amino-1, 2-dihydroisoquinoline-3-4(*H*)-one derivatives as antimicrobial and antioxidant agents.

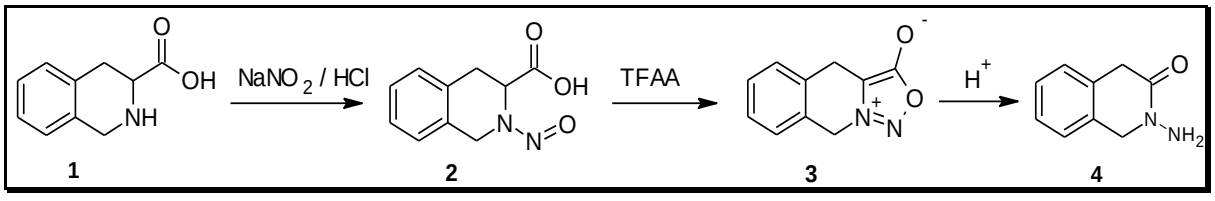
MATERIALS AND METHODS:

All the chemicals were procured from Sigma Aldrich with laboratory grade. Melting points were determined by using the capillary method on a POLMON digital melting point apparatus are uncorrected. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker Advance 400 spectrometer operating at 400.00 MHz. Chemical shift values (ppm) were reported relative to TMS as internal standard. Mass spectra (CG/MS) were recorded on a Agilent MSD VL mass spectrometer. The IR spectra were recorded from KBr pellets with JASCO spectrometer and frequencies are expressed in cm^{-1}. The antioxidant activity measurement was carried out using a Shimadzu UV-2450 spectrophotometer. The purity of the compounds was determined by HPLC and found to be >95%.

A commercially available tetrahydroisoquinoline-3-carboxylic acid (TIC) **1** was treated with $NaNO_2$ in HCl to generate the *N*-nitrosocompound **2,** [24] which on subsequent reaction with trifluoroacetic anhydride gave the corresponding sydnone **3**. The sydnone was treated with Conc. HCl under reflux condition for 12 h to give the corresponding *N*-amino compound **4** as shown in **scheme 1**. The reaction of the sydnone **3** with acetic acid under reflux for 7 h gave the corresponding amide in good yield. [23] To expand the scope of the reaction, we undertook a systematic study of the reaction of sydnone derived from TIC **1** with various substituted stilbene carboxylic acids. This cyclic hydrazide is a very useful precursor for the synthesis of various heterocyclic compounds. The reaction of **3** with one equivalent of substituted stilbene carboxylic acids in refluxing xylene for 5-8 h gave amide derivatives as shown in scheme 2.

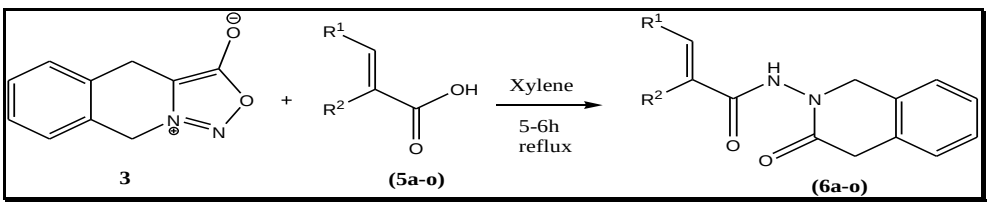
SCHEME 1

Synthesis of 2-amino-1, 2-dihydroisoquinoline-3-4(*H*)-one (4)



SCHEME 2

Synthesis of the compounds (6a-o)



The compound **6e** was confirmed by Single crystal X-ray diffraction [25] **(Fig.1).**

