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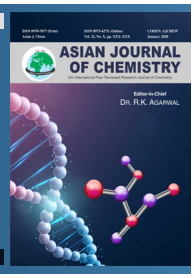

Synthesis, *in vitro* and *in silico* Studies of Naphthalene Pyrazoline Prop-2-en-1-one Derivatives

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The synthesized new naphthalene pyrazoline prop-2-en-1-one derivatives (**NDPP 1-8**) were obtained by the Michael addition reaction of ethyl propanoate, hydrazine hydrate with NPD as a multicomponent scaffold. (*E*)-1-(naphthalen-3-yl)-3-phenylprop-2-en-1-one (NPD) was formed from 2-acetyl naphthalene and substituted aldehyde *via* Claisen-Schmidt condensation reaction. The NDPP skeleton structures were confirmed by infrared, ^{1}H & ^{13}C NMR spectral data and elemental analysis. The structure of NDPP compounds was subjected to molecular docking and ADME studies. The result of ADME prediction, compound **NDPP 2**, which contains electron withdrawing -Cl group has high drug-likeness value 4.21 than the compounds **NDPP 4** and **7** which had electron donating CH_3 and OCH_3 group shows the drug-likeness value 2.62. The **NDPP 2** also has high drug score 0.63 than **NDPP 4** and **NDPP 7** have drug score 0.60 and 0.69, respectively. Docking studies shows that compound **NDPP 5** which also contain electron withdrawing NO_2 group has good binding affinity value -8.8 Kcal/mol were docked with 1UAG protein. These compounds showed good drug-likeness value 2.25 and drug score 0.65. *in vitro* Studies have a high inhibition value for the same NO_2 substituted derivative. All the compounds have higher binding affinity value than standards binding affinity value.

Keywords: Naphthalene pyrazoline, Prop-2-en-1-one, ADME.

INTRODUCTION

Infectious diseases are believed to occur sometimes due to resistance to the action of drugs. Some of the infectious disease may lead to many dangerous health conditions in humans. To overcome this problem, we need to design and create new compounds that are averse to infectious pathogens with a high number of multidrug properties along with biodegradable, less toxic and good soluble properties. Pyrazole is a five-membered heterocyclic core with a wide pharmaceutical impact [1]. The alternative presence of C-N, C-C and C-N bonds in the pyrazole ring formed by cross linking of electrophile or condensation of unsaturated ketones with hydrazine [2-4] and the pyrazole ring structure also formed by Schiff base reaction [5]. The pyrazoles moiety has antimicrobial [6,7], antimalarial [8], anti-inflammatory [9], anti-proliferative [10], anti-tumor [11] and anti-hyperglycemic [12] properties and is used in the field of herbicides [13], agrochemicals [14], corrosion inhibition [15] *etc*.

Naproxen containing naphthalene moiety is a propionic acid class of non-steroidal anti-inflammatory drug [16-18]. Nabumetone another important anti-inflammatory drug used to blocks the COX-2 activity in human system [19]. The bedaquiline used as a antituberculosis drug which is approved by FDA [20] and rifampicin also a drug, used in the treatment of tuberculosis [21]. Tolnaftate and natifine are the drugs used as an antifungal [16,22,23]. Nafcillin is an antibiotic and particularly used to the treatment of infections, which are caused by gram positive bacteria [16,24].

Present decades, computational method is consider as one of the best and beneficial method to analyses the chemical structure of the compounds [25] and these are accepted over the world. Many applications are available to predict the various pharmacokinetics property of the chemical compounds [26,27]. Molecular docking studies are used to predict the affinity value and the manner of interaction of organic structured compounds with various proteins. This method is quite effective to predict the binding score and the binding of small or macromolecules with protein targets, which helps to identify the medicinal applications of compounds in various fields [28]. ADME property prediction of the compounds helps to find out their drug-likeness and toxicity.

The naphthalene pyrazoline prop-2-en-1-one derivatives (**NDPP 1-8**) were synthesized by Michael addition reaction as multicomponent ones. The synthesized NDPP compounds structure were confirmed by IR, ^{1}H & ^{13}C NMR spectral and elemental analysis. The confirmed structures were screened to *in-silico* ADME and molecular docking *in-vitro* antimicrobial studies.

EXPERIMENTAL

The physical data of NDPP derivatives were done by using suitable instruments. The instruments Shimadzu 8400s, Bruker 400 MHz and 100 MHz were used to evaluate the infrared, ^{1}H & ^{13}C NMR values of the target compounds in the usual range.

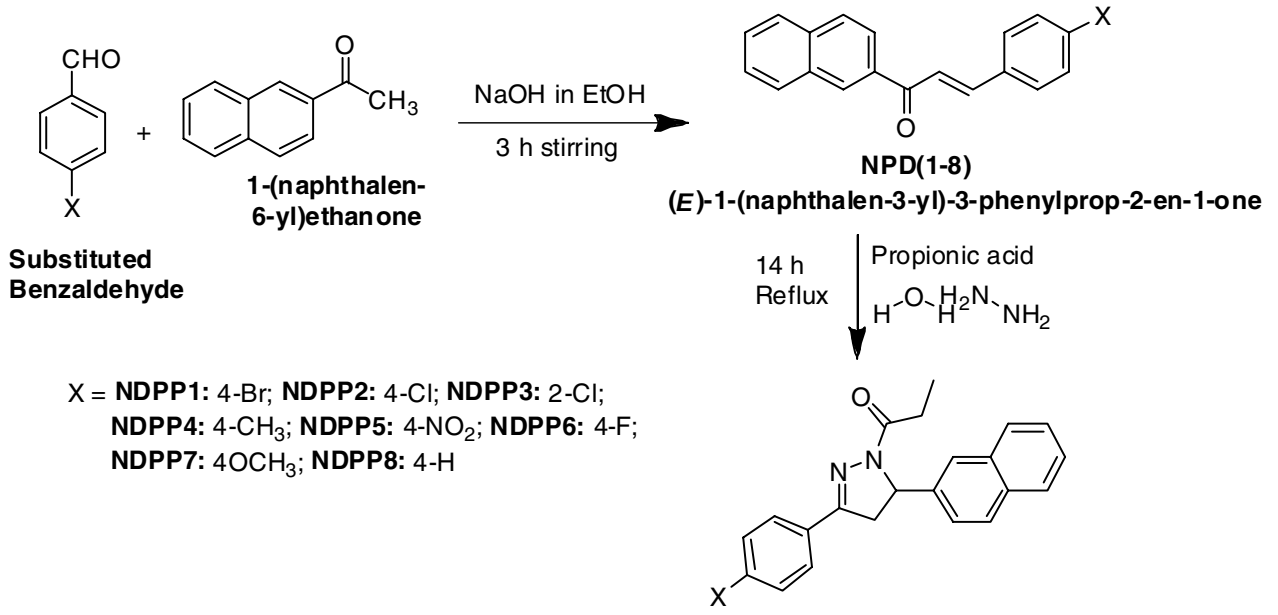
Synthesis of (*E*)-1-(naphthalen-3-yl)-3-phenylprop-2-en-1-one (NPD): The literary method was followed to synthesize NPD compound [29]. In brief, substituted benzaldehyde (1 mol) and 2-acetyl naphthalene (1 mol) were mixed in 250 mL Erlenmeyer containing NaOH dissolved ethanol. The reaction mixture was stirred for 3 h with ice cold conditions. The TLC was used to monitor the completion of reaction. The reaction mixture was poured into 400 mL beaker containing crushed ice and kept in a refrigerator for overnight and then filtered, washed with excess of water, dried and recrystallized from ethanol.

