Regular Article

Environment Friendly Synthesis of *N*′-(1,3-Diphenylallylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazides: Crystal Structure and Their Anti-oxidant Potential

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An environment friendly synthesis of novel hybrid pharmacophores derived from synergism of nalidixic acid and 1,3-diphenylprop-2-en-1-ones is described. Percent yield and reaction times of microwave assisted reactions have been compared with the reactions carried out under conventional reaction conditions which show marked decrease in reaction times and significant increase in yields. Besides, anti-oxidant potential of the synthesized hybrid compounds was evaluated and some of the compounds showed marked ascorbic acid equivalence Ferric reducing anti-oxidant power (FRAP) and metal chelating capacities. Crystal study of one representative of the synthesized series is also presented.

Key words microwaves assisted reaction; hybrid molecule; chalcone; anti-oxidant; nalidixic acid

Introduction

Concept of hybrid molecule synthesis for multifunctional organic compounds in a single moiety provides innovation in organic synthesis. Earlier in nineteenth century, the term pharmacophore was introduced for hybrid molecules that contain therapeutic properties.[1)] These structures based on two or more independent units may act indifferently to their precursor molecules[2)] and this approach may help in dealing with treatment of diseases where a single drug fails to act solely.[3)] Numerous examples are there in literature where combining of two or more moieties in a single pharmacophore alters the biological potential of the newly synthesized compounds. A number of fluoroquinolone based multi-target hybrid pharmacophores were synthesized by Wang *el al.* as anti-microbial agents through conventional synthetic pathways.[4)] A series of novel chalcone-coumarin hybrid pharmacophores was synthesized by Sashidhara *el al.* which showed considerable cytotoxic and fibroblasts activities.[5)] Halogen derivatives of quinoline, being vastly used as an anti-parasitic compound, were explored through its derivatization to enhance its anti-amoebic activity; compounds synthesized by synergism of imidazole and quinoline moieties possessed marked anti-parasitic activities greater than their precursor molecules.[6)] Similarly, compounds synthesized by the merger of 1,2-benzothiazine and quinazolin moieties exhibited marked effects on anti-bacterial activity in comparison to the individual moieties.[7)] Few examples of compounds bearing hybrid frameworks are illustrated in Fig. 1.

Nalidixic acid is considered as the first antibiotic belonging to the synthetic quinolone group based on 1,8-napthyridine ring system.[8,9)] It is effective against Gram-negative bacteria and has many clinical advantages as an antibiotic drug.[10–12)] However, when applied in lower concentrations, it acts as a bacteriostatic agent and starts inhibiting bacterial reproduction.[13)] Due to its divergent behavior at different concentrations, it is used as a regulatory tool in bacterial cell division studies, as replication of DNA in susceptible bacterial strains is reversibly blocked with nalidixic acid.[14)] Compounds were obtained by the synergism of nalidixic acid with quanidinyl, acetyl coumarin based chalcones and substituted isatin were found effective against *Staphylococcus aureus*, *Escherichia coli* and mycobacterium strains.[15,16)] These studies have opened further ways of derivatizing nalidixic acid to incorporate multifarious medicinal properties to the basic nucleus.

Similarly, chalcones are the compounds well known for their versatile and diverse nature of biological properties such as anti-tuberculosis, anti-cancer, anti-oxidant, anti-inflammatory, anti-amoebicidal, anti-protozoal, immunosuppressive, anti-bacterial and anti-fungal activities.[17)] These also find their

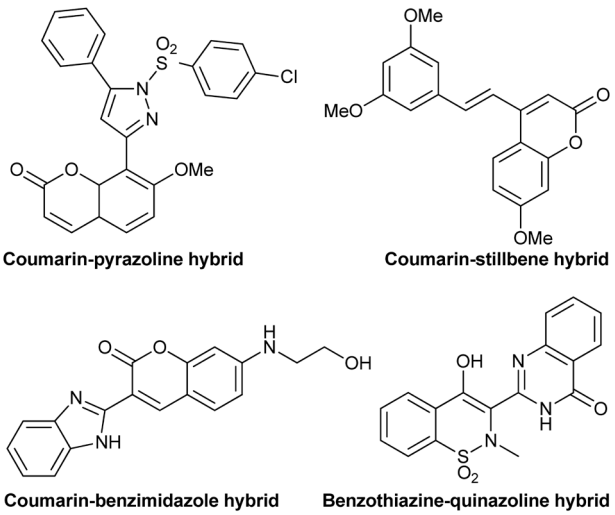

Fig. 1. Examples of Some Known Hybrid Structures

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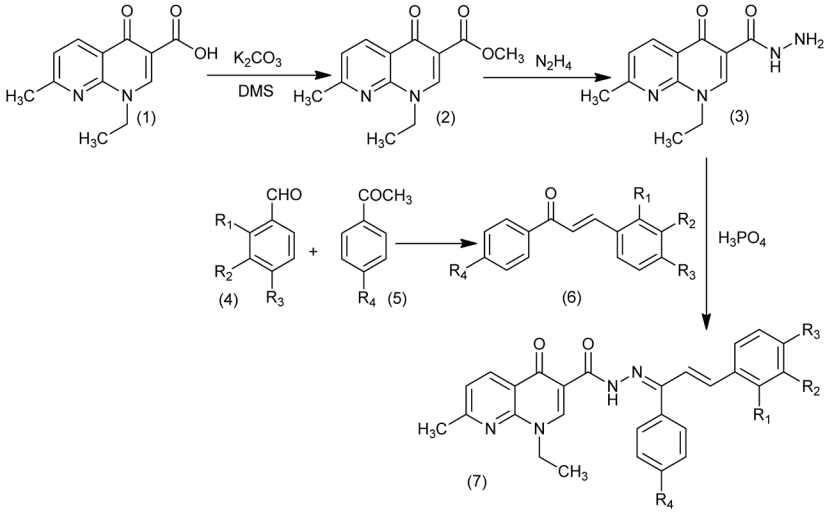

Chart 1. Layout for the Synthetic Scheme of the Title Compounds (**7a**–**7o**)

Table 1. Comparison between Conventional and Microwaves Heating on % Yields and Reaction Times for the Synthesis of Compounds (**7a**–**7o**)

Compd.	R_1	R_2	R_3	R_4	Reaction conditions			
					Conventional		Microwaves	
					Yield %	Time (h)	Yield %	Time (h)
7a	H	H	Cl	H	81.3	48	89.8	1.4
7b	H	H	Cl	OMe	73.9	47.5	80.5	1.2
7c	H	H	Br	OMe	76.2	47	85.7	1.1
7d	H	OMe	H	Br	76.3	47.5	89.4	1.1
7e	H	F	H	Cl	75.3	46	84.2	1.2
7f	Cl	Cl	H	I	64.8	46.5	81.0	1.3
7g	H	H	OMe	Cl	83.6	47	90.1	1.3
7h	Cl	H	H	H	88.2	47.5	92.9	1.3
7i	Cl	H	Cl	Br	86.5	47	90.7	1.2
7j	Cl	H	Cl	Cl	90.3	46	94.9	1.2
7k	H	Cl	Cl	Br	89.6	46	90.8	1.2
7l	H	Cl	H	OMe	82.2	47	85.5	1.2
7m	H	H	Br	Cl	80.6	47	88.7	1.2
7n	H	H	H	H	89.1	54	90.8	2.1
7o	H	Cl	H	H	84.2	48.8	88.4	1.3

applications as polymerization catalysts, optical brighteners, stabilizers, anti-aging and artificial sweetening agents.[18] Literature reveals that much more diversity may be achieved through substitutions on the basic rings of chalcones which can be beneficial to attain compounds with better bioactivities and lesser side effects.

In the quest of making biologically active synthetic molecules, present work is carried out to explore the synthesis of new hybrid pharmacophores based on condensation of nalidixic acid with chalcones in green and non-toxic solvents (mostly ethanol) along with the employment of microwaves as an eco-friendly energy source. Besides these, oxidative stress management capacity of synthesized compounds has also been calculated through different anti-oxidant activities.

