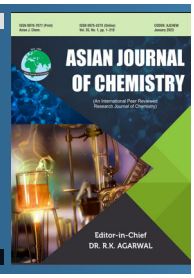
Asian Journal of Chemistry; Vol. 35, No. 6 (2023), 1463-1472

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2023.27878




# Facile One-Pot Synthesis of Nicotinamide Analogs: Biological and Computational Evaluation

JYOTI RASGANIA[1], RENU GAVADIA[1], RAJEEV KUMAR KAPOOR[2], VICKY SAHARAN[2] and KOMAL JAKHAR[1,*]

[1]Department of Chemistry, Maharshi Dayanand University, Rohtak-124001, India
[2]Department of Microbiology, Maharshi Dayanand University, Rohtak-124001, India

*Corresponding author: E-mail: komal.jakhar@rediffmail.com

*Received*: 6 April 2023; *Accepted*: 6 May 2023; *Published online*: 27 May 2023; AJC-21264

An acid-mediated one-pot synthesis of nicotinamide clubbed aliphatic carbo(x/thio)amides has been developed in conventional refluxing conditions as well as under microwave irradiations using dilute HCl as a catalyst. The microwave-assisted synthesis of nicotinamide analogs notably reduces the reaction times and provides considerably enhanced yields. The electronic structures of the synthesized hybrids have been modeled using the DFT framework to ascertain various global reactivity indices. The promising antimicrobial and antioxidant efficacy of the title compounds has been explored through *in vitro* biological screening. The molecular docking studies of the title compounds against enoyl reductase from *E. coli* (PDB: 1C14) revealed a favourable binding propensity. The pharmacokinetics efficacy of the synthesized compounds was screened by ADMET predictions to ascertain their medicinal applications.

**Keywords: Nicotinamide, Microwave irradiation, Molecular modeling, *In silico* ADMET analysis.**

## INTRODUCTION

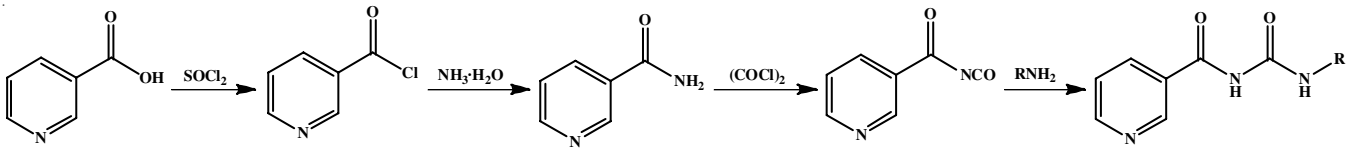
Amides have splendid biological occurrences and remarkable pharmacological competencies [1]. The eminent utility of amides as medicinally active motifs can be inferred by their invariable presence in diverse classes of therapeutics such as immunosuppressants (microcolin A and B), anticancer agents (dolstatin 15), antibiotics (althiomycin), antifeedants (ypaoamide) [2] and in several emerging antibiotics against drug-resistant strains such as avibactam, relebactam, zidebactam, enmetazobactam, ANT 431, *etc.* [3]. In medicinal chemistry explorations of around 66% of synthetic routes involve the formation of an amide linkage [4]. Nicotinamide or niacinamide is a core component of coenzymes vital in glycolysis and other cellular energetic pathways [5,6]. Recent research interests reflect a shift in the study of nicotinamide from an essential nutrient to an effective therapeutic agent due to its versatile pharmaceutical activities, biocompatibility, bioavailability and water solubility. Diversified therapeutic efficacies are exhibited by nicotinamide derivatives such as antimicrobial [7], anti-inflammatory [8], DNA repairing [9], cytotoxic [10] and antioxidant [11]. In addition, nicotinamide drugs have remarkable applications in skin treatment approaches like acne, wrinkles, pigmentation, skin aging and skin cancer, *etc.* [5,6].

Ureas and thioureas are versatile organic compounds with distinct biological occurrences and numerous applications in industries, laboratories, corrosion inhibition, optics and therapeutic sciences [12]. Several urea/thiourea derivatives are known to exhibit antimicrobial [13], CNS stimulant [14], antiviral [15], antioxidant [16], anti-tuberculosis [17], antidiabetic [18] and anticancer [19] capabilities. Carbamoylamides (RCONHCONHR′) are bioactive urea derivatives and possess significant pharmaceutical usage as urease inhibitors [20], antitumor agents [21], anti-Parkinson's drugs [22], $S1P_1$ agonists [23] and fungicides [24], *etc.*

Synthesis of diverse heterocyclic analogs of carbamoyl nicotinamides includes the reaction of nicotinoyl isocyanate with diverse amines [25] as illustrated in **Scheme-I**. Nicotinoyl isocyanate has been synthesized by a three-step reaction starting from nicotinic acid using extremely hazardous and corrosive reagents such as oxalyl chloride, thionyl chloride and phosgene. Nicotinoyl isocyanate itself is an extremely unstable compound imposing handling difficulties. In addition, the multistep synthesis is also associated with several other limitations such as the use of organic solvents, longer reaction times and less reaction yields.

The enduring privilege of carbamoyl motifs in medicinal sciences prompted us to explore an alternate synthetic route

This is an open access journal, and articles are distributed under the terms of the Attribution 4.0 International (CC BY 4.0) License. This license lets others distribute, remix, tweak, and build upon your work, even commercially, as long as they credit the author for the original creation. You must give appropriate credit, provide a link to the license, and indicate if changes were made.



**Scheme-I:** Classical method for the synthesis of carbamoyl nicotinamides

for carbamoyl nicotinamides. Amides have subjacent electrophilicity due to resonance and require initial activation before their condensations with other counterparts. The acid-catalyzed condensation reactions of amides [26-28], prompted us to explore the use of acid to facilitate the desired chemical transformation. The acid-mediated direct one-pot integration of nicotinamide with diverse aliphatic urea and thiourea scaffolds is not previously explored in reported studies. An ever-increasing prevalence of sustainable development has established green chemistry as an imperative line of action to combat the challenges of health risks and environmental degradation. Accompanying the core ideology of environment-benign progression, green chemistry provides a plethora of advantages in chemical synthesis in terms of operational simplicity, reaction time, energy, yield and selectivity.

Microwave irradiation is one of the cleaner alternatives in synthetic organic chemistry utilizing the non-conventional and selective heating power of microwaves with uniform heat distribution. The deliberate choice of water as a reaction medium can significantly reduce the use of hazardous organic solvents. The combination of microwave-assisted synthesis with green aqueous conditions leads to operational simplicity, easy purification, high yields and reduced reaction times [29].

Microbial infections have been encountered as a global threat since ancient times. Although several natural and synthetic remedies are accessible for microbial treatment, there is still an unmet need for alternate drug findings due to the emergence of antimicrobial resistance for the currently used drugs. Therefore, developing more effective and selective therapeutics with an excellent pharmacological profile is of utmost importance in medicinal sciences. Several nicotinamide carbamoyl analogs with diverse amide/thioamide counterparts are reported to possess remarkable antimicrobial and antioxidant activities as shown in Fig. 1 [7,11,30,31]. Herein, a facile and environment-benign one-step synthetic design for the synthesis of nicotinamide clubbed aliphatic carbo(x/thio)amides under conventional reflux and microwave irradiations is presented and also evaluated their biological activities.

## EXPERIMENTAL

For microwave irradiations, a CEM microwave synthesizer was employed. Analytical thin-layer chromatography (TLC) was used to examine the progress of reactions utilizing silica gel G-coated glass plates. Thermo Scientific (Flash 2000) elemental analyzer was used for CHN analysis. Nicolet iS50 FT-IR spectrometer was used for recording IR spectra of chemical compounds using KBr pellets. Bruker Advance Neo 500 MHz spectrometer was used to record proton and $^{13}C$ NMR spectra in deuterated DMSO with TMS as a reference and XEVO G2-XS QTOF-Mass spectrometer was used to record mass spectra.