Synthesis of 1-(4,5-dihydro-5-(naphthalene-3-yl)-3-phenylpyrazole-1-yl)propan-1-one (NDPP): Chalcone derivative (1 mol) was taken in the round bottom flask containing ethyl proponate and hydrazine hydrate (1 mol) was added drop wise. The whole mixture was placed in the heating mantle for 16-18 h of reflux. The TLC was used to monitor the completion of the reaction. After that, the reaction mixture transferred into 400 ml beaker contain crushed ice and it was kept overnight at room temperature. The target compound was filtered, dried and its purity also checked by TLC with 9:1 petroleum ether: chloroform as a solvent (**Scheme-I**).

1-(3-(4-Bromophenyl)-4,5-dihydro-5-(naphthalen-3-yl)pyrazol-1-yl)propan-1-one (NDPP-1): Yield 89%; yellow; m.p.: 416 ºC; m.w.: 407.3; IR (KBr, ν_{max}, cm^{-1}): 1472.47 (C=N), 1660.34 (C=O), 1135.00 (C-N), 3128.18 (Ar-CH), 2902.20 (Al-CH), 805, 605 (Ar-ring); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) 3.23 (dd, $J_{4a,4e}$ = 3.8 Hz, $J_{4a,5a}$ = 17.4 Hz, 2H, H-4a), 3.75 (dd, $J_{4e,4a}$ = 12.2 Hz , $J_{4e,5a}$ = 17.0 Hz, 2H, H-4e), 5.56 (dd, $J_{5a,4a}$ = 4.2 Hz, $J_{5a,4e}$ = 11.4 Hz, 1H, H-5a), 1.14-1.18 (t, CH_3), 2.81-2.84 (m, CH_2), 7.194-8.085 (Ar, H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 172.12 (C=O), 14.02 ($C_{3'}$, CH_2), 36.15 ($C_{2'}$, CH_3), 153.18 (C-3), 41.65 (C-4), 59.13 (C-5), 140.28, 134.58, 133.20 (*ipso* carbons), 127.08-124.23 (Ar-C). Elemental analysis of $C_{22}H_{19}N_2OBr$ calcd. (found) %: C, 64.86 (64.46); H, 4.66 (4.63), N, 6.87 (6.37), O, 3.93 (3.93), Br, 19.65 (19.32).

1-(3-(4-Chlorophenyl)-4,5-dihydro-5-(naphthalen-3-yl)pyrazol-1-yl)propan-1-one (NDPP-2): Yield 94%; pale yellow; m.p.: 386; m.w.: 362.85; IR (KBr, ν_{max}, cm^{-1}): 1477.47 (C=N), 1662.64 (C=O), 1138.00 (C-N), 3138.18 (Ar-CH), 2910.12 (Al-CH), 750.31(Ar-ring); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm) 3.25 (dd, $J_{4a,4e}$ = 4 Hz, $J_{4a,5a}$ = 17.6 Hz, 2H, H-4a), 3.85 (dd, $J_{4e,4a}$ = 12.4 Hz , $J_{4e,5a}$ = 17.2 Hz, 2H, H-4e), 5.58 (dd, $J_{5a,4a}$ = 4 Hz, $J_{5a,4e}$ = 11.6 Hz, 1H, H-5a), 1.19-1.2 (t, CH_3), 2.83-2.86 (m, CH_2), 7.092-7.985 (Ar, H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 171.61 (C=O), 14.04 ($C_{3'}$, CH_2), 36.17 ($C_{2'}$, CH_3), 153.20 (C-3), 41.95 (C-4), 59.63 (C-5), 140.68, 134.18, 133.40 (*ipso* carbons), 129.10-123.29 (Ar-C). Elemental analysis of $C_{22}H_{19}N_2OCl$ calcd. (found) %: C, 72.72 (71.86); H 5.23 (5.23); N, 7.71 (7.37); O, 4.40 (4.43); Cl, 9.64 (9.32).

1-(3-(2-Chlorophenyl)-4,5-dihydro-5-(naphthalen-3-yl)pyrazol-1-yl)propan-1-one (NDPP-3): Yield 92%; pale yellow; m.p.:386 ºC; m.w.: 362.85; IR (KBr, ν_{max}, cm^{-1}): 1427.32 (C=N), 1662.64 (C=O), 1035.77 (C-N), 3050.65 (Ar-CH), 2931.80 (Al-CH), 653.12,724.23 (Ar-ring); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 3.16 (dd, $J_{4a,4e}$ = 3.2 Hz, $J_{4a,5a}$ = 17.6 Hz, 2H,



Scheme-I: Synthetic pathway for the synthesized **NDPP 1-8** compounds

H-4a), 3.74 (dd, $J_{4e,4a}$ = 12.2 Hz , $J_{4e,5a}$ = 17.4 Hz, 2H, H-4e), 5.57 (dd, $J_{5a,4a}$ = 6.2 Hz , $J_{5a,4e}$ = 10.2 Hz, 1H, H-5a), 0.97-1.01 (t, CH_3), 2.30-2.86 (m, CH_2), 6.895-7.776 (Ar, H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): 171.61 (C=O), 14.04 ($C_{3'}$, CH_2), 36.17 ($C_{2'}$, CH_3), 153.20 (C-3), 41.95 (C-4), 59.63 (C-5), 140.68, 134.18, 133.40 (*ipso* carbons), 129.10-123.29 (Ar-C). Elemental analysis of $C_{22}H_{19}N_2OCl$ calcd. (found) %: C, 72.72 (71.86); H, 5.23 (5.23); N, 7.71 (7.37); O, 4.40 (4.43); Cl, 9.64 (9.32).