Chemistry

1-Ethyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid (**1**), commonly known as nalidixic acid, was reacted with dimethyl sulphate in the presence of tetrahydrofuran as solvent to get its methyl ester (**2**). This methyl ester (**2**) was converted to the corresponding hydrazide (**3**) followed by its reaction with a series of substituted 1,3-diphenyl propenones (**6a**–**6o**) to get a novel series of *N*′-(1,3-diphenylallylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazides (**7a**–**7o**) (Chart 1).

Induction of microwaves enhanced the rate of reaction and lowered the reaction times significantly in comparison to the reactions carried out through conventional means. Microwaves are being used for synthesis of organic compounds; energy input in microwaves is provided by spontaneously emitting hot spots resulting in much higher internal temperature and reduced reaction time.[19] Microwave technique is proving itself a cost effective, fast and economical technique. In contrast, conventional heating is associated with many drawbacks such as lengthy reaction processes, higher economical costs and energy loss.

In the present work, overall time of reactions is reduced to 1.1–2.1 h under microwaves from 46–54.0 h on conventional heating (Table 1) with increase in reaction yields. This may be attributed to the fact that heat energy from microwaves is

directly applied to the reactants and reaction media than to the reaction vessels as in conventional methodologies. All the newly synthesized molecules were analyzed using spectroscopic techniques and elemental analysis. One representative compound (4-chlorophenyl derivative, **7b**) from the series is also characterized through single crystal X-ray analysis to confirm the main skeleton of the compounds of the series.

X-Ray Crystallography Single crystal studies were performed on the crystal of newly synthesized compound (**7b**). Hydrogen atoms present on aromatic carbon and nitrogen atoms (CH & NH) were geometrically placed (with C–H = 0.93 Å) and treated as riding atoms [Uiso(H) = 1.2 Ueq(C)], while for methyl, methylene and hydrazide-nitrogen C–H were taken as 0.96 Å, 0.97 Å and 0.86 Å, respectively. Oxygen atom of the water molecule was found disordered over two positions with the (50 : 50) occupancy for O4a and O4b oxygen atoms. Results show that the central allylidine hydrazide is connected to the three different aromatic systems as shown in Fig. 2. The crystallographic parameters are presented in Table 2. Root mean square (RMC) deviation for the fitted atoms (C9/C10/C11/C12/N3/N4) of this backbone is 0.0536(2) Å, where most deviations were observed from the N4 = −0.0872(2) and C9 = 0.700(2) Å. The dihedral angles between the central chain with naphthyridine (C1–C8/N1/N2), 4-chlorophenyl and 4-methoxyphenyl are 12.521(3)°, 7.292(3)° and 66.865(1)°, respectively. The naphthyridine (C1–C8/N1/N2) ring system is oriented at angles (dihedral) of 5.395 (2)° and 75.106 (1)° with respect to methoxyphenyl and 4-chlorophenyl groups. These groups are oriented at dihedral angle of 70.796 (1)° with each other. Oxygen atom of water molecule is found disordered at two positions with 50 : 50 occupancy for each part of the set (O4a and O4b). Intramolecular hydrogen bonding interaction *via* N1–H1n…O1 generates six membered ring motif *S*(6) with the RMS deviation of 0.0492(2)Å. The water molecule connects the molecules in the unit cell through intermolecular hydrogen bonding and generate infinite long chain along *a*-axes. There are two intermolecular hydrogen bonding interactions where C21 atom located at (*x*, *y*, *z*) acts as donor *via* H21 to O4a atom at (1 + *x*, *y*, *z*) on the other hand O4a also acts as donor atom at (*x*, *y*, *z*) *via* H2w to O1 atom at (*x* − 1, *y*, *z*). Both the interactions generate thirteen membered ring motif $R_2^2(13)$. O4b, 2nd part of the disordered water molecule is connected to another molecule *via* O–H…N and O–H…O interactions and generate a six membered ring motif $S_1^2(6)$ Figs. 3 and 4, Table 3. Crystal data of the compound was submitted at the CCD Centre with the deposition number **1876454**. Data regarding crystal structure may be obtained by requesting CCDC at data_request@ccdc.cam.ac.uk

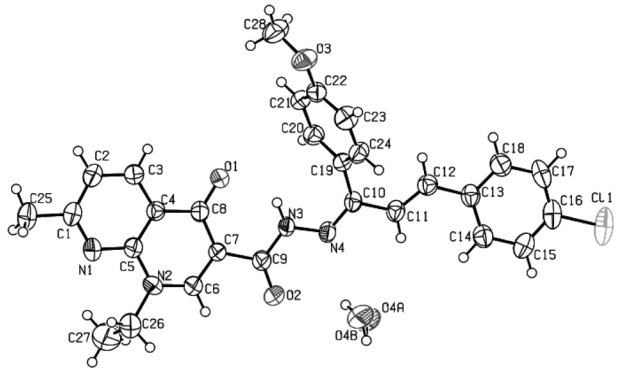

Fig. 2. *ORTEP* Labelled Diagram Where Thermal Ellipsoids Were Drawn at 50% Probability Level

Green Metrics Greenness of the developed processes is calculated by adopting metrics of atom economy, carbon efficiencies and reaction mass efficiency.[20–22] Mass transformation is calculated by process mass intensity measurements. Atom economy was found in range of 96–97.2% which shows that the selected reaction pathway consumes the reactants completely and maximum atoms are converted to the required products with the formation of minimum byproducts with the range of carbon efficiency from 95 (maximum) to 80% (minimum). Reaction mass efficiency was calculated for the conversions and it values fall in the range of 77.8–91.8. Process mass intensity of most of the reactions is found above 1 depicting that the process involved utilizes most of its mass and produces less waste. All the green parameters are summarized in Table 4. Energy consumption and energy efficiencies of conventional and microwave heating are calculated and reported in Table 5 by reported method.[23] It is observed that reactions carried out using conventional methodologies consume more energy from (25–30 kWh) than for those carried out employing microwaves (0.22–0.42 kWh). Further, in order to investigate whether utilization of green protocols has reduced the energy debt of synthetic process or not, energy efficiencies of the reactions are calculated by comparing the energies consumed with the yields obtained of the specific reactions and it revealed that employment of eco-friendly protocols consume less energies for the processes than conventional methodologies.

Table 2. Crystal Data and Structure Refinement for the Compound (**7b**)

Empirical formula	$C_{28}H_{27}ClN_4O_4$	ρ_{calc} mg/mm^3	1.352
Formula weight	518.98	F(000)	544.0
Space group	P-1	Radiation	Mo$K\alpha$ ($\lambda = 0.71073$)
Temperature/K	296(2)	Crystal size/mm^3	$0.26 \times 0.21 \times 0.18$
Crystal system	Triclinic	Data/restraints/parameters	5924/0/343
a/Å	8.9387(10)	α/°	63.118(12)
b/Å	12.7144(15)	β/°	83.065(10)
c/Å	12.9777(15)	γ/°	75.686(10)
Volume/Å^3	1274.6(3)	*Z*	2
Goodness of fit on F^2	1.006	Reflections collected	10079
Index ranges	$-11 \le h \le 12$, $-17 \le k \le 17$, $-17 \le l \le 16$	2θ range for data collection	5.904 to 58.106
Independent reflections	5924 [$R_{int} = 0.0549$, $R_{sigma} = 0.1169$]	Final R indexes [all data]	$R_1 = 0.1639$, $wR_2 = 0.1955$