### Synthesis of *N*-carbamoyl/carbamothioylnicotinamides (3a-j)

**Method-A (reflux):** In 30 mL water, 1 mmol of urea/thiourea was dissolved. The solution was acidified by addition of 2 mL of 0.01 N HCl and mechanically stirred for few minutes. An equimolar amount of nicotinamide was added to the stirred solution and refluxed on a water bath. The reaction was completed in 4-5 h as indicated by TLC (benzene:methanol/8:2). The solid obtained by addition of crushed ice was separated and recrystallized with ethanol to obtain *N*-carbamoyl/carbamothioylnicotinamides **(3a-j)**.

**Method-B (MWI):** In 1 mL water, 1 mmol of urea/thiourea was dissolved. The solution was acidified by addition of few drops of 0.01 N HCl and mechanically stirred for few minutes. An equimolar amount of nicotinamide was added to the stirred solution and irradiated under MWI at 120 ºC and 180 W. Within

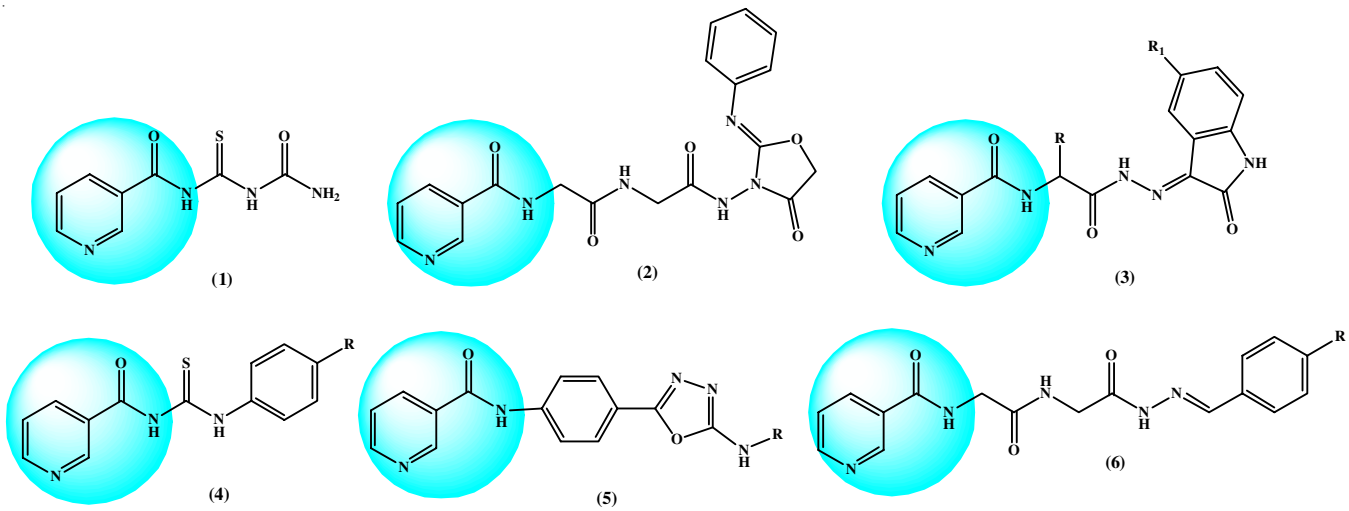
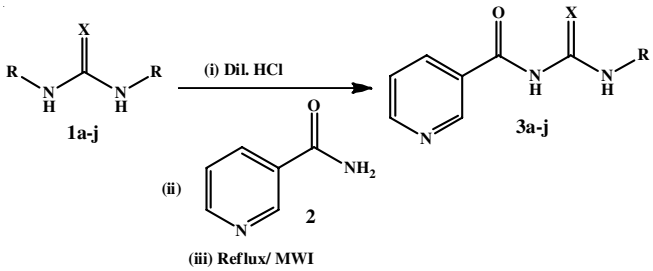


Fig. 1. Nicotinamide derivatives as efficient antimicrobials

3-7 min, the reaction gets completed as indicated by TLC (benzene:methanol/8:2). The solid obtained by addition of crushed ice was separated and recrystallized with ethanol to obtain *N*-carbamoyl/carbamothioylnicotinamides (**3a-j**).

The synthesis of N-carbamoyl/carbamothioyl derivatives (**3a-j**) from nicotinamide and ureas/thioureas by water refluxing or microwave-assisted methodology is depicted in **Scheme-II**.




**Scheme-II:** Synthesis of nicotinamide derivative of urea/thioureas

***N*-(Carbamoyl)nicotinamide (3a):** Colourless solid; m.p.: 231-233 ºC; yield (reflux/MWI): 81/93%; $R_f$ value: 0.33 ($C_6H_6$:MeOH/8:2); m.w.: 165; FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3381 (s, N-H), 3074 (m, C-$H_{Ar}$), 1700, 1688 (s, C=O), 1574 (s, N-$H_{bend}$), 1432 (s, C-N); $^1$H NMR (500 MHz, DMSO): δ 9.06 (s, 1H, NH), 8.73 (s, 1$H_{py}$), 8.25 (d, *J* = 7.9Hz, 1$H_{py}$), 7.99 (d, *J* = 7.9Hz, 1$H_{py}$), 7.54 (dd, *J* = 7.8 and 6.15Hz, 1$H_{py}$), 5.53 (s, 2H, $NH_2$); $^{13}$C NMR (500 MHz, DMSO): δ 166.27 ($C_f$), 159.49 ($C_g$), 151.70 ($C_e$), 148.51 ($C_a$), 135.13 ($C_c$), 129.60 ($C_d$), 123.33 ($C_b$); HR-MS (*m/z*): 165.2844 (38%), 149.0315, 121.3882 (100%), 106.8151, 79.4011, 78.4206, 59.4240, 51.4118, 44.3941; Elemental analysis for $C_7H_7N_3O_2$ calcd. (found) %: C, 50.91 (50.75); H, 4.27 (4.44); N, 25.44 (25.65).

***N*-(Methylcarbamoyl)nicotinamide (3b):** Colourless solid; m.p.: 207-208 ºC; yield (reflux/MWI): 80/89%; $R_f$ value: 0.31 ($C_6H_6$:MeOH/8:2); m.w.: 179; FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3362 (s, N-H), 3028 (m, C-$H_{Ar}$), 1716, 1694 (s, C=O), 1567 (m, N-$H_{bend}$), 1441 (m, C-N); $^1$H NMR (500 MHz, DMSO): δ 9.03 (s, 1H, NH), 8.69 (s, 1$H_{py}$), 8.34 (d, *J* = 7.85 Hz, 1$H_{py}$), 7.96 (d, *J* = 8.2 Hz, 1$H_{py}$), 7.60 (dd, *J* = 7.65 and 5.95 Hz, 1$H_{py}$), 5.93 (s, 1H, NH), 3.44 (s, 3H, $CH_3$); $^{13}$C NMR (500 MHz, DMSO): δ 165.21 ($C_f$), 160.59 ($C_g$), 153.90 ($C_e$), 147.50 ($C_a$), 136.26 ($C_c$), 127.67 ($C_d$), 121.42 ($C_b$), 23.91 ($C_h$); HR-MS (*m/z*): 179.0511 (66%), 149.4138, 121.5339 (100%), 106.8978, 79.5242, 78.5195, 73.1120, 58.0151, 51.5724; Elemental analysis for $C_8H_9N_3O_2$ calcd. (found) %: C, 53.63 (53.36); H, 5.06 (5.28); N, 23.45 (23.24).