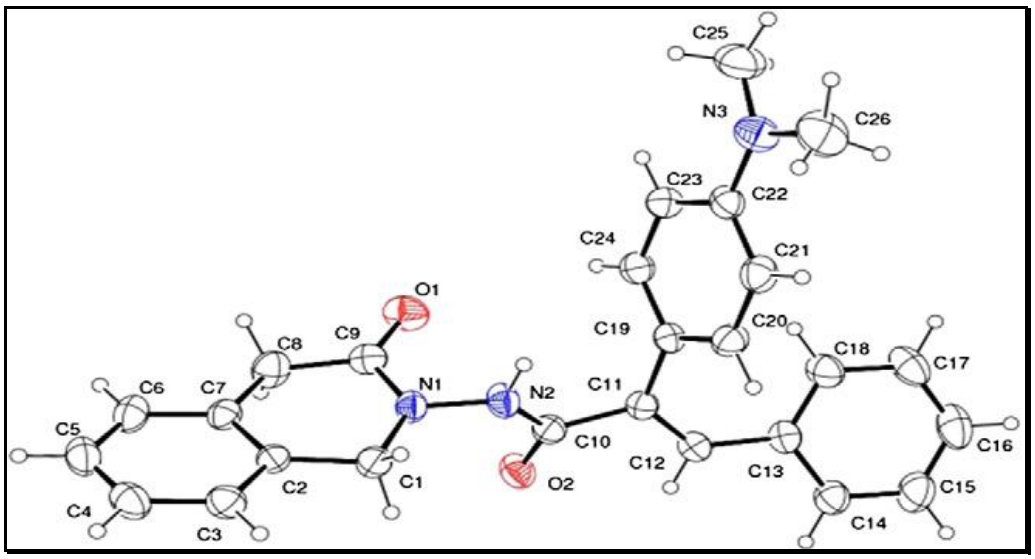


FIG. 1. X-ray STRUCTURE OF THE COMPOUND 6e.

TABLE 1
Synthesis of compounds (6a-o) by conventional method

Compounds	R_1	R_2	Time (h)	Yield[a] (%)	Mp[b] (ºC)
6a	4-SCH_3 - phenyl	4-F-phenyl	6	92	**168-171**
6b	4-CN-phenyl	4-F-phenyl	5	89	**161-164**
6c	3,4-diOCH_3-Phenyl	4-F-phenyl	8	87	**171-173**
6d	3,4-diOCH_3-Phenyl	2-F-phenyl	6	88	**166-168**
6e	Phenyl	4-N,N-diCH_3-Phenyl	5	93	**163-166**
6f	Phenyl	2-Cl-4-F-Phenyl	6	88	**174-176**
6g	Phenyl	*p*-Tolyl	7	86	**180-183**
6h	3,4-di-F-Phenyl	*p*-Anisyl	5	89	**186-188**
6i	3,4-di-F-Phenyl	2-Thiophenyl	7	87	**178-181**
6j	Phenyl	Naphthyl	6	91	**173-175**
6k	3-NO_2-Phenyl	4-F-phenyl	5	86	**159-161**
6l	2-NO_2-Phenyl	4-F-phenyl	7	88	**156-158**
6m	3,4-diOCH_3-Phenyl	3-Cl-Phenyl	5	94	**169-171**
6n	4-F-phenyl	3-Indolyl	6	91	**175-177**
6o	Phenyl	2-F-phenyl	7	89	**158-160**

[a]Isolated yield
[b] Uncorrected

General procedure for the synthesis of the compound 4

Sydnone**3** (0.5 g, 1 mmol) was taken into 20 mL of Conc. HCl and stirring was continued for overnight under reflux condition. Progress of the reaction was monitored by TLC. After completion of the reaction, Conc. HCl was evaporated using rota vapour at 50^0C. Resulting crude product was taken in ethyl acetate (50 mL) and sonicated for 10 min and filtered to give the product **4** as its HCl salt**.** Isolated as pale yellow solid.Yield 91%.m.p.: 94-98°C; IR ν_{max} (KBr) 1682, 1639, 3382 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 3.79 (s, 2H), 4.81 (s, 2H), 7.23-7.34 (m, 4H); ^{13}C NMR (DMSO-d_6) δ (ppm): 35.52, 51.08, 125.75, 126.73, 127.53, 127.73, 129.61, 130.65, 166.94; MS (*m/z*): 163 (M^+ +1).

General procedure for the synthesis of the compounds (6a-o)

Sydnone **3**, (1 mmol) and xylene (30 mL) were charged to a double necked 100 mL round-bottomed flask, equipped with a water cooled condenser. The stirred solution was purged with nitrogen and heated to 140–145°C and carboxylic acid (1 mmol) was added slowly over a period of 15 min. The reaction was held at 140-145°C for 5-8

h. After completion of the reaction, the solvent was removed and the product was purified by column chromatography using hexane-ethylacetate mixture (6:4) as eluent to afford the product. Spectroscopic data for representative 2-amino-1, 2-dihydroisoquinoline-3(4*H*)-one and its amide derivatives are given below.

2 - (4-Fluoro - phenyl) – 3 - (4-methylsulfanyl-phenyl) – N - (3-oxo-3, 4-dihydro-1H-isoquinolin-2-yl) - acrylamide 6a: IR ν_{max} (KBr) 1691, 1733, 3298 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 2.44 (s, 3H), 3.77 (s, 2H), 4.85 (s,2H), 6.92 (2H, d, J=12 Hz), 7.03 (d, 2H, J=12Hz) 7.15-7.26 (4H, m), 7.39-7.42 (m, 3H), 7.52 (s, 1H), 7.84 (s, 1H), 9.89 (s, 1H); ^{13}C NMR (400MHz, DMSO-d_6) δc 23.3, 37.0, 49.9, 53.6, 115.9, 116.1, 125.2, 125.4, 126.4, 126.6, 127.2, 127.4, 128.1, 128.6, 130.3, 130.7, 131.8, 132.7, 135.2, 139.7, 160.8, 163.3, 166.4, 166.8; MS (*m/z*): 432.5 (M^+ +1).