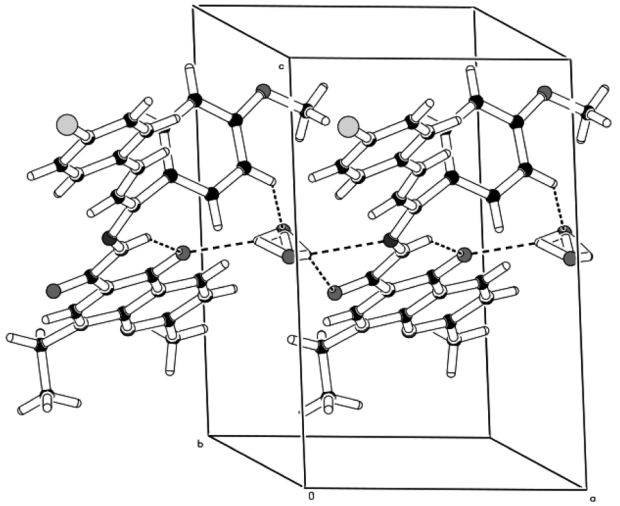

Fig. 3. Intra- and Inter-molecular Hydrogen Bonding Interactions among Molecules in the Unit Cell

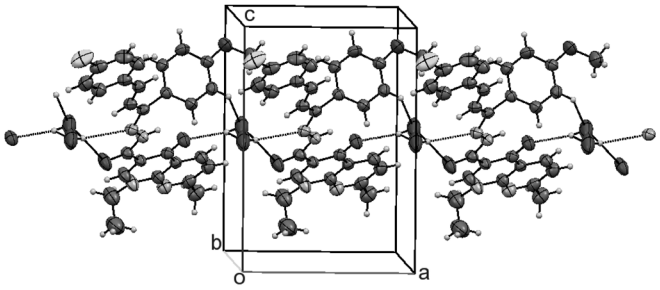

Fig. 4. A View of Unit Cell, Showing the Expansion in Hydrogen Bonding Interactions along *a*-Axes

Table 3. Crystallographic Data for Hydrogen Bonding for the Compound (**7b**)

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
C21	H21	O4A[a)]	0.93	2.58	3.234(10)	128.2
N3	H1N	O1	0.86	2.02	2.693(3)	134.6
O4B	H1W	N4	0.89(5)	2.43(6)	3.105(9)	133(5)
O4B	H1W	O2	0.89(5)	2.32(6)	3.108(9)	146(5)
O4A	H2W	O1[b)]	0.79(6)	2.15(6)	2.921(9)	165(6)

[a)] 1 + X, + Y, + Z; [b)] -1 + X, + Y, + Z

Anti-oxidant Activity Total anti-oxidant assay was carried out by taking butylated hydroxy toluene (BHT) as standard while following the phosphomolybdenum based procedure.[24] Study was performed by varying compound's concentration to check anti-oxidant capacity for minimum and maximum values. Test compounds were taken in three concentrations *i.e.*, 125, 250 and 500 μM and the results are presented in Table 6. Data showed that at 695 nm for concentration 125 μM, values ranged from 0.037 to 0.47, for 250 μM ranged from 0.184 to 0.604 and for maximum concentration of 500 μM, compounds showed absorbance from 0.280 to 0.888. Structure–activity relationship (SAR) indicates that maximum value (0.888) was observed for 500 μM solution of compound **7c** bearing bromo and methoxy groups at para position around the ring. Compounds **7a**, **7g** and **7h** were found to have value less than that of **7c** (with chloro and methoxy substitutions at para and *ortho* positions). The assay involves transfer of electron(s) from the test samples to phosphor-molybdenum complex and this reduction takes place in prolonged incubation (90 min). Rest of the derivatives possessed lesser but varied anti-oxidant values in the range of 0.50–0.70 (Fig. 5). Value of nalidixic acid and chalcone as control at 500 μM is reported in Table 6.

Ferric reducing anti-oxidant power (FRAP) studies were carried out by taking ascorbic acid as standard and are reported as ascorbic acid equivalents. Data showed that values ranged from 6.64 to 376.6 A.EμM for ascorbic acid equivalence. The value of 376.6 A.EμM $\pm$0.41 was found maximum in the series for the compound **7o** which may be due to chloro group present at meta position while minimum FRAP values (6.64 ± 0.21 and 16.1 ± 0.55) were observed for compounds **7l** and **7m**, respectively due to presence of methoxy groups. Assay showed quick and reproducible values for assessment of anti-oxidant potential based on reducing power of metal ion(s) by the test compounds. It measures a large range of individual anti-oxidant capacity of the compounds in dose–response manner. Compounds **7n** and **7h** showed no considerable

Table 4. Green Metrics for the Compounds (**7a**–**7o**)

Compound	Atom economy (%)	Carbon efficiency (%)	RME %	PMI
7a	96.3	89.8	86.5	1.16
7b	96.5	80.5	77.8	1.29
7c	96.8	85.7	83.0	1.20
7d	96.8	89.4	86.6	1.16
7e	96.4	84.2	81.2	1.23
7f	97.2	81.0	78.7	1.27
7g	96.5	90.1	87.0	1.15
7h	96.3	92.9	89.5	1.12
7i	96.8	90.7	87.8	1.23
7j	96.8	94.9	91.8	1.09
7k	97.0	90.8	88.1	1.13
7l	96.5	85.5	82.5	1.21
7m	96.8	89.6	86.7	1.15
7n	96.0	90.8	87.2	1.15
7o	96.3	88.4	85.1	1.17

Table 5. Energy Consumption Data of the Compounds (**7a**–**7o**)

Compound	Energy consumption (kWh)		Energy efficiency	
	Conventional	Microwaves	Conventional	Microwaves
7a	26.4	0.28	0.325	0.003
7b	26.1	0.24	0.353	0.003
7c	25.9	0.22	0.339	0.003
7d	26.1	0.22	0.343	0.002
7e	25.3	0.24	0.336	0.003
7f	25.6	0.26	0.394	0.003
7g	25.9	0.26	0.309	0.003
7h	26.1	0.26	0.296	0.003
7i	25.9	0.24	0.324	0.003
7j	25.3	0.24	0.280	0.003
7k	25.3	0.24	0.282	0.003
7l	25.9	0.24	0.314	0.003
7m	25.9	0.24	0.305	0.003
7n	29.7	0.42	0.333	0.005
7o	26.8	0.26	0.319	0.003

Table 6. Total Anti-oxidant Capacity for the Compounds (**7a**–**7o**)

Compound ID	Reading (**7a**–**i**)			Reading (Corresponding chalcone)	Compound ID	Reading (**7j**–**o**)			Reading (Corresponding chalcone)
	Concentration (μM)					Concentration (μM)			
	125	250	500	500		125	250	500	500
7a	0.131	0.514	0.801	0.136	**7j**	0.187	0.214	0.318	0.226
7b	0.470	0.522	0.605	0.012	**7k**	0.187	0.319	0.464	0.035
7c	0.232	0.604	0.888	0.02	**7l**	0.059	0.359	0.501	0.010
7d	0.110	0.315	0.562	0.411	**7m**	0.037	0.184	0.280	0.036
7e	0.177	0.199	0.317	0.250	**7n**	0.102	0.204	0.345	0.051
7f	0.304	0.321	0.408	0.263	**7o**	0.112	0.224	0.399	0.254
7g	0.459	0.523	0.601	0.086	BHT	0.165	0.311	0.451	—
7h	0.428	0.528	0.777	0.012	N.A	0.044	0.125	0.067	—
7i	0.110	0.213	0.345	0.295	Blank	0.123			

N.A = Nalidixic acid.