***N*-(Ethylcarbamoyl)nicotinamide (3c):** Colourless solid; m.p.: 121-22 ºC; yield (reflux/MWI): 82/91%; $R_f$ value: 0.29 ($C_6H_6$:MeOH/8:2); m.w.: 193; FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3373 (s, N-H), 3059 (w, C-$H_{Ar}$), 1709, 1686 (s, C=O), 1551 (s, N-$H_{bend}$), 1437 (s, C-N); $^1$H NMR (500 MHz, DMSO): δ 9.09 (s, 1H, NH), 8.70 (s, 1$H_{py}$), 8.30 (d, *J* = 7.95 Hz, 1$H_{py}$), 7.91 (d, *J* = 7.8 Hz, 1$H_{py}$), 7.56 (dd, *J* = 8.15 and 5.6 Hz, 1$H_{py}$), 5.77 (s, 1H, NH), 2.98 (q, 2H, $CH_2$), 0.96 (t, 3H, $CH_3$); $^{13}$C NMR (500 MHz, DMSO): δ 169.24 ($C_f$), 158.69 ($C_g$), 152.64 ($C_e$), 148.46 ($C_a$), 134.44 ($C_c$), 128.78 ($C_d$), 120.53 ($C_b$), 33.16 ($C_h$), 13.56 ($C_i$); HR-MS (*m/z*): 193.0957 (83%), 149.3497, 121.6608 (100%), 106.3673, 87.2924, 79.6672, 78.0912, 72.5401, 51.2658, 44.1910; Elemental analysis for $C_9H_{11}N_3O_2$ calcd. (found) %: C, 55.95 (55.63); H, 5.74 (5.56); N, 21.75 (21.46).

***N*-(Butylcarbamoyl)nicotinamide (3d):** Colourless solid; m.p.: 95-97 ºC; yield (reflux/MWI): 79/88%; $R_f$ value: 0.31 ($C_6H_6$:MeOH/8:2); m.w.: 221; FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3375 (s, N-H), 3038 (s, C-$H_{Ar}$), 1710, 1688 (s, C=O), 1551 (s, N-$H_{bend}$), 1431 (s, C-N); $^1$H NMR (500 MHz, DMSO): δ 9.04 (s, 1H, NH), 8.72 (s, 1$H_{py}$), 8.22 (d, *J* = 7.9 Hz, 1$H_{py}$), 7.96 (d, *J* = 7.8 Hz, 1$H_{py}$), 7.50 (dd, *J* = 7.9 and 6.0 Hz, 1$H_{py}$), 5.84 (s, 1H, NH), 2.78 (t, 2H, $CH_2$), 1.53-1.23 (m,4H, $CH_2$-$CH_2$), 0.88 (t, 3H, $CH_3$); $^{13}$C NMR (500 MHz, DMSO): δ 167.24 ($C_f$), 161.49 ($C_g$), 150.77 ($C_e$), 146.57 ($C_a$), 136.26 ($C_c$), 126.67 ($C_d$), 122.42 ($C_b$), 37.35 ($C_h$), 29.21 ($C_i$), 17.40 ($C_j$), 12.35 ($C_k$); HR-MS (*m/z*): 221.1710 (55%), 149.0472, 121.5678 (100%), 115.2204, 106.2180, 100.2816, 79.0815, 78.1849, 72.0442, 51.6210; Elemental analysis for $C_{11}H_{15}N_3O_2$ calcd. (found) %: C, 59.71 (59.50); H, 6.83 (6.56); N, 18.99 (18.63).

***N*-(Cyclohexylcarbamoyl)nicotinamide (3e):** Colourless solid; m.p.: 146-147 ºC; yield (reflux/MWI): 80/90%; $R_f$ value: 0.70 ($C_6H_6$:MeOH/8:2); m.w.: 247; FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3327 (s, N-H), 3033 (w, C-$H_{Ar}$), 1712, 1680 (s, C=O), 1559 (s, N-$H_{bend}$), 1436 (s, C-N); $^1$H NMR (500 MHz, DMSO): δ 9.07 (s, 1H, NH), 8.69 (s, 1$H_{py}$), 8.21 (d, *J* = 7.75 Hz, 1$H_{py}$), 7.94 (d, *J* = 7.6 Hz, 1$H_{py}$), 7.48 (dd, *J* = 7.9 and 5.6 Hz, 1$H_{py}$), 5.91 (s, 1H, NH), 3.32 (s, 1$H_{cyclohexyl}$), 1.74-1.00 (m, 10$H_{cyclohexyl}$); $^{13}$C NMR (500 MHz, DMSO): δ 166.21 ($C_f$), 158.63 ($C_g$), 152.48 ($C_e$), 148.51 ($C_a$), 134.41 ($C_c$), 131.75 ($C_d$), 123.54 ($C_b$), 51.96 ($C_h$), 45.71 ($C_i$), 31.14 ($C_k$), 21.48 ($C_j$); HR-MS (*m/z*): 247.1841 (100%), 164.3916, 149.0841, 141.4904, 126.2089, 121.2138, 106.0414, 98.2639, 83.7061, 79.6175, 78.3808, 51.4726; Elemental analysis for $C_{13}H_{17}N_3O_2$ calcd. (found) %: C, 63.14 (63.34); H, 6.93 (7.01); N, 16.99 (16.62).

***N*-Carbamothioylnicotinamide (3f):** Colourless solid; m.p.: 209-211 ºC; yield (reflux/MWI): 82/92%; $R_f$ value: 0.33 ($C_6H_6$:MeOH/8:2); m.w.: 181; FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3325 (s, N-H), 3021 (w, C-$H_{Ar}$), 1702 (s, C=O), 1592 (s, N-$H_{bend}$), 1437 (s, C-N); $^1$H NMR (500 MHz, DMSO): δ 9.11 (s, 1H, NH), 8.75 (s, 1$H_{py}$), 8.32 (d, *J* = 7.9 Hz, 1$H_{py}$), 8.01 (d, *J* = 8.0 Hz, 1$H_{py}$), 7.62 (dd, *J* = 8.15 and 5.65 Hz, 1$H_{py}$), 7.29 (s, 2H, $NH_2$); $^{13}$C NMR (500 MHz, DMSO): δ 182.22 ($C_g$), 167.23 ($C_f$), 152.62 ($C_e$), 147.49 ($C_a$), 135.49 ($C_c$), 128.80 ($C_d$), 122.56 ($C_b$); HR-MS (*m/z*): 181.2359 (54%), 165.9179, 121.0481 (100%), 106.9699, 79.2351, 78.4251, 75.1227, 59.9384, 51.1523; Elemental analysis for $C_7H_7N_3OS$ calcd. (found) %: C, 46.40 (46.70); H, 3.89 (4.13); N, 23.19 (23.09); S, 17.69 (17.49).

***N*-(Methylcarbamothioyl)nicotinamide (3g):** Colourless solid; m.p.: 177-179 ºC; yield (reflux/MWI): 81/89%; $R_f$ value: 0.50 ($C_6H_6$:MeOH/8:2); m.w.: 195; FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3314 (s, N-H), 3058 (m, C-$H_{Ar}$), 1708 (s, C=O), 1597 (s, N-$H_{bend}$), 1440 (s, C-N); $^1$H NMR (500 MHz, DMSO): δ 9.03 (s, 1H, NH), 8.71 (s, 1$H_{py}$), 8.23 (d, *J* = 7.95 Hz, 1$H_{py}$),

7.98 (d, *J* = 7.7 Hz, $1H_{py}$), 7.52 (dd, *J* = 7.9 and 5.5 Hz, $1H_{py}$), 7.41 (s, NH), 2.79 (s, 3H, $CH_3$); $^{13}C$ NMR (500 MHz, DMSO): δ 184.22 ($C_g$), 165.43 ($C_f$), 154.62 ($C_e$), 143.59 ($C_a$), 136.94 ($C_c$), 132.80 ($C_d$), 124.56 ($C_b$), 30.18 ($C_h$); HR-MS (*m/z*): 195.0350 (19%), 165.0722, 121.1213, 106.2061 (100%), 89.5311, 79.0819, 78.2795, 74.9882, 51.9550; Elemental analysis for $C_8H_9N_3OS$ calcd. (found) %: C, 49.22 (49.47); H, 4.65 (4.51); N, 21.52 (21.39); S, 16.42 (16.23).