3- (4-Cyano-phenyl) – 2 - (4-fluoro-phenyl) – N - (3-oxo- 3, 4 – dihydro - 1H – isoquinolin – 2 - yl)- acrylamide 6b: IR ν_{max} (KBr) 1667, 1693, 2228, 3331 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 3.78 (s, 2H), 4.87 (s,2H), 6.94 (2H, d, J=12 Hz), 7.07 (d, 2H, J=8Hz), 7.17-7.28 (4H, m), 7.42-7.51 (m, 3H), 7.56 (s, 1H), 7.84 (s, 1H), 9.92 (s, 1H); ^{13}C NMR (400MHz, DMSO-d_6) δc37.2, 49.9, 54.6, 116.7, 116.9, 125.2, 125.4, 126.5, 126.9, 127.2, 127.6, 128.1, 128.6, 130.7, 130.8, 131.8, 132.7, 135.9, 139.8, 160.8, 164.2, 166.5, 166.9; MS (*m/z*): 411.4 (M^+ +1).

3- (3, 4-Dimethoxy-phenyl)-2-(4-fluoro-phenyl)-N - (3-oxo-3, 4-dihydro- 1H – isoquinolin – 2 - yl)- acrylamide 6c: IR ν_{max} (KBr) 1646, 1692, 3276 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H3.40 (s, 3H), 3.70 (s, 2H), 3.72 (s, 3H), 4.68 (2H, s), 6.49 (d, 1H, J=2 Hz), 6.56 (d, 1H, J=4Hz), 6.87 (d, 1H, J=8Hz), 7.23-7.31 (m, 8H), 7.47 (s, 1H), 9.89 (s, 1H); ^{13}C NMR (400MHz, DMSO-d_6) δ_C 36.6, 52.4, 56.1, 111.5, 111.7, 115.4, 122.5, 125.5, 125.9,127.2, 127.4, 128.0, 128.5, 129.4, 132.3, 132.4, 141.2, 149.0, 149.7, 162.1, 165.9, 174.2; MS (*m/z*): 445.5 (M^+ +1).

3- (3, 4-Dimethoxy-phenyl) – 2 - (2-fluoro-phenyl) – N - (3-oxo-3,4-dihydro-1H-isoquinolin-2-yl) - acrylamide 6d: IR ν_{max} (KBr) 1661, 1691, 3331 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ_H3.32 (s, 3H), 3.69 (s, 2H), 3.73 (s, 3H), 4.68 (2H, s), 6.49 (d, 1H, J=4 Hz), 6.88 (d, 1H, J=8Hz), 7.25-7.33 (m, 7H), 7.48 (s, 1H), 7.61 (s, 1H), 10.07 (s, 1H); ^{13}C NMR (400MHz, DMSO-d_6) δ_C 37.1, 53.6, 54.7, 55.4, 111.5, 116.2, 123.4, 124.1, 125.1, 125.5, 126.4, 126.8, 127.2, 127.3, 130.6, 131.6, 131.8, 132.2, 137.7, 148.1, 149.7, 158.6, 161.0, 165.6, 166.8; MS (*m/z*): 445.5 (M^+ +1).

2- (4-(dimethylamino) phenyl) – N - (3-oxo-3, 4-dihydroisoquinolin - 2 (1H) -yl) - 3-phenylacrylamide 6e: Isolated as pale brown solid. Yield 89%.m.p. 163-166°C; IR ν_{max} (KBr) 1678, 1698, 3368 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H2.93 (s, 6H), 3.70 (s, 2H), 4.69 (s, 2H), 6.71(d, 2H), 7.05 (d, 2H), 7.13 (d, 2H), 7.22-7.23 (m, 3H), 7.25-7.28 (m, 5H), 9.87 (1H, s); ^{13}C NMR (400MHz, DMSO-d_6) δ_C 36.96, 53.51, 112.19, 122.02, 125.44, 126.40, 127.16, 127.30, 128.14, 128.27, 129.59, 130.33, 131.68, 131.59, 131.76, 133.12, 134.99, 135.39, 149.92, 166.75, 167.40; MS (*m/z*): 412.2 (M^+ +1).