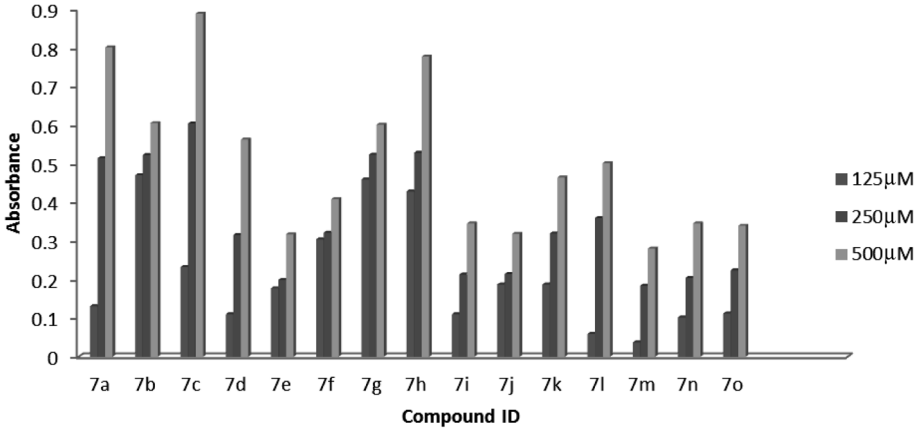

Fig. 5. Total Anti-oxidant Properties of the Synthesized Compounds (**7a**–**7o**)

ascorbic acid equivalence capacity having values <5.0 bearing chloro group at *ortho* position. Nalidixic acid also showed values <5.0. FRAP values of the compounds and chalcones as control of the series are reported in the Table 7.

Phenolic Content Effect as an anti-oxidant measure was investigated by studying total phenolic content (TPC) assay. Compounds of the series showed varied results from maximum value of 255.2 (GAE μM) for **7g** derivative to minimum value of 12.6 (GAE μM) for the compound **7f**. Second highest value among the series was of **7m** with 247.1 (GAE μM). Derivatives **7a**, **7b**, **7l** showed values less than 20 (GAE μM) while the values for the compounds **7d**, **7n** and **7o** were found above 100 (GAE μM). An insight into the structure activity relationship shows that compounds with noticeable TPC values possess methoxy, chloro or bromo groups. Iodo group is found as a retarder group to the TPC assay as very low value (12.6 ± 0.83 GAEμM) was observed. The assay based on response of the compounds under study to the F–C reagent (Folin–Ciocalteu) for their phenolic content effect. The values changes as the derivatization of various substitutes around the main structure changes. TPC value of nalidixic acid and corresponding chalcones were found as 88.2 (GAE μM) and 1.5–5.3 (GAE μM), respectively.

All the compounds of the series were checked for their metal scavenging assay using Fe(II)–ferrozine method[25] and results are presented in Table 7. Synthesized compounds exhibited different chelating abilities to interact with iron by affecting the ferrozine–Fe(II) complex. These values ranged from maximum value of 46.1% for the compound **7b** to 4.1% for the compound **7n**. Greater value of **7b** may be attributed to the presence of chloro and methoxy groups at *para* positions on both the rings (R_3 and R_4) which may enhance their metal chelating capabilities. On the other hand, **7n** was found to possess minimum activity due to absence of any such substituent on the ring system. Nalidixic acid gave even lesser activity (3.4%) while the corresponding chalcones showed values in the range of 0.7 to 7.6%. Most of the derivatives showed activity in range of 12–30%. On the whole, all the synthesized derivatives have shown some metal chelating activity.

Biological Screening Preliminary anti-microbial effects were studied by adopting agar well diffusion technique. Results of the anti-microbial activity against the bacterial strains are presented in Table 8. No considerable inhibition was found against the tested strains. (<6 mm inhibition zone considered as non-significant).

Experimental

All the chemicals used were of renowned companies with known high-grade purities. Microwave oven used was a domestic oven (eNNe 781JF, Orient Model) modified for reflux system. It was equipped with a fixed frequency generator with microwave operations at multiples of 100 to 1000 W. Melting

Table 7. Anti-oxidant Potentials (FRAP, TPC and Metal Chelating Activity) of the Compounds (**7a–7o**)

Compd.	FRAP value (AEμM) ± S.E.M.		TPC (GAE μM) ± S.E.M.		Metal chelating activity (%)	
	(**7a–o**)	Corresponding chalcone	(**7a–o**)	Corresponding chalcone	(**7a–o**)	Corresponding chalcone
7a	47.7 ± 3.6	2.1 ± 0.11	13.8 ± 0.83	3.1 ± 0.24	32.3	5.7
7b	62.4 ± 0.41	1.1 ± 0.12	14.5 ± 1.6	2.7 ± 0.2	46.1	7.6
7c	41.4 ± 0.36	1.3 ± 0.11	84.4 ± 0.83	3.6 ± 0.12	20.6	3.2
7d	47.3 ± 0.75	2.5 ± 0.19	109.4 ± 0.83	2.1 ± 0.11	28.2	3.0
7e	193.9 ± 0.95	3.4 ± 0.45	97.4 ± 1.66	3.3 ± 0.14	7.3	2.1
7f	29.7 ± 0.21	0.85 ± 0.50	12.6 ± 0.83	1.9 ± 0.10	8.9	1.8
7g	29.5 ± 0.36	0.91 ± 0.49	255.2 ± 0.83	4.1 ± 0.41	36.8	3.7
7h	0.07 ± 0.1	0.08 ± 0.3	50.1 ± 1.66	2.5 ± 0.19	20.8	1.7
7i	32.2 ± 0.55	0.81 ± 0.33	169.6 ± 0.83	5.3 ± 0.26	21.1	3.1
7j	162.2 ± 5.5	2.3 ± 0.27	55.3 ± 1.44	1.8 ± 0.22	22.4	2.8
7k	19.5 ± 0.36	0.07 ± 0.51	24.7 ± 0.83	2.9 ± 0.19	39.2	3.4
7l	16.1 ± 0.55	0.05 ± 0.37	15.8 ± 1.8	1.5 ± 0.15	16.2	1.4
7m	6.64 ± 0.21	0.08 ± 0.31	247.1 ± 1.66	3.4 ± 0.22	20.4	2.3
7n	0.05 ± 0.19	0.06 ± 0.27	102.1 ± 0.83	1.7 ± 0.11	4.1	0.7
7o	376.6 ± 0.41	3.8 ± 0.11	107.9 ± 1.66	3.1 ± 0.13	9.2	1.0
N.A.	0.06 ± 0.12	—	88.2 ± 0.83	—	3.4	—

N.A = Nalidixic acid.

Table 8. Antimicrobial Activity (Zone of Inhibition, mm) of Synthesized Compounds (**7a–7o**)

Compound ID	*Bacillus subtilis*	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	Compound ID	*Bacillus subtilis*	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*
7a	—	—	—	—	**7j**	—	—	—	—
7b	—	—	—	—	**7k**	—	—	—	—
7c	—	—	—	—	**7l**	—	—	—	—
7d	—	—	—	—	**7m**	—	—	—	—
7e	—	—	—	—	**7n**	—	—	—	—
7f	—	—	—	—	**7o**	—	—	—	—
7g	—	—	—	—	0 (Control)	—	—	—	—
7h	—	—	—	—	*N.A	15	16	17	14
7i	—	—	—	—			—		

Note: (*) Nalidixic acid, (—) non-significant (<6 mm).

points were recorded on GallenKamp apparatus. For Fourier transformed (FT)-IR spectra, Bruker Tensor 27 spectrometer was used while mass spectral analysis was conducted on Agilent 5973 inert equipped with a direct probe. For ^{1}H-NMR and ^{13}C-NMR spectra, AVANCE AV-75 MHz, 300 and 500 MHz spectrometers were used.

Synthesis of 1-Ethyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic Acid Hydrazide (3) A mixture of 1-ethyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid (**1**) [1.0 g; 4.305 mmoles], dimethylsulphate [0.81 mL, 6.46 mmol], potassium carbonate [2.98 g; 21.5-mmol] and tetrahydrofuran (25 mL) was refluxed for five hours. Contents were cooled to 25°C and the ester formed was extracted with chloroform, dried over sodium sulphate and was precipitated out. Methyl 1-ethyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylate thus obtained (**2**) [1.0 g; 4.08 mmoles] and hydrazine hydrate [70%; 0.48 g; 6.12 mmol] was refluxed in ethanol [50 mL] for five hours till completion of the reaction.[26] Contents were cooled, neutralized with dilute hydrochloric acid and concentrated by evaporation of ethanol till the settling of precipitates. Precipitates were washed with water and crystallized from ethanol. mp 185–187°C; Lit. mp 186–188°C.[27] Yield 78%.