***N*-(Ethylcarbamothioyl)nicotinamide (3h):** Colourless solid; m.p.: 104-105 ºC; yield (reflux/MWI): 80/88%; $R_f$ value: 0.69 ($C_6H_6$:MeOH/8:2); m.w.: 209; FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3318 (s, N-H), 3040 (m, C-$H_{Ar}$), 1704 (s, C=O), 1581 (s, N-$H_{bend}$), 1449 (m, C-N); $^1H$ NMR (500 MHz, DMSO): δ 9.06 (s, 1H, NH), 8.72 (s, $1H_{py}$), 8.23 (d, *J* = 8.05 Hz, $1H_{py}$), 7.93 (d, *J* = 7.55 Hz, $1H_{py}$), 7.54 (dd, *J* = 7.8 and 5.8 Hz, $1H_{py}$), 7.31 (s, NH), 3.36 (q, 2H, $CH_2$), 1.05 (t, 3H, $CH_3$); $^{13}C$ NMR (500 MHz, DMSO): δ 183.32 ($C_g$), 168.29 ($C_f$), 152.62 ($C_e$), 144.46 ($C_a$), 132.94 ($C_c$), 128.80 ($C_d$), 122.65 ($C_b$), 38.49 ($C_h$), 14.38 ($C_i$); HR-MS (*m/z*): 209.1081 (43%), 165.0722, 121.2283, 106.1451 (100%), 103.2441, 88.3124, 79.0284, 78.4103, 51.5507, 44.1312; Elemental analysis for $C_9H_{11}N_3OS$ calcd. (found) %: C, 51.66 (51.40); H, 5.30 (5.19); N, 20.08 (19.94); S, 15.32 (15.68).

***N*-(Butylcarbamothioyl)nicotinamide (3i):** Colourless solid; m.p.: 98-100 ºC; yield (reflux/MWI): 79/87%; $R_f$ value: 0.41 ($C_6H_6$:MeOH/8:2); m.w.: 237; FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3315 (m, N-H), 3064 (m, C-$H_{Ar}$), 1711 (s, C=O), 1580 (m, N-$H_{bend}$), 1448 (s, C-N); $^1H$ NMR (500 MHz, DMSO): δ 9.04 (s, 1H, NH), 8.69 (s, $1H_{py}$), 8.21 (d, *J* = 7.85 Hz, $1H_{py}$), 7.91 (d, *J* = 7.55 Hz, $1H_{py}$), 7.51 (dd, *J* = 7.65 and 5.5 Hz, $1H_{py}$), 7.17 (s, 1H, NH), 3.31 (t, 2H, $CH_2$), 1.56-1.10 (m, 4H, $CH_2$-$CH_2$), 0.85 (t, 3H, $CH_3$); $^{13}C$ NMR (500 MHz, DMSO): δ 184.09 ($C_g$), 168.70 ($C_f$), 151.13 ($C_e$), 146.51 ($C_a$), 133.35 ($C_c$), 129.90 ($C_d$), 123.27 ($C_b$), 43.96 ($C_h$), 32.19 ($C_i$), 21.57 ($C_j$), 18.73 ($C_k$); HR-MS (*m/z*): 237.1295 (42%), 165.1751, 121.2274 (100%), 106.2320, 79.1411, 78.2724, 72.1301, 51.7358; Elemental analysis for $C_{11}H_{15}N_3OS$ calcd. (found) %: C, 55.67 (55.70); H, 6.37 (6.34); N, 17.71 (17.73); S, 13.51 (13.48).

***N*-(Cyclohexylcarbamothioyl)nicotinamide (3j):** Colourless solid; m.p.: 154-56 ºC; yield (reflux/MWI): 81/91%; $R_f$ value: 0.50 ($C_6H_6$:MeOH/8:2); m.w.: 263; FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3309 (s, N-H), 3059 (s, C-$H_{Ar}$), 1716 (s, C=O), 1575 (m, N-$H_{bend}$), 1453 (s, C-N); $^1H$ NMR (500 MHz, DMSO): δ 9.05 (s, 1H, NH), 8.72 (s, $1H_{py}$), 8.26 (d, *J* = 7.35 Hz, $1H_{py}$), 7.99 (d, *J* = 7.9 Hz, $1H_{py}$), 7.57 (dd, *J* = 7.25 and 6.05 Hz, $1H_{py}$), 7.29 (s, 1H, NH), 2.91 (s, $1H_{cyclohexyl}$), 1.90-1.06 (m, $10H_{cyclohexyl}$); $^{13}C$ NMR (500 MHz, DMSO): δ 182.13 (Cg), 166.44 ($C_f$), 152.09 ($C_e$), 147.55 ($C_a$), 135.49 ($C_c$), 130.12 ($C_d$), 123.95 ($C_b$), 52.60 ($C_h$), 44.75 ($C_i$), 29.42 ($C_k$), 22.16 ($C_j$); HR-MS (*m/z*): 263.2409 (45%), 180.4475, 165.1109, 157.1909, 142.0709, 136.1917, 121.2728 (100%), 106.1379, 98.1893, 83.5121, 79.3513, 78.0988, 51.3035; Elemental analysis for $C_{13}H_{17}N_3OS$ calcd. (found) %: C, 59.29 (59.24); H, 6.51 (6.49); N, 15.96 (15.92); S, 12.18 (12.14).

**Antimicrobial assay:** The Resazurin-based microdilution method [24] was employed for accessing the antimicrobial efficacy of the title compounds using ampicillin and fluconazole as standard antimicrobial drugs against various microbial strains. Different concentrations of tested compounds (20 to 0.078 mg/mL) prepared by two-fold serial dilution were screened against chosen microbial strains on 96-well microtiter tarsons plates. The wells retaining the blue colour show inhibition of the microorganisms while those with pink indicate microbial growth. The minimum concentration illustrating nil microbial growth was considered the minimum inhibitory concentration for a particular sample.

**Antioxidant assay:** Using ascorbic acid as reference, the radical scavenging potency of examined compounds was evaluated against DPPH radicals [16]. DPPH solution (0.004%) in DMSO with various concentrations (20, 40, 60, 80 and 100 µg/mL) of the sample solution was evaluated to obtain the radical scavenging potential. The absorbance of the tested compound was recorded at 517 nm with a UV spectrophotometer and a decreased absorbance signifies higher radical scavenging activity.

$$\text{Radical scavenging (\%)} = \frac{Abs_{control} - Abs_{sample}}{Abs_{control}} \times 100$$

**Optimized molecular structure and HOMO-LUMO analysis:** The geometry optimization, determination of HOMO-LUMO and other quantum parameters of nicotinamide analogs were estimated using DFT method within Orca 4.2.0 program [32] under B3LYP/def2-TZVP basis set. An interface program Avogadro [17] was used to visualize the output file in a three-dimensional view.

**Molecular docking:** The software programs Autodock Vina [33] was used along with Biovia Discovery Studio Visualizer [24] for molecular docking studies. The 3D receptor was downloaded from RCSB-PDB site. The initial protein preparation include elimination of water molecules and heteroatoms followed by the addition of polar hydrogens and blind docking was performed by selecting the synthesized compounds as ligands for the investigation.

***In silico* ADMET analysis:** The *in silico* ADME profile of synthesized nicotinamide derivatives was obtained through an online platform, SwissADME [16], while toxicity assessment was accessed through a free Java interface OSIRIS property explorer [17]. These computational tools provide insight into different physiochemical and pharmacokinetic parameters related to the ADMET efficacy of the anticipated drug candidates. Drug likeliness and oral bioavailability of examined compounds are also predicted with the help of a bio-radar illustrating an optimum range of selected pharmacokinetic parameters enclosed within a pink region as explained in the coming section.