1-(3-(4-Methylphenyl)-4,5-dihydro-5-(naphthalen-3-yl)pyrazol-1-yl)propan-1-one (NDPP-4): Yield 90%; pale Yellow; m.p.: 367 ºC; m.w.: 342.43; IR (KBr, ν_{max}, cm^{-1}): 1447.32 (C=N), 1660.42 (C=O), 1115.77 (C-N), 3065.24 (Ar-CH), 2911.23 (Al-CH), 792.32, 801.21 (Ar-ring); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 3.14 (dd, $J_{4a,4e}$ = 3.8 Hz, $J_{4a,5a}$ = 17.8 Hz, 2H, H-4a), 3.78 (dd, $J_{4e,4a}$ = 12.2 Hz , $J_{4e,5a}$= 17.4 Hz, 2H, H-4e), 5.56 (dd, $J_{5a,4a}$ = 3.8 Hz , $J_{5a,4e}$ = 11.4 Hz, 1H, H-5a), 0.97-1.01 (t, CH_3), 2.74-2.82 (m, CH_2), 7.132-7.965 (Ar, H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 171.75 (C=O), 14.00 ($C_{3'}$, CH_2), 36.08 ($C_{2'}$, CH_3), 153.17 (C-3), 41.86 (C-4), 59.63 (C-5), 142.93, 139.71, 140 (*ipso* carbons), 130.13-125.88 (Ar-C). Elemental analysis of $C_{23}H_{22}N_2O$ calcd. (found) %: C, 80.70 (79.86); H, 6.43 (6.23); N, 8.18 (7.97), O, 4.67 (4.53).

1-(3-(4-Nitrophenyl)-4,5-dihydro-5-(naphthalen-3-yl)-pyrazol-1-yl)propan-1-one (NDPP-5): Yield 85%; brownish yellow; m.p.: 392 ºC; m.w.: 375; IR(KBr, ν_{max}, cm^{-1}): 1457.21 (C=N), 1659.64 (C=O), 1095.25 (C-N), 3002.12 (Ar-CH), 2952.30 (Al-CH), 692.21,795.54 (Ar-ring); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 3.16 (dd, $J_{4a,4e}$ = 4 Hz, $J_{4a,5a}$ = 17.6 Hz, 2H, H-4a), 3.84 (dd, $J_{4e,4a}$ = 12.4 Hz, $J_{4e,5a}$ = 17.6 Hz, 2H, H-4e), 5.66 (dd, $J_{5a,4a}$ = 4.2 Hz, $J_{5a,4e}$ = 11.4 Hz, 1H, H-5a), 0.98-1.02 (t, CH_3), 2.74-2.89 (m, CH_2), 7.114-8.098 (Ar, H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 171.53 (C=O), 14.01 ($C_{3'}$, CH_2), 36.21 ($C_{2'}$, CH_3), 153.26 (C-3), 42.09 (C-4), 59.60 (C-5), 141.43, 139.71 (*ipso* carbons), 129.87-124.18 (Ar-C). Elemental analysis of $C_{22}H_{19}N_3O_3$ calcd. (found) %: C, 70.77 (70.56); H, 5.09 (5.02); N, 11.26 (11.23); O, 12.86 (12.46).

1-(3-(4-Fluorophenyl)-4,5-dihydro-5-(naphthalen-3-yl)pyrazol-1-yl)propan-1-one (NDPP-6): Yield 84%; yellow; m.p.: 357 ºC; m.w.: 346.15; IR(KBr, ν_{max}, cm^{-1}): 1447.12 (C=N), 1663.14 (C=O), 1145.17 (C-N), 3080.82 (Ar-CH), 2951.78 (Al-CH), 784.32, 823.13 (Ar-ring); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 3.18(dd, $J_{4a,4e}$ = 3.8 Hz, $J_{4a,5a}$ = 17.4 Hz, 2H, H-4a), 3.76 (dd, $J_{4e,4a}$ = 12.2 Hz , $J_{4e,5a}$= 17 Hz, 2H, H-4e), 5.51 (dd, $J_{5a,4a}$ = 3.6 Hz , $J_{5a,4e}$ = 11.8 Hz, 1H, H-5a), 0.97-1.0 (t, CH_3), 2.72-2.85 (m, CH_2), 6.956-7.984 (Ar, H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 171.41 (C=O), 13.92 ($C_{3'}$, CH_2), 36.03 ($C_{2'}$, CH_3), 153.16 (C-3), 41.96 (C-4), 59.44 (C-5), 140.19, 134.38 (*ipso* carbons), 130.53-126.93 (Ar-C). Elemental analysis of $C_{22}H_{19}N_2OF$ calcd. (found) %: C, 76.30 (76.26); H, 5.49 (5.43); N, 8.09 (8.07); O, 4.62 (4.53); F, 5.49 (5.32).

1-(3-(4-Methoxyphenyl)-4,5-dihydro-5-(naphthalen-3-yl)-pyrazol-1-yl)propan-1-one (NDPP-7): Yield 92%; yellowish white; m.p.: 389 ºC; m.w.: 358.17; IR (KBr, ν_{max}, cm^{-1}): 1435.24 (C=N), 1658.23 (C=O), 1098.05 (C-N), 3100.61 (Ar-CH), 2982.54 (Al-CH), 768.21, 813.45 (Ar-ring); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 3.18 (dd, $J_{4a,4e}$ = 3.8 Hz, $J_{4a,5a}$ = 17.8 Hz, 2H, H-4a), 3.80 (dd, $J_{4e,4a}$ = 12.2 Hz , $J_{4e,5a}$ = 17.4 Hz, 2H, H-4e), 5.52 (dd, $J_{5a,4a}$ = 3.6 Hz , $J_{5a,4e}$ = 11.2 Hz, 1H, H-5a), 0.98-1.02 (t, CH_3), 2.73-2.84 (m, CH_2), 7.102-7.975 (Ar, H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 171.75 (C=O), 14.00 ($C_{3'}$, CH_2), 36.08 ($C_{2'}$, CH_3), 153.17 (C-3), 41.86 (C-4), 59.63 (C-5), 142.42, 140.66, 133.16 (*ipso* carbons), 130.13-125.88 (Ar-C). Elemental analysis of m.f. $C_{23}H_{22}N_2O_2$ calcd. (found) %: C, 77.05 (76.96), H, 6.14 (6.12); N, 7.81 (7.65); O, 8.93 (8.83).