Synthesis of 1,3-Diphenylprop-2-en-1-ones (6a–6o) A number of 1,3-diphenylprop-2-en-1-ones were synthesized by the reaction of different substituted benzaldehydes with different acetophenones through aldol condensation following literature methods.[28–30] To the solutions of benzaldehydes (1 mmol) in dry ethanol (50 mL), appropriate acetophenone (1 mmol) and ethanolic sodium hydroxide (5%) were added and the contents were stirred till the completion of reaction. Precipitates were obtained after neutralization with dilute hydrochloric acid (5%) which was crystallized from ethanol.

Synthesis of *N*′-(1,3-Diphenylallylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazides (7a–7o)

a) Conventional Synthesis

A mixture of hydrazide (**3**) (0.246 g; 1 mmol), corresponding 1,3-diphenylprop-2-en-1-one (1 mmol), orthophosphoric acid (0.2 g) and absolute ethanol (100 mL) was refluxed for 16–24 h till completion of the reactions (as indicated by TLC [TLC system: chloroform/ethanol (90 : 10)]. Reaction mixture was then poured over ice and was neutralized with aqueous sodium hydroxide solution (0.1 M). Precipitated products were then filtered, washed with ethanol (30%) followed by crystallization from chloroform.

b) Microwave Synthesis

Same reaction mixtures (as discussed above) were irradiated under microwaves at 300 Watts for 60–180 min till completion

of reactions (as indicated by TLC [TLC system: chloroform/ethanol (90 : 10)]. Contents were then poured in crushed ice and were neutralized with aqueous sodium hydroxide solution (0.1 M). Precipitated products were then filtered, washed with ethanol (30%) followed by crystallization from chloroform.

N′-(3-(4-Chlorophenyl)-1-phenylallylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (**7a**)

Pale yellow crystals; mp 241–243°C; IR (KBr) cm^{-1}: 3041, 1633, 1605; ^{1}H-NMR: ($CDCl_3$, 300 MHz) δ: 1.46 (3H, t, J = 7.1 Hz, C*H*$_3$), 2.63 (3H, s, C*H*$_3$), 4.51 (2H, q, J = 7.2 Hz, C*H*$_2$), 6.34 (1H, d, J = 16.2 Hz, C*H*), 7.17 (1H, d, J = 8.1 Hz, C*H*), 7.28 (1H, d, J = 8.2 Hz, C*H*), 7.34–7.65 (9H, m, Ar*H*), 8.44 (1H, d, J = 8.2 Hz, C*H*), 8.94 (1H, s, C*H*), 12.63 (1H, s, N*H*); ^{13}C-NMR: (75 MHz, $CDCl_3$) δ: 15.3, 25.1, 103.1, 120.9, 122.5, 128.2, 128.3, 128.4, 128.6, 128.9, 129.2, 129.4, 129.5, 129.7, 130.3, 132.9, 136.7, 138.1, 140.4, 143.3, 147.8, 150.7, 152.9, 157.7, 160.9, 161.4, 174.9. MS electron ionization (EI), *m/z*: $[M]^+$ 470.9, $[M^+ + 2]$ 472.9. *Anal.* Calcd for $C_{27}H_{23}ClN_4O_2$: C, 68.86; H, 4.97; N, 11.91. Found: C, 68.71; H, 4.93; N, 11.82.

N′-(3-(4-Chlorophenyl)-1-(4-methoxyphenyl)allylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (**7b**)

Yellow crystals; mp 248–249°C; IR (KBr) cm^{-1}: 3042, 1658, 1609; ^{1}H-NMR ($CDCl_3$ 300 MHz) δ: 1.46 (3H, t, J = 7.1 Hz, C*H*$_3$), 2.63 (3H, s, C*H*$_3$), 3.94 (3H, s, C*H*$_3$), 4.51 (2H, q, J = 7.2 Hz, C*H*$_2$), 6.36 (1H, d, J = 16.4 Hz, C*H*), 7.19 (1H, d, J = 8.1 Hz, C*H*), 7.31 (1H, d, J = 5.7 Hz, C*H*), 7.48–7.10 (8H, m, Ar*H*), 8.47 (1H, d, J = 8.0 Hz, C*H*), 8.94 (1H, s, C*H*), 12.6 (1H, s, *NH*); ^{13}C-NMR ($CDCl_3$) δ: 15.2, 25.1, 46.9, 55.5, 55.3, 114.9, 120.0, 121, 122.3, 129.1, 129.2, 129.4, 129.8, 130.7, 133.6, 134.1, 135.1, 135.8, 136.1, 136.5, 136.7, 142.4, 147.8, 148.4, 156.3, 161.7, 163.2,176.4. MS EI, *m/z*: $[M]^+$ 500.9, $[M^+ + 2]$ 502.9. *Anal.* Calcd for $C_{28}H_{25}ClN_4O_3$: C, 67.13; H, 5.03; N, 11.18. Found: C, 66.93; H, 5.06; N, 11.10.

N′-(3-(4-Bromophenyl)-1-(4-methoxyphenyl)allylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (**7c**)

Pale crystals; mp 245–246°C; IR (KBr) cm^{-1}: 3043, 1653, 1611; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.47 (3H, t, J = 7.0 Hz, C*H*$_3$), 2.64 (3H, s, C*H*$_3$), 3.98 (3H, s, C*H*$_3$), 4.52 (2H, q, J = 7.1 Hz, C*H*$_2$), 6.36 (1H, d, J = 16.2 Hz, C*H*), 7.17 (1H, d, J = 6.3 Hz, C*H*), 7.29 (1H, d, J = 8.7 Hz, C*H*), 7.14–7.54 (8H, m, Ar*H*), 8.47 (1H, d, J = 8.1 Hz, C*H*), 8.94 (1H, s, C*H*), 12.71 (1H, s, N*H*); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 15.2, 25.1, 46.9, 55.3, 55.5, 104.1, 113.9, 114.9, 121.2, 121.6, 122.4, 128.4, 128.7, 129.7, 129.8, 130.8, 130.9, 131.8, 132.0, 132.1, 134.0, 135.9, 136.7, 142.4, 147.8,160.7, 163.2, 178.1. MS EI, *m/z*: $[M]^+$ 545.4, $[M^+ + 2]$ 547.4. *Anal.* Calcd for $C_{28}H_{25}BrN_4O_3$: C, 61.66; H, 4.62; N, 10.27. Found: C, 61.6; H, 4.65; N, 10.23.

N′-(1-(4-Bromophenyl)-3-(3-methoxyphenyl)allylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (**7d**)

White powder; mp 246–247°C; IR (KBr) cm^{-1}: 3104, 1678, 1610; ^{1}H-NMR ($CDCl_3$, 300 MHz) : δ1.47(3H, t, J = 14.1 Hz, C*H*$_3$), 2.67 (3H, s, C*H*$_3$), 3.79 (3H, s, C*H*$_3$), 4.55 (2H, q, J = 7.1 Hz, C*H*$_2$), 6.34 (1H, d, J = 16.2 Hz, C*H*), 6.95 (1H, d, J = 6.3 Hz, C*H*), 7.31 (1H, d, J = 8.4 Hz, C*H*), 7.18–7.79 (8H, m, Ar*H*), 8.49 (1H, d, J = 8.2 Hz, C*H*), 8.94 (1H, s, C*H*), 12.70 (1H, s, N*H*); ^{13}C-NMR (75 MHz $CDCl_3$) δ: 15.2, 25.1, 46.9, 55.3, 55.2, 111.0, 115.3, 115.4, 118.0, 120.0, 121.1, 129.7, 130.1, 131.2, 131.4, 131.9, 132.0, 136.7, 137.4, 137.6, 145.3, 147.8, 148.4, 155.4, 159.8, 161.8, 163.3, 176.4. MS EI, *m/z*: $[M]^+$ 545.4, $[M^+ + 2]$ 547.4. *Anal.* Calcd for $C_{28}H_{25}BrN_4O_3$: C, 61.66; H, 4.62; N, 10.27. Found: C, 61.61; H, 4.65; N, 10.23.