## RESULTS AND DISCUSSION

As the lipophilicity of nicotinamide-based therapeutics should not be significantly altered compared to the native nicotinamide system for optimum absorption and retention in biological systems, therefore, urea/thiourea substrates, especially with small aliphatic chains were chosen to use as drugs instead of large hydrophobic aromatic counterparts. Initially, the direct one-step condensation of nicotinamide with urea was explored under refluxing conditions. Since both of the

starting compounds are water-soluble, therefore water as a green solvent media was employed. A negligible amount of the desired *N*-carbamoylnicotinamide was obtained in this trial reaction. Inspired by the condensation reactions of amides under acidic conditions and transamidation reactions [26,27], the second trial reaction for integrating nicotinamide with urea was explored under acidic environment employing dilute HCl solution. The reaction gets completed in 4 h, as indicated by TLC plates. The solid obtained by addition of crushed ice was filtered purified and identified as *N*-carbamoylnicotinamide by spectral characterization.

The spectral interpretations were used to deduce the structure of the synthesized molecules. The infrared spectroscopic data of *N*-carbamoylnicotinamide (**3a**) showed an absorption band at 3381 $cm^{-1}$, characterizing the N-H stretching. The other characteristic IR peaks such as N-H bending, C=O stretching and C-N stretching further confirms the structure of the integrated molecule. In the $^{1}H$ NMR spectra of compound **3a**, a singlet at 9.06 ppm for NH proton confirms the formation of the reported product. The protons of nicotinamide ring resonate in the region of 8.73-7.54 ppm with their respective splitting patterns. The protons of amide resonate as a singlet at 5.53 ppm. In $^{13}C$ NMR, compound **3a** shows peaks at 166 and 159 ppm, which corresponds to the carbon atom of amide groups ($C_f$ and $C_g$, respectively). The peaks corresponding to the aromatic carbons of nicotinamide ring were recorded at 151, 148, 135, 129 and 123 ppm in accordance with the proposed structure. In mass spectral studies of compound **3a**, a molecular ion peak at *m/z* 165 confirms its proposed molecular formula. The other fragments were recorded at *m/z* 149, 121, 106, 79, 78, 59, 51 and 44 with differential intensities which justify the spitting pattern of this organic molecule. The elemental analysis data further validate the spectral characterization of *N*-carbamoylnicotinamide. The spectral illustrations of the other nicotinamide hybrids are included in supplementary file.

The developed synthetic protocol comprises the protonation of urea under acidic conditions and the resultant activation of its carbonyl group [28]. Through a transamidation-type reaction, the condensed product carbamoylnicotinamide is formed with the release of ammonia. Diverse nicotinamide hybrids with aliphatic urea and thiourea substrates were efficiently synthesized using a similar methodology. Ammonia or other liquid/gaseous amines formed as a byproduct during the synthesis of the title compounds can be conveniently removed during the workup stage. The condensation of nicotinamide with ureas/thioureas was also explored under microwave irradiations as an alternate and greener approach and substantially higher yields with reduced reaction time were recorded compared to the previous method.

**Antimicrobial activity:** In accordance with the measured MIC values, the synthesized nicotinamide hybrids display average to good antibacterial efficacy against diverse bacterial strains. Among all the nicotinamide derivatives, compound **3e** was identified to be the most active against selected bacterial strains. It is hereby noted that the nicotinamide analogs showed considerable antifungal potential on the agar plates when tested as neat samples while negligible antifungal activity is recorded at the tested concentrations. The antifungal results are, therefore, reported as > 20 mg/mL on the selected MIC range (Table-1).

**Antioxidant evaluation:** All the synthesized compounds exhibited comparable free radical scavenging activity with ascorbic acid. The observed inhibitory effects at various concentrations in terms of % scavenging and $IC_{50}$ for the synthesized nicotinamide hybrids are presented in Table-2. The % radical scavenging at 100 µg/mL concentration and $IC_{50}$ values of the compounds lies in the range of 61.45-87.57% and 24.33-66.41 µg/mL, respectively. Among all the examined hybrids, compounds **3a** and **3f** were found to have the best $IC_{50}$ values (34.75 and 24.33 µg/mL, respectively).

**Optimized geometries and DFT calculations:** The DFT-based quantum mechanical simulations are used for the nicotinamide hybrids and their optimized molecular structures are shown in Fig. 2. Various calculated thermodynamic parameters obtained from DFT calculations reflecting the comparative stability and reactivity of the nicotinamide analogs as shown in Table-3. The compiled result revealed that compound **3i** is the most reactive among all the synthesized derivatives with a minimum energy gap. The FMO illustration of compounds **3a**, **3f** and **3i** are presented in Fig. 3.

**Molecular docking analysis:** Several bioactive urea/thiourea as well as nicotinamide derivatives have been reported as efficient inhibitors of bacterial enoyl reductase [34,35]. Therefore, the synthesized compounds were docked against enoyl reductase (PDB: 1C14) to find the binding interactions.

TABLE-1
MIC (mg/mL) OF THE NICOTINAMIDE HYBRIDS AND REFERENCE COMPOUNDS **3a-j**

| Compound | *E. coli* | *S. typhi* | *B. subtilis* | *S. aureus* | *A. niger* | *R. oryzae* |
|---|---|---|---|---|---|---|
| **3a** | 0.625 | 0.15625 | 0.625 | 0.625 | >20 | >20 |
| **3b** | 0.625 | 0.15625 | 0.625 | 0.625 | >20 | >20 |
| **3c** | 0.625 | 0.15625 | 0.625 | 0.625 | >20 | >20 |
| **3d** | 0.625 | 0.3125 | 1.25 | 1.25 | >20 | >20 |
| **3e** | 0.15625 | 0.07812 | 0.3125 | 0.3125 | >20 | >20 |
| **3f** | 0.625 | 0.15625 | 1.25 | 0.625 | >20 | >20 |
| **3g** | 1.25 | 0.15625 | 0.3125 | 0.625 | >20 | >20 |
| **3h** | 1.25 | 0.15625 | 0.625 | 0.625 | >20 | >20 |
| **3i** | 0.3125 | 0.3125 | 0.625 | 0.3125 | >20 | >20 |
| **3j** | 0.3125 | 0.625 | 1.25 | 0.625 | >20 | >20 |
| Ampicillin | 0.07812 | 0.03906 | 0.15625 | 0.07812 | – | – |
| Fluconazole | – | – | – | – | 0.15625 | 0.3125 |

TABLE-2
PERCENTAGE SCAVENGING EFFECT AND $IC_{50}$ VALUES OF THE SYNTHESIZED NICOTINAMIDE DERIVATIVES (**3a-j**)

| Compound | Scavenging effect (%) | | | | | $IC_{50}$ (µg/mL) |
|---|---|---|---|---|---|---|
| | 20 µg/mL | 40 µg/mL | 60 µg/mL | 80 µg/mL | 100 µg/mL | |
| **3a** | 39.04 | 52.93 | 68.79 | 80.04 | 87.57 | 34.75 |
| **3b** | 38.75 | 42.86 | 50.29 | 54.89 | 62.13 | 60.72 |
| **3c** | 37.47 | 42.56 | 48.82 | 54.89 | 61.45 | 63.18 |
| **3d** | 32.19 | 41.19 | 48.14 | 54.89 | 68.39 | 62.42 |
| **3e** | 23.78 | 35.62 | 42.17 | 58.02 | 71.53 | 66.41 |
| **3f** | 48.34 | 54.70 | 59.78 | 63.89 | 69.86 | 24.33 |
| **3g** | 33.36 | 45.01 | 53.42 | 63.99 | 76.42 | 51.55 |
| **3h** | 35.02 | 42.17 | 53.42 | 59.39 | 63.3 | 58.20 |
| **3i** | 29.68 | 36.59 | 47.61 | 57.23 | 73.11 | 62.15 |
| **3j** | 31.38 | 39.15 | 47.52 | 56.23 | 68.01 | 63.41 |
| Ascorbic acid | 42.95 | 55.77 | 68.88 | 78.67 | 90.12 | 30.52 |