1-(4,5-Dihydro-5-(naphthalene-3-yl)-3-phenylpyrazole-1-yl)propan-1-one (NDPP-8): Yield 82%; pale yellow; m.p.: 343 ºC; m.w.: 328.16; IR(KBr, ν_{max}, cm^{-1}): 1440.12 (C=N), 1656.42 (C=O), 1095.25 (C-N), 3060.72 (Ar-CH), 2971.24 (Al-CH), 784.32, 823.13 (Ar-ring); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 3.19 (dd, $J_{4a,4e}$ = 4 Hz, $J_{4a,5a}$ = 17.4 Hz, 2H, H-4a), 3.74 (dd, $J_{4e,4a}$ = 12.2 Hz , $J_{4e,5a}$= 17.4 Hz, 2H, H-4e), 5.62 (dd, $J_{5a,4a}$ = 3.8 Hz , $J_{5a,4e}$ = 11.4 Hz, 1H, H-5a), 0.99-1.12 (t, CH_3), 2.81-2.84 (m, CH_2), 7.095-7.895 (Ar, H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 171.41 (C=O), 13.92 ($C_{3'}$, CH_2), 36.03 ($C_{2'}$, CH_3), 153.16 (C-3), 41.96 (C-4), 59.44 (C-5), 140.99, 136.38 (*ipso* carbons), 130.53-125.83 (Ar-C). Elemental analysis of $C_{22}H_{20}N_2O$ calcd. (found) %: C, 80.44 (80.26); H, 6.09 (6.03); N, 4.26 (4.23); O, 4.87 (4.83).

Antimicrobial activity: The disk diffusion method is used to carry out the antimicrobial studies of synthesized NDPP compounds. Sterilized inoculums and sterile swab were used. The *C. albicans* strain was used for the screening of antifungal study. Ciprofloxacin and clotrimazole were used as standard drugs in the microbial studies. Other steps were adopted from the reference [5].

Molecular docking: The Auto dock 4.2.5.1 version program was used for the molecular docking studies of synthesized NDPP derivatives. The given literary method was followed to find the docking scores [29].

ADME studies: The NDPP compound structure was subjected to Absorption, Distribution, Metabolism and Excretion (ADME) studies using Osiris online tool. The tool has the basic information about solubility (S), log P, polar surface area (TPSA), hydrogen bond acceptor (Hd. Ac.), hydrogen bond donor (Hd. Dn.), drug-likeness score and drug score. The above parameters are helpful to understand the ADME property of any drugs or organic molecule. The compound has a drug property, which means it must obey the rule of five described by Lipinski. The Lipinski's rules are: the compound must have molecular weight ≤ 500, Hydrogen bond acceptor ≤ 10, hydrogen bond donor ≤ 5, log p ≤ 5 and molar refractivity ≤ 140. The other most important properties of the compounds are that they have polar surface area range between 7 to 200, S range above-4, the drug score value above 0.5 and drug-likeness score as in positive values for synthesized organic compounds [30].

RESULTS AND DISCUSSION

The target NDPP compounds were synthesized from the reactant α,β-unsaturated ketone with ethyl proponate and hydrazine hydrate. The Michael addition reaction was performed to create the target NDPP (**1-8**) compounds as a multi-component reaction. Multicomponent reaction is the best reaction method for organic synthesis nowadays due to its less reaction time and minimum or no solvents usage. The starting material

TABLE-1
ADME PREDICTION VALUE OF TARGET COMPOUNDS **NDPP 1-8**

Compd.	log P	m.w.	Hd. Ac.	Hd. Dn.	Mol. Ref.	No. of violation	Solubility	TPSA
1	5.60	407.31	3	0	108.64	1	-6.33	32.67
2	5.48	362.86	3	0	105.55	0	-6.23	32.67
3	5.48	362.86	3	0	105.45	0	-6.23	32.67
4	5.22	342.43	3	0	106.84	0	-5.84	32.67
5	4.97	373.14	6	1	107.52	0	-5.95	72.98
6	4.98	346.40	3	0	101.35	0	-5.81	32.67
7	4.81	358.44	4	0	106.84	0	-5.51	41.90
8	4.6	328.41	3	0	100.94	0	-5.49	32.67

NPD was synthesized from Claisen-condensation between substituted benzaldehyde and 2-acetyl naphthalene. The NDPP compound structures were elucidated with the help of infrared and ^{1}H & ^{13}C NMR data. The confirmed structures were screened by *in silico* and *in vitro* screening methods to find the drug-likeness, binding ability and inhibition rate of the targets.

IR studies: The IR spectrum of **NDPP-2** compounds shows that absorption peak appeared in the range 1477.47 cm^{-1} due to presence of C=N stretching of pyrazole ring. The absorption peaks present at 1662.64 and 1138.00cm^{-1} belong to the C=O and C-N stretching, respectively. The aromatic and aliphatic absorption frequencies appeared in the range of 3138.18 and 2910.12 cm^{-1}. The aromatic ring stretching also appeared in the range of 800-601 cm^{-1}.

^{1}H NMR studies: The ^{1}H NMR of NDPP-2 compound exhibits dd value at 3.25 ppm $J_{4a,4e}$ = 4 Hz and $J_{4a,5a}$ = 17.6 Hz allocated to the H-4a proton of pyrazole moiety. Another two dd values appeared at 3.85 ppm ($J_{4e,4a}$ = 12.4 Hz & $J_{4e,5a}$ = 17.2 Hz due to presence of H-4e proton and 5.58 ppm ($J_{5a,4a}$ = 4 Hz & $J_{5a,4e}$ = 11.6 Hz) assigned for H-5a of pyrazole moiety. The signal present at δ 1.19-1.20 ppm as a triplet which belongs to the methyl group of propanoyl chain and the multiplet appeared in the range 2.83-2.86 ppm attribute to the -CH_2 of propanoyl chain.

^{13}C NMR studies: The carbon NMR spectrum of compound NDPP-2 shows that ^{13}C NMR resonance at 171.61 ppm is attributed due to C=O. The ^{13}C NMR resonance at 14.04 ppm is due to the presence of methyl group of propanoyl moiety. The ^{13}C NMR resonance at 36.17 ppm is assigned to ethyl group of propanoyl moiety while 153.20 ppm is attributed due to C-3 of pyrazole ring. The ^{13}C NMR resonances of 41.95 and 59.63 ppm are attributed due to C-4 and C-5 of pyrazole ring, respectively. The ^{13}C NMR resonance at 140.68, 134.18 and 133.40 ppm were *ipso* carbons. The aromatic carbons appeared in the ranges of 129.10-123.29 ppm.

ADME property: All the synthesized compounds [**NDPP 1-8**] have excellent ADME prediction values. The drug-likeness score of all the compounds in the positive values indicates that all the compounds have drug ability property. Mostly all the target compounds *in silico* ADME values are adopted with the Lipinski′s rule of five. All the compounds should obey the Lipinski′s rule with 0 violations except NDPP-1, which has one violation. The polar surface area value is high for **NDPP-5** and **NDPP-7** compounds rather than others in the series. The target compounds have solubility in the range of -6 to -5 (Table-1).