2-(2-Chloro-4-fluoro-phenyl) - N- (3-oxo- 3, 4-dihydro- 1H - isoquinolin-2-yl) – 3 - phenyl-acrylamide 6f: IR ν_{max} (KBr) 1599, 1660, 3436, 2924 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 3.72 (s, 2H), 4.69 (s,2H), 6.51 (2H, s), 6.79 (d, 1H, J=4Hz), 6.89 (d, 1H, J=8Hz), 7.28-7.32 (5H, m), 7.48 (s, 1H), 7.61 (s, 2H), 9.86 (s, 1H); ^{13}C NMR (400MHz, DMSO-d_6) δc 36.6, 52.4, 113.6, 117.8, 125.9, 127.2, 127.4, 127.9, 128.5, 128.6, 129.4, 130.9, 132.4, 132.7, 138.2, 141.2, 163.5, 165.9; MS (*m/z*): 420.9 (M^+ +1).

N- (3-Oxo-3, 4 - dihydro - 1H - isoquinolin-2-yl) - 3- phenyl-2-p-tolyl-acrylamide 6g: IR ν_{max} (KBr) 1696, 1677, 3370 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 2.37 (s, 3H), 3.78 (s, 2H), 4.81 (s,2H), 7.05 (2H, d, J=4Hz), 7.13-7.22 (m, 2H), 7.25-7.28 (2H, m), 7.37 (d, 2H, J=8Hz), 7.37-7.51 (m, 5H), 7.91 (s, 1H), 9.89 (s, 1H); ^{13}C NMR (400MHz, DMSO-d_6) δc 21.5, 36.7, 52.6, 125.9, 126.9, 127.2, 127.4, 127.9, 128.5, 128.9, 129.4, 132.3, 132.4, 134.6, 135.4, 137.8, 138.6, 141.4, 165.9, 174.4; MS (*m/z*): 382.5 (M^+ +1).

3 - (3, 4-Difluoro-phenyl)-2-(4-methoxy-phenyl)-N-(3-oxo-3, 4-dihydro-1H-isoquinolin – 2 - yl)- acrylamide 6h: IR ν_{max} (KBr) 1691, 1733, 3298 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 3.85 (s, 3H),

3.78 (s, 2H), 4.87 (s, 2H), 6.94 (2H, d, J=12 Hz), 7.05 (d, 2H, J=8Hz) 7.17-7.28 (4H, m), 7.39-7.42 (m, 3H), 7.38-7.41 (m, 3H), 7.51 (s, 1H), 7.84 (s, 1H), 9.87 (s, 1H); ^{13}C NMR (400MHz, DMSO-d_6) δc 36.6, 52.6 55.8, 112.6, 114.3, 122.4, 125.2, 125.9, 126.0, 127.4, 129.2, 130.2, 132.3, 132.4, 138.2, 141.2, 148.6, 149.2, 159.8, 165.9, 174.2; MS (*m/z*): 434.5 (M^+ +1).

3 - (3, 4-Difluoro-phenyl) - N- (3- oxo- 3, 4-dihydro-1H-isoquinolin-2-yl) – 2 - thiophen-2-yl-acrylamide 6i: IR ν_{max} (KBr) 1688, 1732, 3365 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.76 (s, 2H), 4.86 (s,2H), 6.57 (1H, d, J=4 Hz), 6.78 (d, 1H, J=8Hz), 6.98-7.13 (2H, m), 7.15-7.19 (m, 3H), 7.22-7.27 (m, 2H), 7.58 (d, 1H, J=4Hz), 7.85 (s, 1H), 9.86 (s, 1H); ^{13}C NMR (400MHz, DMSO-d_6) δc 36.8, 52.7, 112.8, 125.2, 125.9, 126.2, 127.2, 127.4, 127.8, 128.3, 129.4, 130.2, 132.4, 136.8, 141.2, 145.7, 148.6, 149.4, 165.8, 174.2; MS (*m/z*): 410.5 (M^+ +1).

2- Naphthalen - 2- yl- N- (3-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-3-phenyl-acrylamide 6j: IR ν_{max} (KBr) 1651, 1681, 3436 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.78 (s, 2H), 4.83 (s,2H), 7.04 (d, 1H, J=8Hz), 7.17-7.26 (4H, m), 7.27-7.28 (4H, m), 7.37 (d, 2H, J=4Hz), 7.39-7.50 (m, 5H), 7.92 (s, 1H), 9.82 (s, 1H); ^{13}C NMR (400MHz, DMSO-d_6) δc 36.6, 52.4, 123.5, 125.0, 125.8, 126.2, 126.4, 127.4, 127.6, 127.8, 127.9, 128.2, 128.4, 128.6, 129.6, 132.3, 132.4, 133.2, 133.6, 138.2, 141.4, 165.9, 174.2; MS (*m/z*): 418.5 (M^+ +1).