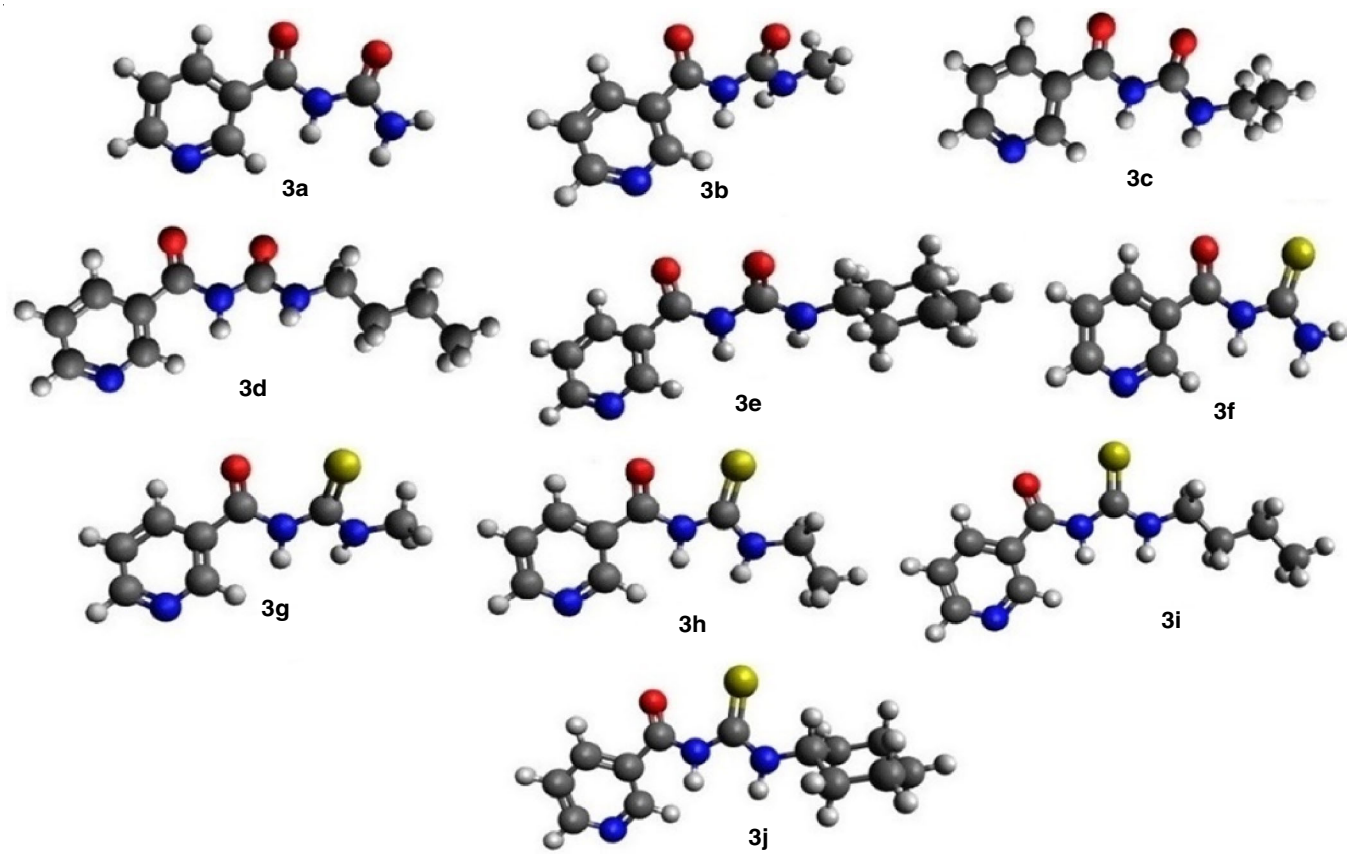



Fig. 2. Fully optimized structures of the nicotinamide derivatives (**3a-j**); colour code: blue-N, red-O, yellow-S, grey-C and white-H

TABLE-3
CALCULATED QUANTUM MECHANICAL DESCRIPTORS OF THE NICOTINAMIDE HYBRIDS (**3a-j**)

| Compd. | HOMO (eV) | LUMO (eV) | ΔE (eV) | Ionization potential (I) | Electron affinity (A) | Electro-negativity (χ) | Hardness (η) | Softness (σ) | Chemical potential (µ) | Electro-philicity (ω) |
|---|---|---|---|---|---|---|---|---|---|---|
| **3a** | -7.108 | -1.946 | 5.162 | 7.108 | 1.946 | 4.527 | 2.581 | 0.1937 | -4.527 | 3.970 |
| **3b** | -7.146 | -1.829 | 5.317 | 7.146 | 1.829 | 4.487 | 2.658 | 0.1881 | -4.487 | 3.787 |
| **3c** | -7.071 | -1.804 | 5.267 | 7.071 | 1.804 | 4.437 | 2.633 | 0.1899 | -4.437 | 3.739 |
| **3d** | -7.101 | -1.803 | 5.298 | 7.101 | 1.803 | 4.452 | 2.649 | 0.1887 | -4.452 | 3.741 |
| **3e** | -7.001 | -1.774 | 5.227 | 7.001 | 1.774 | 4.387 | 2.613 | 0.1913 | -4.387 | 3.683 |
| **3f** | -5.693 | -2.136 | 3.557 | 5.693 | 2.136 | 3.914 | 1.779 | 0.2811 | -3.914 | 4.308 |
| **3g** | -5.760 | -1.970 | 3.790 | 5.760 | 1.970 | 3.865 | 1.895 | 0.2638 | -3.865 | 3.942 |
| **3h** | -5.548 | -2.007 | 3.541 | 5.548 | 2.007 | 3.777 | 1.770 | 0.2824 | -3.777 | 4.029 |
| **3i** | -5.522 | -1.992 | 3.530 | 5.522 | 1.992 | 3.757 | 1.765 | 0.2833 | -3.757 | 3.998 |
| **3j** | -5.553 | -1.897 | 3.656 | 5.553 | 1.897 | 3.725 | 1.828 | 0.2735 | -3.725 | 3.795 |