N′-(1-(4-Chlorophenyl)-3-(2-fluorophenyl)allylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (**7e**)

Pale powder; mp 254–256°C; IR (KBr) cm^{-1}: 3032, 1665,1604; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.51 (3H, t, J = 14.4 Hz, C*H*$_3$), 2.68 (3H, s, C*H*$_3$), 4.60 (2H, d, J = 7.0 Hz, C*H*$_2$), 6.59 (1H, d, J = 16.5 Hz, C*H*), 7.15(1H, d, J = 7.5, C*H*), 7.35(1H, d, J = 8.1, C*H*), 7.40–7.93 (8H, m, Ar*H*), 8.52 (1H, d, J = 8.1 Hz, C*H*), 8.98 (1H, s, C*H*), 12.76 (1H, s, N*H*); ^{13}C-NMR ($CDCl_3$) δ: 15.2, 25.1, 46.9, 112.0, 115.8, 116.4, 120.0, 121.1,124.3, 127.2, 128.4, 128.9, 129.5, 129.8, 129.9, 130.7, 131.3, 132.0, 136.7, 138, 147.8, 148.3, 155.4, 158.7, 161.8, 163.3, 176.4. MS EI, *m/z*: $[M]^+$ 488.9, $[M^+ + 2]$ 490.9. *Anal.* Calcd for $C_{27}H_{22}ClFN_4O_2$: C, 66.32; H, 4.54; N, 11.46. Found: C, 66.25; H, 4.51; N, 11.4.

N′-(3-(2,4-Dichlorophenyl)-1-(4-iodophenyl)allylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (**7f**)

Off white powder; mp 258–260°C; IR (KBr) cm^{-1}: 3050, 1674,1607; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.47 (3H, t, J = 7.1 Hz, C*H*$_3$), 2.65 (3H, s, C*H*$_3$), 4.56 (2H, q, J = 7.2 Hz, C*H*$_2$), 6.73 (1H, d, J = 16.4 Hz, C*H*), 7.13 (1H, d, J = 8.4 Hz, C*H*), 7.34 (1H, d, J = 6.9 Hz, C*H*), 7.21–8.11 (7H, m, Ar*H*), 8.49 (1H, d, J = 8.2 Hz, C*H*), 8.93 (1H, s, C*H*), 12.81 (1H, s, N*H*); ^{13}C-NMR ($CDCl_3$) δ: 15.2, 25.1,46.9, 100.9, 121.2, 124.4, 127.4, 127.5, 128.5, 129.5, 129.7, 129.9, 130.0, 130.9, 131.2, 132.1, 132.2, 136.7, 138.2, 138.8, 139.8, 147.9, 147.8, 154.9, 161.9, 163.4, 189.3. MS EI, *m/z*: $[M]^+$ 631.2, $[M^+ + 2]$ 633.2, $[M^+ + 4]$635.2, $[M^+ + 6]$ 637.2. *Anal.* Calcd for $C_{27}H_{21}Cl_2IN_4O_2$: C, 51.37; H, 3.35; N, 8.87. Found: C, 51.43; H, 3.33; N, 8.84.

N′-(1-(4-Chlorophenyl)-3-(4-methoxyphenyl)allylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (**7g**)

White powder; mp 254–256°C; IR (KBr) cm^{-1}: 3016, 1681, 1616; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.46 (3H, t, J = 14.1 Hz, C*H*$_3$), 2.64 (3H, s, C*H*$_3$), 3.79 (3H, s, C*H*$_3$), 4.56 (2H, q, J = 7.2 Hz, C*H*$_2$), 6.36 (1H, d, J = 16.2 Hz, C*H*), 7.21 (1H, d, J = 8.1 Hz, C*H*), 7.32 (1H, d, J = 10.5 Hz, C*H*), 7.40–7.69 (8H, m, Ar*H*), 8.48 (1H, d, J = 8.1 Hz, C*H*), 8.93 (1H, s, C*H*), 12.67 (1H, s, N*H*); ^{13}C-NMR ($CDCl_3$) δ: 15.2, 25.1, 46.9, 55.3, 55.4, 114.2, 114.4, 119.1, 121.1, 128.5, 128.7, 128.8, 129.0, 129.1, 129.3, 129.4, 129.6, 129.7, 129.8, 130.3, 136.7, 145.2, 147.7, 157.4, 161.7, 161.8, 163.2, 176.4. MS EI, *m/z*: $[M]^+$ 500.9, $[M^+ + 2]$ 502.9. *Anal.* Calcd for $C_{28}H_{25}ClN_4O_3$: C, 67.13; H, 5.03; N, 11.18. Found: C, 66.97; H, 5.05; N, 11.13.

N′-(3-(2-Chlorophenyl)-1-phenylallylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (**7h**)

Yellow crystals; mp 252–254°C; IR (KBr) cm^{-1}: 3024, 1668, 1611; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.45 (3H, t, J = 7.1 Hz, C*H*$_3$), 2.63 (3H, s, C*H*$_3$), 4.52 (2H, q, J = 7.2 Hz, C*H*$_2$), 6.34 (1H, d, J = 16.2 Hz, C*H*), 7.16 (1H, d, J = 8.1 Hz, C*H*), 7.28 (1H, d, J = 8.2 Hz, C*H*), 7.32–7.61 (9H, m, Ar*H*), 8.44 (1H, d, J = 8.2 Hz, C*H*), 8.94 (1H, s, C*H*), 12.61 (1H, s, N*H*); ^{13}C-NMR ($CDCl_3$) δ: 15.2, 25.1, 48.1, 106.1, 120.9, 122.4,

128.2, 128.4, 128.6, 128.8, 129.1, 129.4, 129.5, 129.6, 130.1, 132.9, 136.9, 138.1, 140.2, 143.4, 147.8, 150.7, 152.7, 157.8, 160.9, 161.4, 174.8. MS EI, *m/z*: $[M]^+$ 470.9, $[M^+ + 2]$ 472.9. *Anal.* Calcd for $C_{27}H_{23}ClN_4O_2$: C, 68.86; H, 4.92; N, 11.90. Found: C, 68.77; H, 4.95; N, 11.9.

N′-(1-(4-Bromophenyl)-3-(2,4-dichlorophenyl)allylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (**7i**)

Off-white powder; mp 262–264°C, IR (KBr) cm^{-1}: 3043, 1683, 1611; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.52 (3H, t, $J = 7.1$ Hz, CH_3), 2.70 (3H, s, CH_3), 4.59 (2H, q, $J = 7.2$ Hz, CH_2), 7.24 (1H, s, C*H*), 7.28–7.33 (3H, m, Ar*H*), 7.38–7.67 (5H, m, Ar*H*), 8.04 (1H, d, $J = 8.4$ Hz, C*H*), 8.67 (1H, d, $J = 8.1$ Hz, C*H*), 9.03 (1H, s, C*H*), 13.53 (1H, s, N*H*); ^{13}C-NMR ($CDCl_3$) δ: 15.2, 25.1, 46.9, 115.4, 121.2, 124.5, 127.2, 127.5,128.5, 129.5, 129.8, 129.9, 130.0, 130.5, 131.4, 132.1, 132.6, 136.1, 138.2, 138.8, 139.8, 147.9, 147.7, 154.9, 161.9, 163.7, 189.6. MS EI, *m/z*: $[M]^+$ 584.2, $[M^+ + 2]$ 586.2, $[M^+ + 4]$ 588.2, $[M^+ + 6]$ 590.2. *Anal.* Calcd for $C_{27}H_{21}BrCl_2N_4O_2$: C, 55.5; H, 3.62; N, 9.59. Found: C, 55.62; H, 3.64; N, 9.51.