The target compound NDPP-2 which has electron withdrawing substitution exhibit high drug-likeness value 4.21 than the compounds **NDPP-4** and **7**, which have electron donating substitution. Also the compound NDPP-2 has high drug score value 0.63 than the compounds NDPP-4 have a drug score 0.60. The **NDPP-5** have good drug-likeness value 2.25 and drug score 0.65. All the NDPPs compounds have + values in the drug-likeness column and have the best drug score above 0.5. This showed that the synthesized **NDPP 1-8** compounds must have pharmacokinetics property. So the target compounds have the ability to act as a drug. The drug-likeness score and drug score are tabulated in Table-2.

TABLE-2
DRUG-LIKENESS AND DRUG SCORE
VALUE OF COMPOUNDS **NDPP 1-8**

Drug-likeness	Drug score	Drug-likeness	Drug score
1.20	0.52	2.25	0.65
4.21	0.63	2.67	0.68
2.15	0.60	2.62	0.69
1.19	0.60	2.47	0.69

Docking results: All the target compounds **NDPP 1-8** have high binding score above -8.0. The docking result also shows that the electron-withdrawing NDPP-5 (-NO_2) group has the best high binding affinity value among the other NDPP compounds and the standard drug. All the target NDPP compounds have high binding affinity value rather than the standard ciprofloxacin. The compound NDPP-5 shows the 4 Hydrogen bond interaction between LYS A: 115, GLY A: 114, LYS A: 319 and SER A: 116 and NO_2 substitution and one hydrophobic bond interaction between LEU A: 416 and aromatic ring of naphthalene moiety without unfavourable bonds.

The NDPP-1 compound has affinity score -8.3 with H-bond interaction between carbonyl group in the propionoic acid chain and LYS A: 319, hydrophobic interaction through naphthalene ring with ALA A: 414, LEU A: 416; NDPP-2,4 compounds have affinity score -8.2, -8.3 with two hydrogen bond interaction SER A: 415 and LEU A: 416; NDPP-3 also has affinity score -8.2 and two hydrogen bond interactions LEU A: 15, THR A: 16; NDPP-6 has -8.3 as its affinity score with one hydrogen bond interaction ARG A: 313; NDPP-6,7 has second high affinity score -8.7.

The binding affinity scores, hydrogen bond interaction and hydrophobic interaction are given in Table-3 and the 2D & 3D image of docking results given in Table-4.

TABLE-3
MOLECULAR DOCKING RESULTS FOR PYRAZOLE DERIVATIVES NDPP **1-8** DOCKED WITH BACTERIAL PROTEIN 1UAG

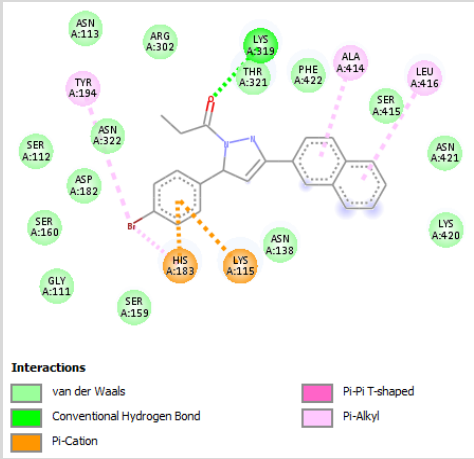
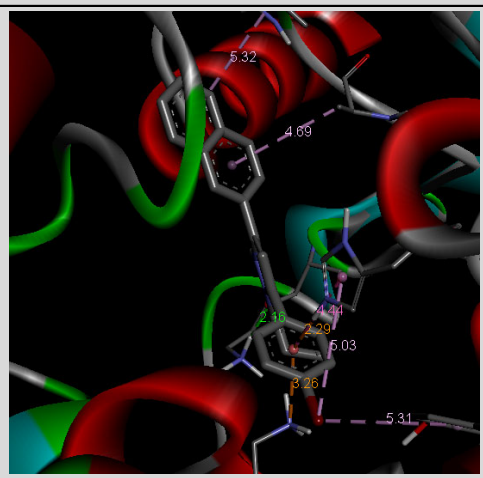
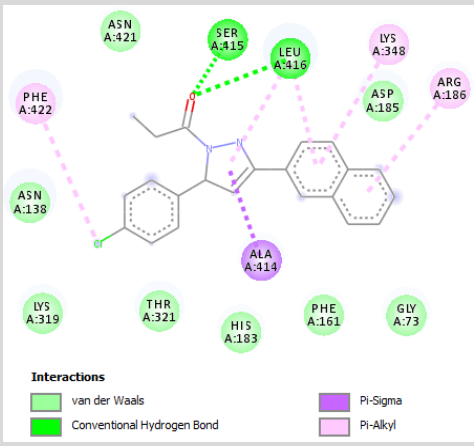
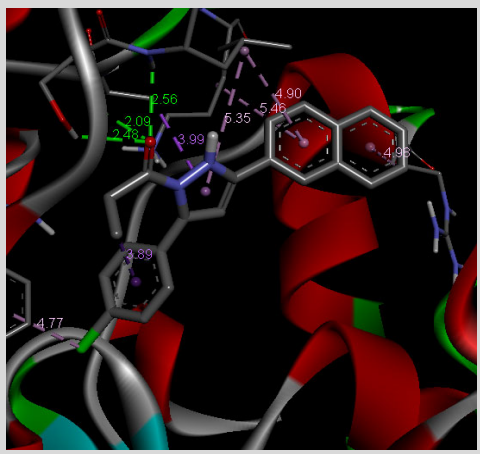
Compound	Binding affinity score	H-Bond interaction	Hydrophobic interaction
NDPP-1	-8.3	LYS A: 319	ALA A: 414
			LEU A: 416
NDPP-2	-8.2	SER A: 415	LYS A: 348
		LEU A: 416	ARG A: 186
NDPP-3	-8.2	LEU A: 15	ILE A: 74
		THR A: 16	
NDPP-4	-8.3	SER A: 415	PHE A: 422
		LEU A: 416	LYS A: 348
			ARG A: 186
NDPP-5	-8.8	LYS A: 115	
		GLY A: 114	LEU A: 416
		LYS A: 319	
		SER A: 116	
NDPP-6	-8.3	ARG A: 313	LEU A: 333
NDPP-7	-8.7	–	–
NDPP-8	-8.7	–	LEU A: 333
		ASN A: 178	
Ciprofloxacin	-7.7	ASN A: 271	ALA A: 328
		GLU A: 327	

Antimicrobial result: The result of NDPP compounds binding affinity was subjected to screening activity against *S. pyogenes*, *S. aureus* and Gram-negative *E.coli*, *P. aeruginosa* bacterial strains, while the fungal activity was done by using *C. albicans* fungal strain. The study was done in the concentration range 1 mg/mL and the inhibition values are given in the Table-5. The **NDPP-2, 5, 6** (-Cl, -NO_2, -F) substitutions have high inhibition value averse to Gram negative and Gram-positive strains. The fungal activity data of NDPP compounds showed that the electron donating CH_3 group has better inhibition value against *C. albicans* strain.