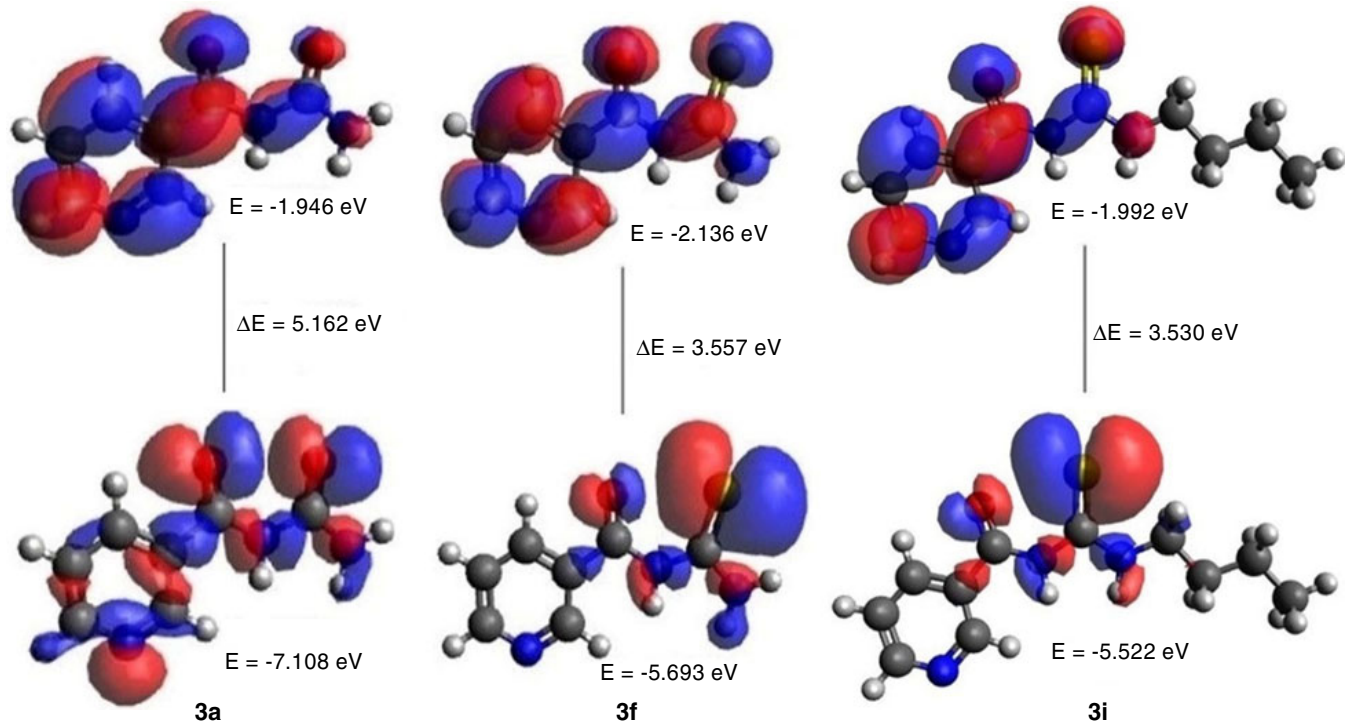



Fig. 3. FMO illustration for the compounds **3a**, **3f** and **3i**

The docking results of the synthesized compounds with binding interactions and corresponding distances are tabulated in Table-4. The protein-ligand interactions were identified as polar hydrogen bonds, van der Waals forces, carbon-hydrogen bonds and pi-pi bonds within the docked molecules. The best binding energy of -7.8 kcal/mol with RSMD value 0.00 was recorded for nicotinamide hybrid with cyclohexyl scaffold (**3e**). The amino acid residue ALA A: 196 interacts through hydrogen bonding while residues LEU A: 100, TYR A: 146, ALA A: 196 and ALA A: 197 interact through other types of interactions. The docking illustrations for compound **3e** are presented in Fig. 4.

***In silico* ADMET analysis:** Various parameters and descriptors are used to decide the ADMET profile of a drug compound *i.e.* lipophilicity, solubility, TPSA, insaturation, molecular weight, skin permeation, various toxicity risks, *etc*. High lipophilicity (log P) results in negligible oral absorption and poor solubility of the drug candidates. The significantly low log P value for all the synthesized compounds, as predicted

TABLE-4
BINDING PATTERN OF THE NICOTINAMIDE HYBRIDS (**3a-j**) WITH ENOYL ACYL REDUCTASE

| Compd. | Binding energy (kcal/mol) | H-bonding interactions | Distance (Å) | Other interactions | Distance (Å) |
|---|---|---|---|---|---|
| **3a** | -6.3 | THR A: 38, THR A: 38, GLN A: 40, VAL A: 65 | 2.28, 2.40, 2.86, 2.07 | VAL A: 65, ILE A: 92, ILE A: 119 | 5.29, 3.48, 5.15 |
| **3b** | -6.2 | THR A: 194, THR A: 194, ALA A: 197 | 1.99, 2.34, 2.81 | SER A: 91, TYR A: 146, ALA A: 197 | 3.33, 4.62, 5.21 |
| **3c** | -6.6 | GLY A: 13, GLN A: 40, GLN A: 40 | 2.08, 2.48, 2.51 | ILE A: 92 | 4.98 |
| **3d** | -7 | ALA A: 21, SER A: 91 | 2.85, 3.03 | GLY A: 13, ILE A: 20, TYR A: 146, TYR A: 146, THR A: 194, ALA A: 196, ALA A: 197, PHE A: 203 | 3.36, 2.98, 3.87, 5.11, 1.33, 5.21, 4.33,4.84 |
| **3e** | -7.8 | ALA A: 196 | 2.31 | LEU A: 100, TYR A: 146, ALA A: 196, ALA A: 197 | 5.36, 4.93, 4.99, 4.74 |
| **3f** | -5.6 | SER A: 145 | 2.68 | TYR A: 146, LYS A: 163, LYS A: 163, PRO A: 191, PRO A: 191, MET A: 206 | 3.76, 5.03, 3.73, 5.41, 3.29, 5.81 |
| **3g** | -5.6 | GLY A: 148, GLY A: 148, ARG A: 151, GLY A: 160, | 2.35, 3.03, 2.48, 2.54 | TYR A: 104, ALA A: 152 | 5.07, 3.92 |
| **3h** | -5.9 | ILE A: 192 | 2.41 | GLY A: 13, ILE A: 20, THR A: 194 | 3.68, 3.20, 1.49 |
| **3i** | -6.5 | GLY A: 190, ILE A: 192 | 3.60, 2.82, | GLY A: 13, ILE A: 20, TYR A: 146, TYR A: 156, ALA A: 196, ILE A: 200 | 3.52, 2.96, 3.63, 5.39, 5.35, 5.29 |
| **3j** | -7.6 | SER A: 145, THR A: 194 | 3.56, 2.13 | GLY A: 13, ILE A: 20, TYR A: 146, ALA A: 196 | 3.31, 3.09, 4.07, 5.15 |

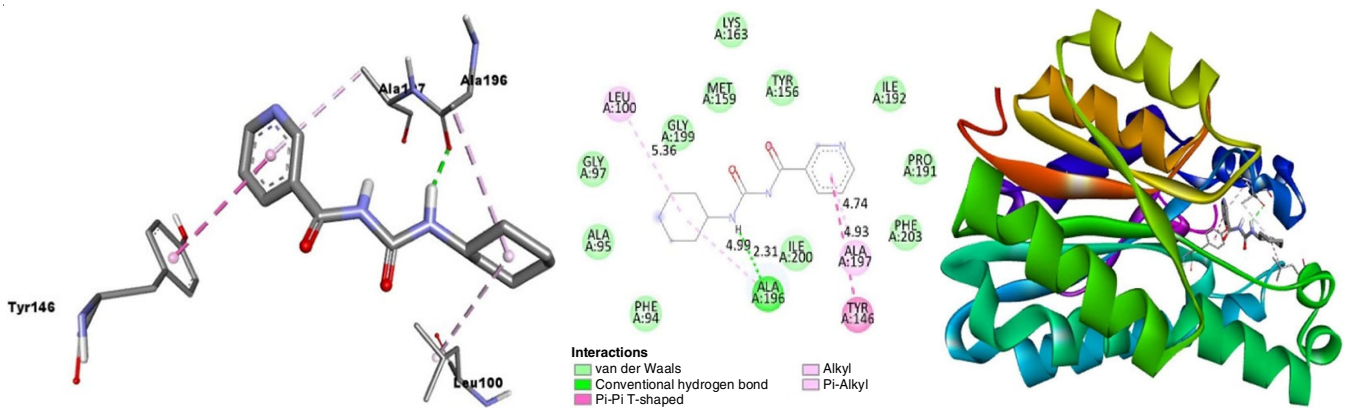



Fig. 4. Docking pattern of the compound **3e** with 1c14

by SwissADME, signifies their optimum lipophilicity for oral absorption. A well-determined range of log S values as predicted by SwissADME, describes the optimum water solubility of examined compounds [24]. TPSA (topological polar surface area) of a drug candidate is related to its transport involving absorption and permeation. A drug must have a lower TPSA value for efficient permeability across biological membranes. The predicted negative value of log S for the title compounds declares them sufficiently water-soluble, while the lower TPSA values reveal their optimum permeability [16,17]. To exhibit significant drug likeliness, a drug must follow a defined range of selected molecular descriptors referred to as the Lipinski rule of five. The title compounds follow Lipinski's rule of five ascertaining their appreciable druggability as displayed in Table-5. The oral bioavailability of the synthesized compounds can be predicted by bioavailability radar based on the acceptable range of molecular weight for size; XlogP3 for lipophilicity; TPSA for polarity; log S for insolubility; number of rotatable bonds for flexibility and number of $sp^3$ hybridized carbons for insaturation [24]. The bioavailability of the examined derivatives is predicted by ADME data in Table-6 and Fig. 5.