2 - (4-Fluoro-phenyl) - 3 - (3-nitro-phenyl) – N - (3-oxo- 3, 4- dihydro- 1H –isoquinolin – 2 - yl) - acrylamide 6k: IR ν_{max} (KBr) 1699, 1750, 3465 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.78 (s, 2H), 4.87 (s,2H), 6.97 (2H, d, J=12 Hz), 7.05 (d, 2H, J=8Hz), 7.17-7.28 (4H, m), 7.41-7.44 (m, 3H), 7.57 (s, 1H), 7.85 (s, 1H), 9.87 (s, 1H); ^{13}C NMR (400MHz, DMSO-d_6) δc 36.9, 49.9, 53.5, 116.2, 123.1, 123.8, 125.4, 126.5, 127.2, 127.5, 128.1, 128.5, 129.5, 129.9, 130.6, 130.7, 131.6, 131.8, 133.1, 136.2, 136.4, 147.6, 160.9, 163.4, 166.0, 166.8; MS (*m/z*): 431.5 (M^+ +1).

2 - (4-Fluoro-phenyl) – 3 - (2-nitro-phenyl) - N-(3-oxo- 3, 4-dihydro-1H – isoquinolin – 2 - yl) - acrylamide 6l: IR ν_{max} (KBr) 1697, 1734, 3437 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.76 (s, 2H), 4.87 (s, 2H), 6.54 (s, 1H), 6.73 (d, 1H, J=8Hz), 6.92 (d, 2H, J=12Hz), 7.17-7.28 (m, 4H), 7.39-7.43 (3H, m), 7.57 (s, 1H), 7.87 (s, 1H), 9.89 (s, 1H); ^{13}C NMR (400MHz, DMSO-d_6) δc 36.7, 49.9, 53.8, 115.3, 124.2, 124.8, 125.4, 126.7, 127.2, 127.5, 128.1, 128.5, 129.5, 129.9, 130.9, 132.8, 133.1, 136.4, 136.8, 147.8, 160.9, 163.5, 166.3, 166.9; MS (*m/z*): 431.5 (M^+ +1).

2 - (3-Chloro-phenyl) - 3 -(3, 4-dimethoxy-phenyl)-N-(3-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acrylamide 6m: IR ν_{max} (KBr) 1660, 1694, 2924 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.48 (3H,s), 3.78 (2H, s), 3.86 (3H, s), 4.86 (2H, s), 6.39 (1H, d, J=4 Hz), 6.75 (1H, d, J=8 Hz), 6.79 (2H, s), 7.15-7.49 (7H, m), 7.86 (s, 1H), 9.86 (s, 1H); ^{13}C NMR (400MHz, DMSO-d_6) δc 37.0, 53.5, 54.8, 55.4, 111.4, 112.1, 124.4, 124.6, 125.4, 126.4, 126.6, 126.7, 127.2, 127.3, 127.8, 128.1, 128.6, 128.7, 131.6, 131.8, 135.6, 138.1, 148.1, 149.8, 165.7, 166.8; MS (*m/z*): 461.9 (M^+ +1).

3 - (4-Fluoro-phenyl) - 2 - (1H-indol-3-yl)- N -(3-oxo-3, 4-dihydro - 1H – isoquinolin – 2 - yl) - acrylamide 6n: IR ν_{max} (KBr) 1674, 1698, 2924,3317 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.78 (s, 2H), 4.88 (s,2H), 6.61 (1H, d, J=4 Hz), 6.78 (d, 1H, J=8Hz), 7.18-7.29 (5H, m), 7.38-7.42 (m, 3H), 7.51 (s, 1H), 7.87 (s, 1H), 9.89 (s, 1H), 11.01 (s, 1H); ^{13}C NMR (400MHz, DMSO-d_6) δc 23.9, 37.0, 53.5, 114.7, 115.4, 116.1, 119.9, 123.4, 124.5, 125.0, 125.4, 126.4, 127.2, 127.4, 127.7, 128.4, 131.4, 131.6, 131.9, 135.4, 136.9, 160.8, 163.3, 165.5, 166.8, 169.7; MS (*m/z*): 425.5 (M^+ +1).

2 - (2-Fluoro-phenyl) - N - (3-oxo- 3, 4-dihydro - 1H-isoquinolin-2-yl) - 3 - phenyl - acrylamide 6o: IR ν_{max} (KBr) 1644, 1703, 3435 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.78 (s, 2H), 4.86 (s,2H), 7.05 (d, 2H, J=8Hz), 7.13-7.27 (3H, m), 7.28-7.32 (m, 2H), 7.37 (d, 2H, J=4Hz), 7.41-7.47 (m, 4H), 7.91 (s, 1H), 9.82 (s, 1H); ^{13}C NMR (400MHz, DMSO-d_6) δc 36.7, 52.6, 115.4, 121.9, 124.3, 125.9, 127.2, 127.4, 127.8, 128.0, 128.5, 128.7, 129.2, 129.5, 132.4, 132.6, 135.2, 141.8, 156.9, 165.2, 174.2; MS (*m/z*): 386.4 (M^+ +1).