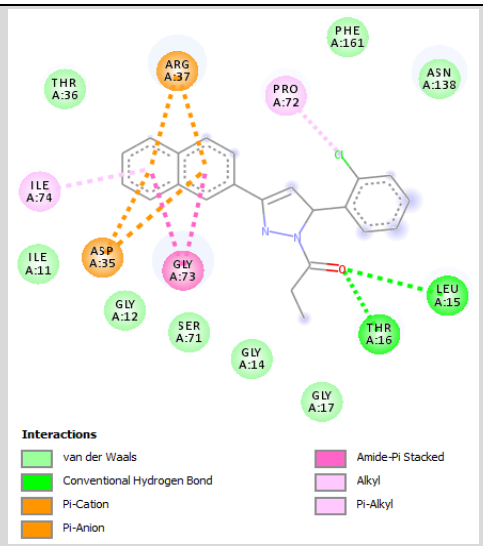
Conclusion

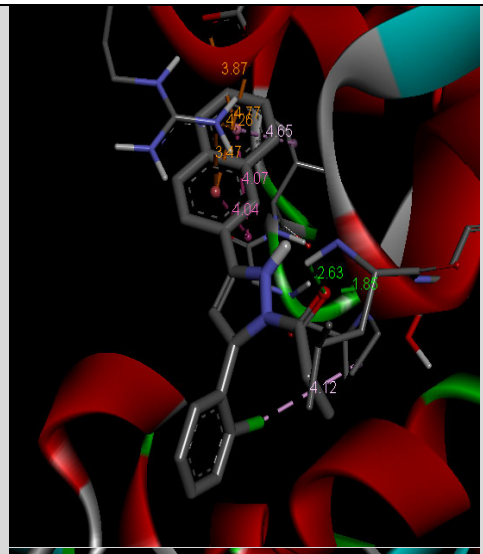
Naphthalene pyrazoline prop-2-en-1-one derivatives (**NDPP 1-8**) were successfully synthesized and characterized from the multicomponent reaction *via* Michael addition method. The molecular docking and ADME results indicated that compound NDPP-5, which has a large Total polar surface area (TPSA), gets a high binding affinity score and a high number of hydrogen-bonding. Moreover, compound **NDPP-5** also exhibited excellent inhibition values in the antibacterial studies compared to other NDPP compounds. Finally, it is concluded that compound **NDPP 5** has high total polar surface area exhibiting excellent scores in the *in-silico* as well as in *in-vitro* studies.

TABLE-4
2D AND 3D IMAGE FOR THE SYNTHESIZED COMPOUNDS (**NDPP 1-8**)

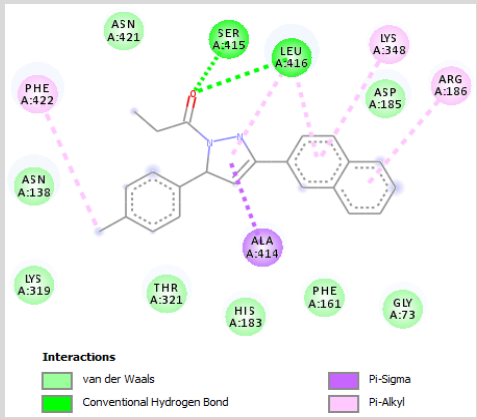
Compound	2D IMAGE	3D IMAGE
NDPP-1		
NDPP-2		