N′-(1-(4-Chlorophenyl)-3-(2,4-dichlorophenyl)allylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (**7j**)

Off white powder; mp 266–268°C, IR (KBr) cm^{-1}: 3036, 1683, 1613; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.50 (3H, m, CH_3), 2.65 (3H, s, CH_3), 4.53 (2H, q, $J = 7.2$ Hz, CH_2), 6.72 (1H, d, $J = 16.4$ Hz, C*H*), 7.24 (1H, s, C*H*), 7.29–7.43 (5H, m, Ar*H*), 8.04–8.49 (2H, m, C*H*), 8.67 (1H, d, $J = 8.2$ Hz, C*H*), 9.04 (1H, s, C*H*), 12.77 (1H, s, C*H*), 13.50 (1H, s, N*H*); ^{13}C-NMR ($CDCl_3$) δ: 15.2, 25.2, 46.9, 120.4, 121.2, 124.4, 127.3, 127.5, 128.4, 129.4, 129.7, 129.8, 130.3, 130.7, 131.2, 132.1, 132.2, 136.4, 138.2, 138.5, 139.9, 147.6, 147.8, 154.7, 161.9, 163.3, 189.1. MS EI, *m/z*: $[M]^+$ 539.8, $[M^+ + 2]$ 541.8, $[M^+ + 4]$ 543.8, $[M^+ + 6]$ 545.8. *Anal.* Calcd for $C_{27}H_{21}Cl_3N_4O_2$: C, 60.07; H, 3.92; N, 10.38. Found: C, 60.02; H, 3.96; N, 10.31.

N′-(1-(4-Bromophenyl)-3-(2,3-dichlorophenyl)allylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (**7k**)

White powder; mp 286–287°C, IR (KBr) cm^{-1}: 2993, 1686, 1619; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.52 (3H, t, $J = 8.2$ Hz, CH_3), 2.70 (3H, s, CH_3), 4.60 (2H, q, $J = 7.2$ Hz, CH_2), 7.25–7.41 (4H, m, Ar*H*), 7.48 (1H, dd, $J = 8.0$, 1.5 Hz, C*H*), 7.51–8.00 (5H, m, Ar*H*), 8.67 (1H, d, $J = 8.2$ Hz, C*H*), 9.04 (1H, s, C*H*), 13.52 (1H, s, N*H*); ^{13}C-NMR ($CDCl_3$) δ: 15.2, 25.3, 46.7, 114.4, 120.2, 123.5, 126.2, 127.5, 128.5, 129.5, 129.8, 129.9, 130.3, 130.5, 131.7, 132.1,132.9, 136.0, 138.1, 138.8, 139.5, 147.3, 147.7, 154.9, 161.9, 164.6, 189.7. MS EI, *m/z*: $[M]^+$ 584.2, $[M^+ + 2]$ 586.2, $[M^+ + 4]$ 588.2, $[M^+ + 6]$ 590.2. *Anal.* Calcd for $C_{27}H_{21}BrCl_2N_4O_2$: C, 55.50; H, 3.62; N, 9.59. Found: C, 55.43; H, 3.65; N, 9.51.

N′-(3-(3-Chlorophenyl)-1-(4-methoxyphenyl)allylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (**7l**)

White powder; mp 275–276°C, IR (KBr) cm^{-1}: 3047, 1660, 1606; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.46 (3H, t, $J = 7.3$ Hz, CH_3), 2.64 (3H, s, CH_3), 3.94 (3H, s, CH_3), 4.51 (2H, q, $J = 7.3$ Hz, CH_2), 6.35 (1H, d, $J = 16.3$ Hz, C*H*), 7.12–7.43 (6H, m, Ar*H*), 8.47 (1H, d, $J = 8.1$ Hz, C*H*), 8.94 (1H, s, C*H*), 12.70 (1H, s, N*H*); ^{13} C NMR ($CDCl_3$) δ: 15.2, 25.4, 46.8, 55.1, 55.3, 114.9, 120.3, 121.1, 122.6, 129.1, 129.2, 129.4, 129.8, 130.7, 133.4, 134.7, 135.3, 135.8,, 136.2, 136.7, 136.8, 142.1, 147.9, 148.7, 156.0, 161.5, 164.2, 176.4. MS EI, *m/z*: $[M]^+$ 500.9, $[M^+ + 2]$ 502.9. *Anal.* Calcd for $C_{28}H_{25}ClN_4O_3$: C, 67.13; H, 5.02; N, 11.18. Found: C, 67.19; H, 5.05; N, 11.13.

N′-(3-(4-Bromophenyl)-1-(4-chlorophenyl)allylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (**7m**)

White powder; mp 280–282°C, IR (KBr) cm^{-1}: 3049, 1680, 1604; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.52 (3H, t, $J = 8.2$ Hz, CH_3), 2.70 (3H, s, CH_3), 4.59 (2H, q, $J = 7.2$ Hz, CH_2), 6.88 (1H, d, $J = 16.3$ Hz, C*H*), 7.34 (1H, d, $J = 8.1$ Hz, C*H*), 7.34–7.44 (3H, m, Ar*H*), 7.50–7.64 (6H, m, Ar*H*), 8.68 (1H, d, $J = 8.2$ Hz, C*H*), 9.03 (1H, s, C*H*), 13.51 (1H, s, N*H*); ^{13}C-NMR ($CDCl_3$) δ: 15.1, 25.1, 46.7, 120.4, 121.3, 124.1, 126.7, 127.4, 128.4, 129.3, 129.7, 129.8, 130.1, 130.4, 131.2, 132.5, 132.7, 136.9, 138.1, 138.5, 139.7, 146.6, 147.9, 154.5, 161.8, 163.5, 189.2. MS EI, *m/z*: $[M]^+$ 549.8, $[M^+ + 2]$ 551.8, $[M^+ + 4]$ 553.8. *Anal.* Calcd for $C_{27}H_{22}BrClN_4O_2$: C, 58.98; H, 4.03; N, 10.19. Found: C, 58.83; H, 4.06; N, 10.11.

N′-(1,3-Diphenylallylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (**7n**)

Off white Powder; mp 220–222°C, IR (KBr) cm^{-1}: 3036, 1662, 1606; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.49 (3H, t, $J = 7.1$ Hz, CH_3), 2.63 (3H, s, CH_3), 4.57 (2H, q, $J = 7.1$ Hz, CH_2), 6.31 (1H, d, $J = 16.3$ Hz, C*H*), 6.88 (1H, d, $J = 16.5$ Hz, C*H*), 7.30 (2H, d, $J = 4.8$ Hz, C*H*), 7.17–7.69 (9H, m, Ar*H*), 8.49 (1H, d, $J = 8.2$ Hz, C*H*), 8.96 (1H, s, C*H*), 12.70 (1H, s, N*H*); ^{13}C-NMR ($CDCl_3$) δ: 15.2, 25.1, 112.1, 120.4, 122.7, 128.1, 128.5, 128.6, 128.8, 128.9, 129.3, 129.4, 129.6, 129.7, 129.9, 131.3, 132.9, 136.7, 138.1, 140.7, 144.3, 147.8, 150.7, 152.9, 156.7, 160.4, 161.4, 176.9. MS EI, *m/z*: $[M]^+$ 436.5. *Anal.* Calcd for $C_{27}H_{24}N_4O_2$: C, 74.29; H, 5.54; N, 12.84. Found: C, 74.34; H, 5.51; N, 12.77.