Microbiology

Bacterial and Fungal strains

The following bacteria and fungi were used for the experiment. Gram-positive bacteria: *Bacillus subtilis* ATCC 6051, *Staphylococcus aureus* ATCC 9144; Gram-negative bacteria: *Pseudomonas aeruginosa* ATCC 2853, *Escherichia coli* ATCC 25922. All bacterial strains were maintained on nutrient agar medium at 37°C. Fungi: *Candida albicans* ATCC 2091 and *Aspergillusniger* ATCC 9029 are used in this study. All fungi strains were maintained on potato dextrose agar (PDA) at 25°C.

Antimicrobial activity

The newly synthesized compounds **6a-o** were screened for their *in vitro* antimicrobial activity against panel of pathogenic organisms including*Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Candida albicans*and *Aspergillus niger.* The well plate method was performed using nutrient agar Agar for bacteria and Potato Dextrose Agar for fungi organism. The molten medium was solidified, inoculated with 0.5 mL of the culture of the specific organism and poured into sterile petri dishes to form a layer of about 4 mm thickness. The sterile swab was used to streak on the surface of the medium to ensure even distribution of the inoculum.

The layer was allowed to cool and harden. With the aid of a sterile cork-borer, well of about 8 mm diameter was done. The compounds were loaded on the well and the plates were incubated at 37°C for 24 h - 48 h. The tested compounds were used in the concentrations of 100 and 200µg/mL in DMSO. The diameters of the zone of inhibition produced by the compounds were compared with the standard drugs of ciprofloxacin and ketoconazole in the concentration of 10 µg/mL for antibacterial and antifungal, respectively.

Antioxidant activity

DPPH assay

Free radical scavenging activity of compounds **6a-o** was measured by the 1, 1 - diphenyl-2-picryl-hydrazyl (DPPH) assay method. Briefly, 0.1 mM solution of DPPH in methanol was prepared and 1mL of this solution was added to samplesolutions in Methanol (2 mL) at different concentrations (5-100 µm/mL). The mixture was vortexed and allowed to stand in dark at room temperature for 30 min. A DPPH blank was prepared without compound and methanol was used for the baseline correction. Ascorbic acid was used as a reference standard. Decrease in the absorbance at 517 nm was measured using UV-Visible spectrophotometer and the remaining DPPH was calculated. The radical scavenging activity was expressed as the percentage inhibition and was calculated using the formula:

% of Inhibition = [(Ao - A1)/Ao] X 100.

Where Ao is the absorbance of the control (without compound) and A1 is the absorbance of the compound. The IC_{50} (concentration causing 50% inhibition) values of each compound was determined graphically.

ABTS assay

The antioxidant activity of synthesized compounds was measured using 2, 2´- azinobis [3-ethylbenzthiazoline] - 6-sulfonic acid (ABTS) assay. The ABTS•+ radical was produced by the reaction between 7 mM ABTS in deionized water and 2.45 mM potassium persulfate, left to stand in the dark at room temperature for 16 h. Then, ABTS•+ solution was diluted with phosphate buffer (0.1M, pH 7.4) to give an absorbance value of ~0.700 at 734 nm.To the reaction mixture containing 1.5 ml of different concentration (5-100 µm/mL) of compounds in ethanol was added to 1mL of ABTS•+ solution. After 30 min, the decrease in absorbance was measured at 734 nm. Ascorbic acid was used as standard (positive control). The % inhibition and the IC_{50} values were calculated as mentioned in the DPPH assay.

RESULTS AND DISCUSSION:

Structure of the synthesized compounds **6a-o** was confirmed by their Mass, IR, ^{1}H NMR, ^{13}C NMR spectroscopy. The compound 6**e** was synthesized by reaction of sydnone **3** with (2*E*)-2-[4-(dimethylamino)phenyl]-3-phenylprop-2-enoic acid under reflux condition for 5 h. Compound 6**e** showed absorption at 3368 cm^{-1} which is due to the NH stretching and 1678 cm^{-1} due to the amide stretching. ^{1}H NMR spectral studies of compound 6**e** showed a singlet appeared at δ 2.93 which is due to the presence of *N*,*N*-dimethyl group. A singlet appeared at δ 3.70 ppm which is due to CH_2 protons of ($COCH_2$) group. Methylene protons (-

NCH_2) is observed as a singlet at δ 4.69 ppm. An aromatic proton was observed as a doublet in the region of (6.71-7.28) ppm and alkenic protons observed as a singlet at δ 7.20 ppm. Amide proton appeared as a singlet, at δ 9.87 ppm. The Mass spectrum of compound **6e** showed molecular ion peak at m/z = 412.2 (M^++1). The characteristic resonance peaks assigned provided the expected results. In ^{13}C NMR, 36.96 ppm is due to the N, N-dimethyl carbon. A distinctive peak in δ 166.75-167.40 ppm range is assigned to carbon attached to the oxygen atom. All the aromatic carbon signals appeared in the range of δ 112.19-149.92 ppm confirming the proposed structure of the compound **6e**.