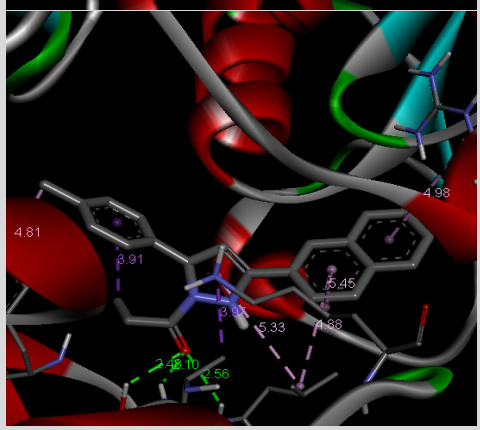
NDPP-3



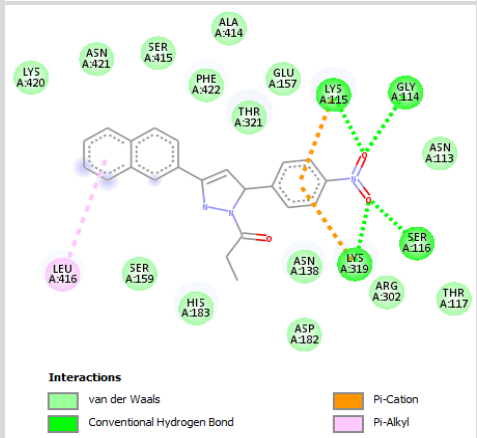


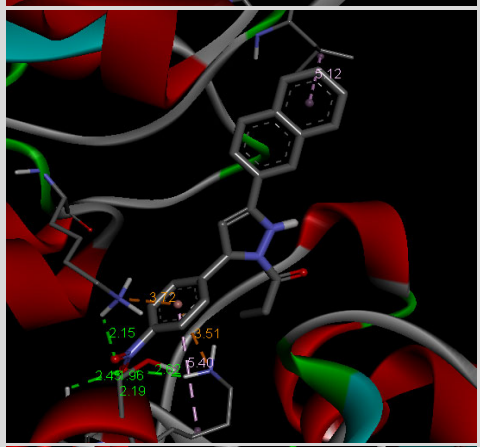
NDPP-4



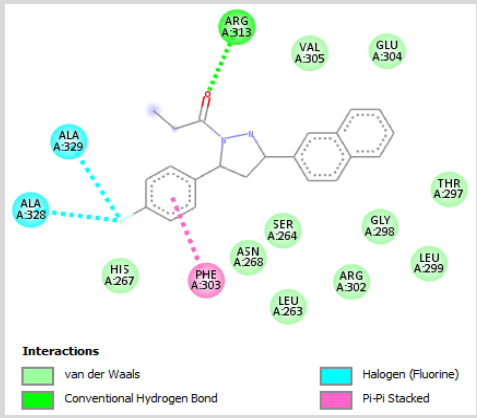


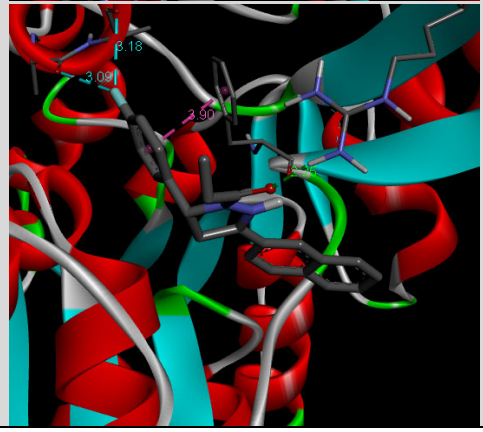
NDPP-5



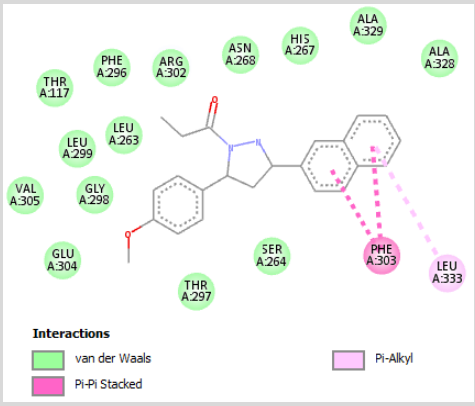


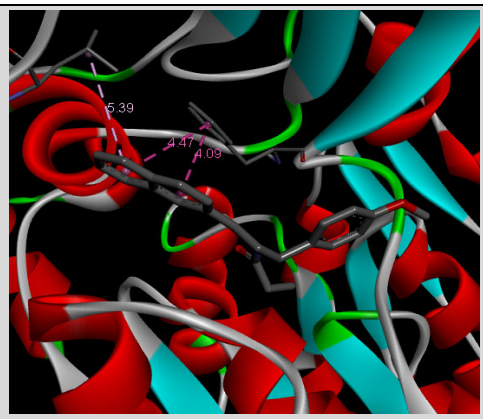
NDPP-6



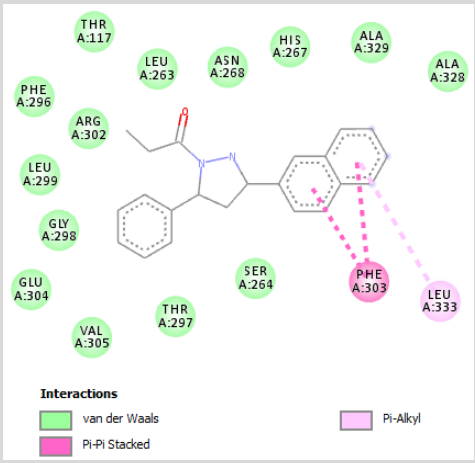


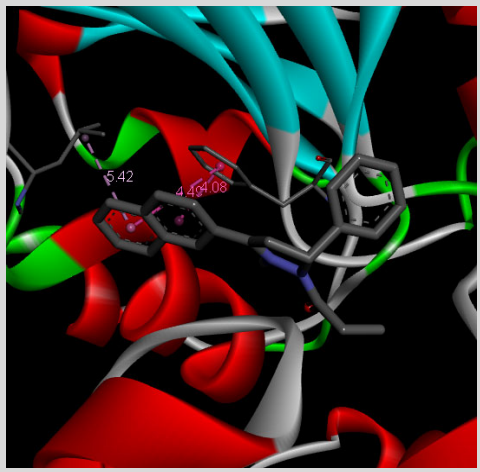
NDPP-7



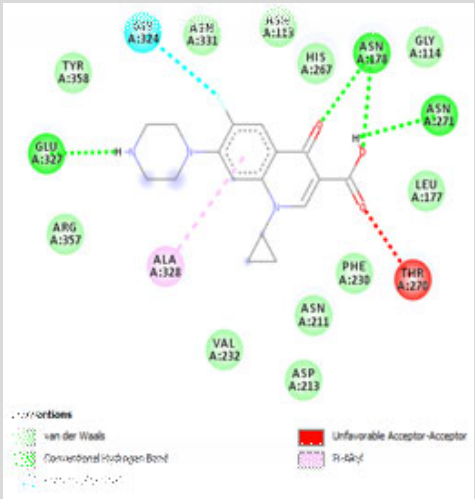


NDPP-8





Ciprofloxacin



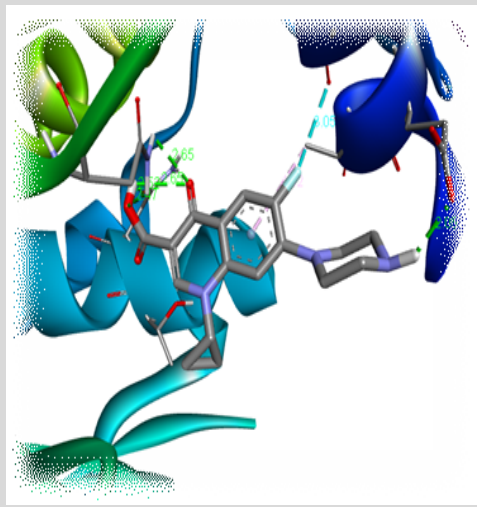


TABLE-5
in vitro STUDIES VALUES OF COMPOUND **NDPP 1-8** AT 1.0 mg/mL

Compound	Bacterial strain				Fungal strain
	S. aureus	*E. coli*	*S. pyogenes*	*P. aeruginosa*	*C. albicans*
NDPP-1	18	17	16	17	12
NDPP-2	23	23	21	24	15
NDPP-3	20	16	14	19	14
NDPP-4	19	18	19	18	16
NDPP-5	24	21	20	21	17
NDPP-6	18	17	16	19	13
NDPP-7	21	20	20	20	19
NDPP-8	17	18	15	16	10
Ciprofloxacin/Clotrimazole	26	19	17	22	24