N′-(3-(3-Chlorophenyl)-1-phenylallylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (**7o**)

White powder; mp 207–209°C, IR (KBr) cm^{-1}: 2919, 1664, 1611; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.49 (3H, t, $J = 7.1$ Hz, CH_3), 2.63 (3H, s, CH_3), 4.57 (2H, q, $J = 7.1$ Hz, CH_2), 6.31 (1H, d, $J = 16.3$ Hz, C*H*), 6.88 (1H, d, $J = 16.5$ Hz, C*H*), 7.30 (2H, d, $J = 4.8$ Hz, C*H*), 7.17–7.69 (9H, m, Ar*H*), 8.49 (1H, d, $J = 8.2$ Hz, C*H*), 8.96 (1H, s, C*H*), 12.70 (1H, s, N*H*); ^{13}C-NMR ($CDCl_3$) δ: 15.2, 25.1, 47.1, 113.1, 120.7, 122.9, 128.1, 128.3, 128.7, 128.9, 129.3, 129.4, 129.6, 129.8, 130.7, 132.3, 136.7, 138.3, 140.1, 146.4, 147.8, 150.3, 152.7, 155.8, 160.7, 162.4, 171.8.MS EI, *m/z*: $[M]^+$ 470.9, $[M^+ + 2]$ 472.9. *Anal.* Calcd For $C_{27}H_{23}ClN_4O_2$: C, 68.86; H, 4.92; N, 11.90. Found: C, 68.75; H, 4.95; N, 11.94.

X-Ray Data Collection and Structure Determination A suitable crystal of compound (**7b**) was selected for the studies of single crystal diffraction. Selected crystal was mounted on the tip of thin glass fiber. Crystal data was collected on Agilent Super Nova diffractometer (microfocus Cu/MoK_α radiation) using CrysAlis Pro software[31] at 296 K. Structure was solved with SHELXS-97[32] employing full-matrix least-squares methods for data refinement on F^2 using SHELXL-97[32]/WinGX[33] software. Anisotropic refinement of non-hydrogen atoms was carried out with full-matrix least squares methods[32] while PLATON,[34] ORTEP[35] in built with WinGX[33] and Olex2[36] were used to generate the figures.

Green Chemistry Parameters To relate present synthetic paths with green chemistry protocols, certain parameters were

adopted ranging from simplified atom economy of a balanced chemical reaction to reaction mass efficiencies of the adopted processes. Green chemistry metrics "carbon efficiency" includes yield and stoichiometry of the reactants and products which measures the carbon fate of the chemical reaction by taking molar ratios.[37]

To have an idea about sustainable reactions at industrial scale, metrics devised by Constable *et al.*[38] for reaction mass efficiency and process mass intensity[39] were used which can be calculated for laboratory scale reactions prior to their upscaling.

$$\text{RME} = \frac{\text{Mass of the product}}{\text{Sum of reactant masses}}$$

$$\text{SMI} = \frac{\text{Mass of all materials used to make product}}{\text{Mass of product}}$$

Reactions used for the synthesis of hybrid molecules are compared for their energy consumption in terms of power and time and are reported as kWh (kilowatt-hour). It was found that the reactions carried out using conventional heating consumed much more energy than those carried out using microwaves. Energy efficiency is calculated to check the efficiency of the protocols by taking the ratio of energy consumed in individual reaction to its percentage yield using the method by Cho *et al.*[23]

Total Anti-oxidant Assay Total anti-oxidant assay was performed using phosphomolybdenum complex method developed by Prieto *et al.* with minor modifications.[24] Experiments were carried out in plain glass capped vials in which freshly prepared phosphomolybdenum reagent (4 mL) was added separately. Test compound solution was then added to these vials in varied concentrations 125, 250 and 500 μM (prepared from 1 mM stock solution of each compound). Along with these test vials, two vials were prepared for standard (using BHT) and a blank without test compounds and BHT and were treated in the same way. Reagent for this study was prepared by dissolving ammonium molybdate (2.4 g) in distilled water (100 mL) and to this solution; sodium phosphate (5.32 g) was added. Contents were stirred with glass rod for proper mixing of both salts followed by its acidification with sulfuric acid (16.7 mL) and making of total volume up to 500 mL with water. All the vials were placed for incubation for 90 min at 55 ± 1°C. Readings were taken at 695 nm on UV-Vis spectrophotometer.

FRAP Assay Ferric reducing anti-oxidant power assay was carried out by Benzie and Strain method[40] with slight modifications. Assay was carried out at pH 3.6 in buffer media (300 mM; sodium acetate/acetic acid). FRAP reducing agent was prepared by mixing ferric chloride solution (20 mM) and 2,4,6-tripyridyl-*s*-triazine solution (10 mM) with sodium acetate buffer solution (300 mM) in 1 : 1 : 10 ratio. Prewarmed FRAP reagent was used for experimentation. Synthesized derivatives (**7a–7o**) 0.1 mL (100 μM) prepared from respective derivative stock solution of 10 mM were taken in separate glass vials and pre-warmed FRAP reagent (2.9 mL) was mixed with test solutions separately at 37°C. Test vials were kept at 37°C for 15–20 min and readings were taken on spectrophotometer at 593 nm. Anti-oxidant capacity was calculated by taking standard calibration curve of ascorbic acid (10–600 μM).

TPC Assay Total phenolic contents were evaluated employing the procedure adopted by Xu *et al.*[41] Gallic acid was used as standard for comparative determination of phenolic contents in the novel derivatives. Sodium bicarbonate solution (10%) was used as color developer and stabilizing aid for TPC experiments. Each test glass vial contains F–C reagent (2N; 0.1 mL) and test solutions 0.1 mL (100 μM; each prepared from stock solutions (10 mM) of respective derivatives). Solution of 10% sodium bicarbonate (2.8 mL) was added in each test vial. Standards were made similarly, by replacing test compounds with gallic acid solution (50–1200 μM). All the vials were kept at room temperature for 40 min and TPC values were determined by taking readings at 761 nm on spectrophotometer. Results were calculated and reported by drawing calibration curve of gallic acid. TPCs final concentration is reported as, Gallic acid equivalence (μM). Readings were recorded as triplicate average and are reported with ± S.E.M. (standard error of measurement).

Metal Chelating Activity Capacity of the synthesized derivatives to complex with metals was investigated by ferrozine assay.[25] Ferrozine reagent (0.1 mL) prepared in 5 mM concentration was added in test glass vial. Freshly prepared ferrous chloride solution (0.05 mL; 2 mM) was added in each test vial. This test requires fresh reagents to avoid any oxidation of ferrous chloride to ferric chloride which makes the reagent inactive for the study. To this 0.1 mL solution (100 μM; prepared from stock solution of 10 mM) of each derivative under investigation were added. Final volume was made to 4 mL by adding methanol. These vials were shaken, capped and kept at 25°C for 10–15 min and readings were recorded at 562 nm. Metal chelating activity was calculated by following formula:

$$\text{Chelating effect (\%)} = (\text{A control} - \text{A sample}/\text{A control}) \times 100$$

Anti-bacterial Screening

In-vitro anti-bacterial activity of the synthesized compounds (dissolved in dimethylsulfoxide) was performed against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* strains using agar well diffusion techniques. The bacteria inocula containing approximately 10^4–10^6 colony forming unit (CFU)/mL were spread on agar nutrient surface. Then 10 μL (10 mM) of each test compounds, 0 (control) and standard Nalidixic acid were introduced in the wells.[42] Plates were incubated at 37°C for 24 h and were inspected by measuring zone of inhibition (mm).

Statistical Analysis All the readings were taken in triplicate and statistical analysis was carried out using MS Excel 2007.

Conclusion

Prompted by well-known examples of structural modifications for making hybrid molecules, a series of novel *N*′-(1,3-diphenylallylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazides (**7a–o**) were synthesized by the merger of two independent moieties *i.e.*, nalidixic acid hydrazide and 1,3-diphenylprop-2-en-1-ones.

These compounds were evaluated for their anti-oxidant potential indicating few of these as potential anti-oxidant compounds which may be used for further exploration towards potent biologically active compounds. Use of microwaves in the reactions instead of conventional heating increased the reaction

rates and percent yields to considerable extent. Single crystal X-ray studies of one representative compound from the series (**7a–7o**) *i.e.*, *N′*-(3-(4-chlorophenyl)-1-(4-methoxyphenyl)allylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide confirms the basic skeleton and merger of the two moieties. Carbon efficiency and reaction mass efficiencies of microwave induced reactions were found to be 95 and 92%.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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