Antimicrobial activity

All the synthesized compounds **6a-o** were evaluated for their *in vitro* antimicrobial activity against *Pseudomonas aeruginosa* ATCC 2853, *Escherichia coli* ATCC 25922, *Bacillus subtilis* ATCC 6051, *Staphylococcus aureus* ATCC 9144 and antifungal activity against *Candida albicans* ATCC 2091 and *Aspergillus niger* ATCC 9029 by well plate method at the concentration of 100 and 200 µg/mL. The activity of the synthesized compounds was compared with standard drugs amikacin and ketoconazole for antibacterial and antifungal activities, respectively.

The zone of inhibition (mm) presented in **Table 2** indicated that the substitution in both the phenyl ring exerted significant influence on the antimicrobial activity. Compound **6e** and **6j** possessing 4-*N, N*-dimethyl and naphthyl group at phenyl ring showed enhanced activity against *E. coli, S. aureus, B. substilis*. Compound **6m** with 3,4-dimethoxy and *m*-chloro substitution showed moderate activity against all bacterial organisms. Interestingly, Compound bearing nitro groups such as (**6k** and **6l**) were demonstrated more active than standard compounds at 200µg/ml concentration. The compounds **6b**, **6c** and **6f** showed good activity against *S. aureus* and *E. Coli* whereas, the compounds **6d** and **6h** exhibited moderate activity against Gram positive bacteria *B. substilis*. The substituted heterocyclic moiety such as thiophene and indole (**6i** and **6n**) resulted less active against all the tested bacterial strains.

Antifungal activity assay revealed that, compounds **6b**, **6d**, **6k** and **6l** showed moderate activity against both the fungal strains, whereas remaining all other compounds are less active in comparison with standard drug ketoconazole. The compound **6m** exhibited maximum zone of inhibition against *Aspergillusniger* and *Candida albicans* at the concentration of 100µg/mL. This enhanced activity of **6m** may be due to presence of methoxy and chloro substitution at phenyl ring. In general most of the synthesized compounds inhibited fungal growth at higher concentration (100µg/mL). The results are summarized in **Table 3**.

TABLE 2: ANTIBACTERIAL ACTIVITY OF THE COMPOUNDS (6a-o). INHIBITORY ZONE (DIAMETER) MM OF THE SYNTHESIZED COMPOUNDS AGAINST TESTED BACTERIAL STRAINS BY WELL PLATE METHOD

Compounds	Zone of inhibition (mm)							
	Gram-positive bacteria				Gram-negative bacteria			
	S.aureus		*B.substilis*		*E.coli*		*P.aeruginosa*	
	100µg	200µg	100µg	200µg	100µg	200µg	100µg	200µg
6a	7	10	6	11	6	9	6	8
6b	10	13	5	9	10	14	7	9
6c	11	14	8	10	11	13	6	11
6d	6	9	11	14	6	9	6	9
6e	8	14	8	15	9	16	8	10
6f	9	16	8	10	11	16	8	12
6g	6	9	6	9	7	9	6	8
6h	7	8	12	14	9	10	6	9
6i	5	7	4	7	5	6	4	7
6j	9	13	9	14	8	13	6	9
6k	12	18	13	18	12	19	10	17
6l	14	20	12	19	13	20	12	17
6m	11	16	12	14	10	15	9	13
6n	6	7	5	6	4	6	4	6
6o	6	8	6	8	7	8	7	9
Amikacin (10µg)	18		17		18		17	

TABLE 3: THE ANTIFUNGAL ACTIVITY OF THE COMPOUNDS (6A-O). INHIBITORY ZONE (DIAMETER) MM OF THE SYNTHESIZED COMPOUNDS AGAINST TESTED FUNGAL STRAINS BY WELL PLATE METHOD.