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. M. Baumann, I.R. Baxendale, S.V. Ley and N. Nikbin, *Beilstein J. Org. Chem.*, **7**, 442 (2011); https://doi.org/10.3762/bjoc.7.57
2. B. Deng, C. Li, J. Yuan, C.B. Rao, Y. Zhao, R. Zhang and D. Dong, *Tetrahedron*, **75**, 2273 (2019); https://doi.org/10.1016/j.tet.2019.01.061
3. N. Kumarswamyreddy and V. Kesavan, *Org. Lett.*, **18**, 1354 (2016); https://doi.org/10.1021/acs.orglett.6b00287
4. N.C. Duncan, C.M. Garner, T. Nguyen, F. Hung and K. Klausmeyer, *Tetrahedron Lett.*, **49**, 5766 (2008); https://doi.org/10.1016/j.tetlet.2008.07.104
5. S. Ozkinali, M. Gur, N. Sener, S. Alkin and M.S. Cavus, *J. Mol. Struct.*, **1174**, 74 (2018); https://doi.org/10.1016/j.molstruc.2018.06.070
6. N. Ribeiro, S. Roy, N. Butenko, I. Cavaco, T. Pinheiro, F. Marques, I. Alho, F. Avecilla, J. Costa-Pessoa and I. Correia, *J. Inorg. Biochem.*, **174**, 63 (2017); https://doi.org/10.1016/j.jinorgbio.2017.05.011
7. S. Samshuddin, B. Narayana, B.K. Sarojini, H.S. Yathirajan, M.T.H. Khan, C.G.D. Raj and R. Raghavendra, *Med. Chem. Res.*, **21**, 2012 (2012); https://doi.org/10.1007/s00044-011-9735-9
8. E. Perez-Sacau, A. Estevez-Braun, A.G. Ravelo, D. Gutiérrez-Yapu and A. Giménez-Turba, *Chem. Biodivers.*, **2**, 264 (2005); https://doi.org/10.1002/cbdv.200590009
9. S.M. El-Shoukrofy, H.A.A. El-Razik, O.M. Aboulwafa, A.E. Bayad and I.M. El-Ashmawy, *Bioorg. Chem.*, **85**, 541 (2019); https://doi.org/10.1016/j.bioorg.2019.02.036
10. J.V. Rao, N. Anitha, S. Kavimani and V. Himabindu, *J. Pharmacol. Toxicol.*, **3**, 409 (2008); https://doi.org/10.3923/jpt.2008.409.413
11. M.K. Vekariya, D.B. Patel, P.A. Pandya, R.H. Vekariya, P.U. Shah, D.P. Rajani and N.K. Shah, *J. Mol. Struct.*, **1175**, 551 (2019); https://doi.org/10.1016/j.molstruc.2018.08.018
12. A. Kumar, R.A. Maurya, S. Sharma, P. Ahmad, A.B. Singh, G. Bhatia and A.K. Srivastava, *Bioorg. Med. Chem. Lett.*, **19**, 6447 (2009); https://doi.org/10.1016/j.bmcl.2009.09.031
13. Y. Fu, M.-X. Wang, D. Zhang, Y.-W. Hou, S. Gao, L.-X. Zhao and F. Ye, *RSC Adv.*, **7**, 46858 (2017); https://doi.org/10.1039/c7ra09858h
14. F. Giornal, S. Pazenok, L. Rodefeld, N. Lui, J.-P. Vors, F.R. Leroux, *J. Fluorine Chem.*, **152**, 2 (2013); https://doi.org/10.1016/j.jfluchem.2012.11.008
15. C. Verma, V.S. Saji, M.A. Quraishi and E.E. Ebenso, *J. Mol. Liq.*, **298**, 111943 (2020); https://doi.org/10.1016/j.molliq.2019.111943
16. S. Markar, T. Saha and S.K. Singh, *Eur. J. Med. Chem.*, **161**, 252 (2019); https://doi.org/10.1016/j.ejmech.2018.10.018
17. R.N. Brogden, R.M. Pinder, P.R. Sawyer, T.M. Speight and G.S. Avery, *Drugs*, **9**, 326 (1975); https://doi.org/10.2165/00003495-197509050-00002
18. F.K. Chan, N.S. Abraham, J.M. Scheiman and L. Laine, *Am. J. Gastroenterol.*, **103**, 2908 (2008); https://doi.org/10.1111/j.1572-0241.2008.02200.x
19. E. Boyle, P. Freemanm, F. Mangan and M. Thomson, *J. Pharm. Pharmacol.*, **34**, 562 (1982); https://doi.org/10.1111/j.2042-7158.1982.tb04794.x
20. S. Yadav, G. Rawal and M. Baxi, *J. Clin. Diagn. Res.,* **10**, FM01 (2016); https://doi.org/10.7860/JCDR/2016/19052.8286
21. Y.L. Janin, *Bioorg. Med. Chem.*, **15**, 2479 (2007); https://doi.org/10.1016/j.bmc.2007.01.030
22. N. Ryder, I. Frank and M. Dupont, *Antimicrob. Agents chemother.,* **29**, 858 (1986) https://doi.org/10.1128/aac.29.5.858
23. J.M. Muhlbacher, *Clin. Dermatol.*, **9**, 479 (1991); https://doi.org/10.1016/0738-081X(91)90076-W
24. F.-Y. Chang, J.E. Peacock Jr., D.M. Musher, P. Triplett, B.B. MacDonald, J.M. Mylotte, A. O'Donnell, M.M. Wagener and V.L. Yu, *Medicine*, **82**, 333 (2003); https://doi.org/10.1097/01.md.0000091184.93122.09
25. R. Thomas, Y.S. Mary, K.S. Resmi, B. Narayana, S.B.K. Sarojini, S. Armakovic, S.J. Armakovic, G. Vijayakumar, C.V. Alsenoy and B.J. Mohan, *J. Mol. Struct.*, **1181**, 599 (2019); https://doi.org/10.1016/j.molstruc.2019.01.014
26. C.S. Abraham, S. Muthu, J.C. Prasana, B.F. Rizwana, S. Armakovic and S.J. Armakovic, *J. Mol. Struct.*, **1171**, 733 (2018); https://doi.org/10.1016/j.molstruc.2018.06.057
27. P. Vennila, M. Govindaraju, G. Venkatesh, C. Kamal, Y.S. Mary, S. Kaya, C.Y. Panicker, S. Armakovic and S.J. Armakovic, *J. Mol. Struct.*, **1151**, 245 (2018); https://doi.org/10.1016/j.molstruc.2017.09.049
28. J. Dhevaraj, M. Gopalakrishnan and S. Pazhamalai, *J. Mol. Struct.*, **1193**, 450 (2019); https://doi.org/10.1016/j.molstruc.2019.05.033
29. R. Chinnamanayakar, M.R. Ezhilarasi, B. Prabha and Kulandhaivel, *Asian J. Chem.*, **30**, 783 (2018); https://doi.org/10.14233/ajchem.2018.20992
30. A.R. Ali, E.R. El-Bendary, M.A. Ghaly and I.A. Shehata, *Eur. J. Med. Chem.*, **75**, 492 (2014); https://doi.org/10.1016/j.ejmech.2013.12.010