Compounds	Zone of inhibition (mm)			
	C.albicans		*A.niger*	
	50µg	100µg	50µg	100µg
6a	7	9	6	8
6b	8	12	8	13
6c	9	6	7	9
6d	7	12	6	11
6e	8	10	7	10
6f	7	9	6	9
6g	6	9	5	9
6h	6	8	5	8
6i	5	8	6	9
6j	6	9	7	9
6k	9	13	6	12
6l	9	12	7	13
6m	**12**	**16**	**13**	**18**
6n	7	9	8	9
6o	8	10	7	9
Ketoconazole (10 µg)	17		18	

Antioxidant activity

In the antioxidant study, DPPH (1,1-diphenyl-2-picryl-hydrazyl) radical scavenging assay [26] and ABTS assay were chosen to evaluate antioxidant potential of the newly synthesized compounds **(6a-o)**.The percentage of inhibition (IC_{50}) was graphically estimated using a linear regression algorithm and the results were depicted in **Table 4** and compared with that of standard L-ascorbic acid. The antioxidant activity of the synthesized compounds are associated with their electron donating capability to DPPH radical and convert into stable diamagnetic molecules. Compounds **6c**, **6d** and **6m** showed good radical scavenging activity, this may be due to the presence of electron donating methoxy groups at phenyl ring. It was observed that most of the tested compounds showed good to moderate antioxidant activity.

TABLE 4: 50% INHIBITION OF DPPH RADICAL AND ABTS ASSAY BY COMPOUNDS (6a-o). EACH VALUE REPRESENTS MEAN ± SD (n=3)

Compounds	DPPH activity IC_{50}[a] (µM/mL)	ABTS assay IC_{50}[b](µM/mL)
6a	57 ± 0.13	72 ± 0.10
6b	55 ± 0.11	64 ± 0.07
6c	21 ± 0.13	29 ± 0.11
6d	18 ± 0.11	32 ± 0.09
6e	62 ± 0.11	58 ± 0.10
6f	53 ± 0.17	82 ± 0.06
6g	54 ± 0.13	59 ± 0.11
6h	54 ± 0.19	62 ± 0.11
6i	54 ± 0.76	56 ± 0.05
6j	52 ± 0.13	78 ± 0.10
6k	76 ± 0.14	84 ± 0.23
6l	69 ± 0.09	92 ± 0.15
6m	22 ± 0.06	28 ± 0.12
6n	48 ± 0.11	71 ± 0.11
6o	52 ± 0.12	63 ± 0.13
L- ascorbic acid	11 ± 0.13	21 ± 0.13

[a]IC_{50} = the concentration (µM/mL) exhibiting 50% inhibition of DPPH radical.
[b]IC_{50} = the concentration (µM/mL) exhibiting 50% inhibition of ABTS radical.

In ABTS assay, the synthesized 2-amino-1,2-dihydroisoquinoline-3(4*H*)-one having different concentrations (5, 20, 50 and 100 µm/mL) were tested in $ABTS^{\cdot+}$ scavenging activity.[27] ABTS radical scavenging method is a rapid and easy method to test the antioxidant activity of the synthesized compounds. In this assay the reaction between ABTS and potassium persulfate directly produced the green or blue colour of $ABTS^{\cdot+}$ radical and interaction of this radical with

synthesized compounds leads to less coloured product. Compounds**6c**, **6d** and **6m** showed good ABTS radical scavenging activity, whereas compounds **6k** and **6l** possessing much lower activity than that of other tested compounds. The results were depicted in **Table 4**.

CONCLUSIONS: In conclusion, we have synthesized a series of novel 2-amino-1, 2-dihydroisoquinoline-3(4*H*)-one and their amide derivatives in short reaction time with good yield. The newly synthesized analogues were evaluated for their *in-vitro* antimicrobial and antioxidant activity. Among the tested compounds **6k** and **6l** displayed potent antibacterial activity and compound **6m** exhibited good antifungal activity. The activity of those compounds was comparable with that of standard drugs. All the compounds are showed comparatively moderate antimicrobial activity in tested organisms. Compounds **6c**, **6d** and **6m** showed maximum antioxidant activity in comparison with all other tested compounds. These results suggested that the further structural modifications on these molecules might provide lead compounds with potent antimicrobial and antioxidant agents.

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25. X-ray crystal data of compound **6e** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number is CCDC – 829819. These data can be obtained free of charge via http:// www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk. Crystal data for compound **6e**: $C_{26}H_{25}N_3O_2$, M = 411.49, monoclinic, space group P21/c, a = 14.7503(6) A^0, b = 10.3737(4) A^0, c = 14.1677(5) A^0, b = 96.176(2), U = 2155.29(14) A^3, Z = 4, μ= 0.081 mm^{-1}, 16224 reflections collected, 2641 independent reflections, Rint = 0.0364, final R indices [I > 2r(I)] R_1 = 0.0430, wR_2 = 0.1068, R indices (all data) R_1 = 0.0631, wR_2 = 0.1289. CCDC – 82981.
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