Skin permeability (log Kp) and human gastrointestinal (GI) absorption indicate the suitability of a drug candidate for transdermal or oral administration, respectively. Blood Brain

TABLE-5
PHYSIOCHEMICAL PROPERTIES EXPLAINING LIPINSKI RULE FOR THE NICOTINAMIDE HYBRIDS (**3a-j**)

| Compd. | m.w. (g/mol) | mLogP | H-bond acceptor | H-bond donor | No. of violations |
|---|---|---|---|---|---|
| Optimum range of selected parameters | ≤ 500 | ≤ 5 | ≤ 10 | ≤ 5 | ≤ 1 |
| **3a** | 165.15 | -0.63 | 3 | 2 | 0 |
| **3b** | 179.18 | -0.29 | 3 | 2 | 0 |
| **3c** | 193.20 | 0.02 | 3 | 2 | 0 |
| **3d** | 221.26 | 0.62 | 3 | 2 | 0 |
| **3e** | 247.29 | 1.17 | 3 | 2 | 0 |
| **3f** | 181.21 | -0.61 | 2 | 2 | 0 |
| **3g** | 195.24 | -0.28 | 2 | 2 | 0 |
| **3h** | 209.27 | 0.04 | 2 | 2 | 0 |
| **3i** | 237.32 | 0.64 | 2 | 2 | 0 |
| **3j** | 263.36 | 1.19 | 2 | 2 | 0 |

TABLE-6
PHYSIOCHEMICAL PROPERTIES EXPLAINING BIO-RADAR FOR THE NICOTINAMIDE HYBRIDS (**3a-j**)

| Compd. | m.w. (g/mol) | XlogP3 | TPSA (Å$^2$) | Log S (ESOL) | Fraction of $sp^3$ carbon | No. of rotatable bonds |
|---|---|---|---|---|---|---|
| Optimum range of selected parameters | 150 to 500 | -0.7 to 5.0 | 20-130 | < 6 | 0.25 to 1 | 0 to 9 |
| **3a** | 165.15 | -0.24 | 85.08 | -0.88 | 0 | 3 |
| **3b** | 179.18 | 0.16 | 71.09 | -1.13 | 0.12 | 4 |
| **3c** | 193.20 | 0.47 | 71.09 | -1.32 | 0.22 | 5 |
| **3d** | 221.26 | 1.06 | 71.09 | -1.7 | 0.36 | 7 |
| **3e** | 247.29 | 2.1 | 71.09 | -2.61 | 0.46 | 5 |
| **3f** | 181.21 | 0.36 | 100.1 | -1.36 | 0 | 3 |
| **3g** | 195.24 | 0.76 | 86.11 | -1.61 | 0.12 | 4 |
| **3h** | 209.27 | 1.07 | 86.11 | -1.8 | 0.22 | 5 |
| **3i** | 237.32 | 1.66 | 86.11 | -2.17 | 0.36 | 7 |
| **3j** | 263.36 | 2.7 | 86.11 | -3.09 | 0.46 | 5 |

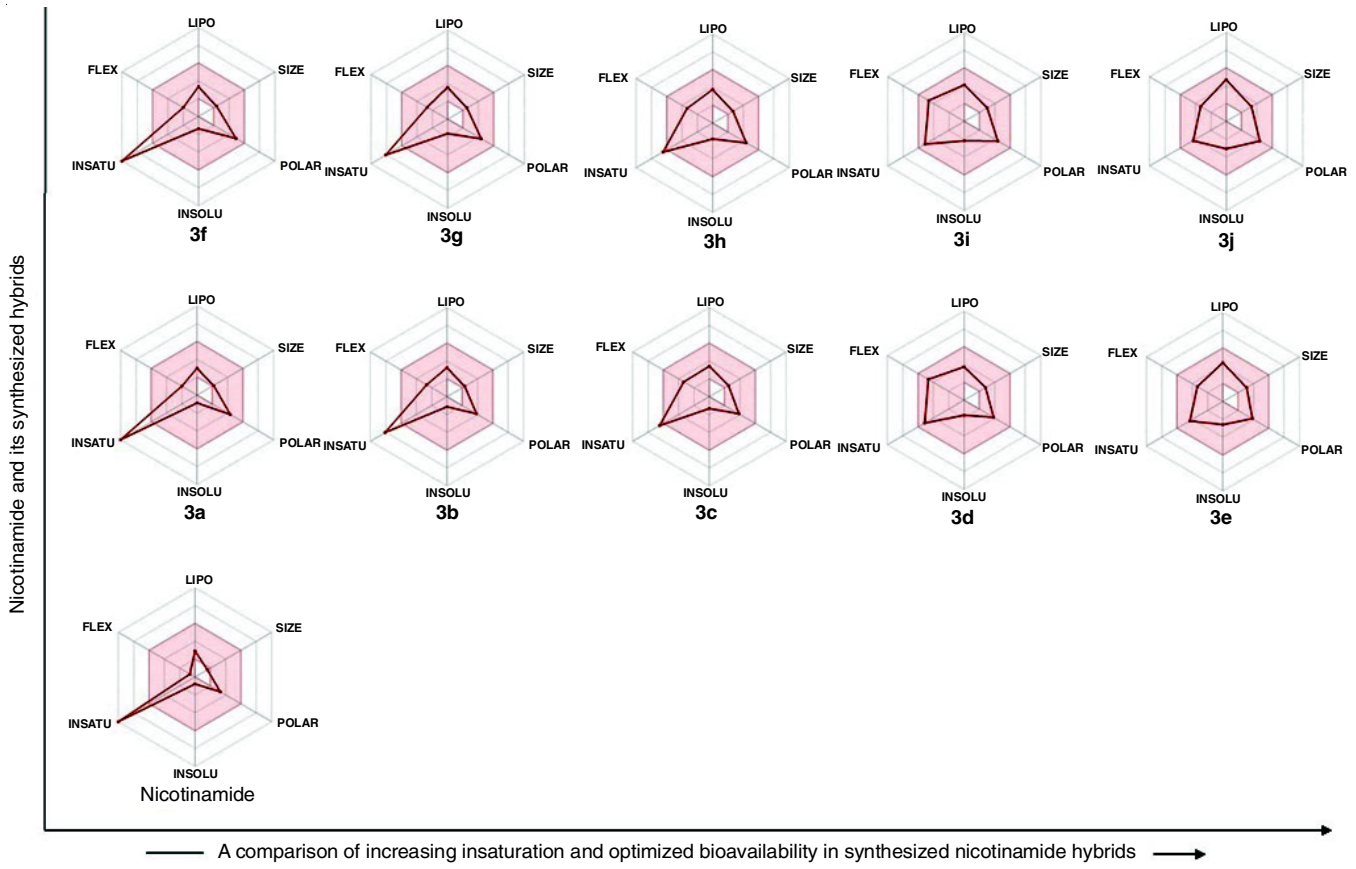



Fig. 5. Bioavailability radar for the synthesized compounds (**3a-j**)

Barrier (BBB) has a crucial role in assessing the effect of the administered drug on the central nervous system. A non-substrate of P-glycoprotein (P-gp) can be easily eliminated from the cell, while a non-inhibitor of any isoform of cytochrome (CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4) is regarded as non-toxic due to forbidden drug-drug interaction and lower bioaccumulation [24]. Table-7 predicts that all the compounds have excellent ADME pharmacokinetics.

The Osiris platform is utilized for toxicity assessment of the synthesized compounds in terms of risk alerts depicted with green, orange or red colour codes. No risk alerts are predicted for compounds **3b**, **3c**, **3e** and **3f** while some orange and red alerts are observed with other examined compounds as displayed in Table-8.

## Conclusion

A series of aliphatic urea/thiourea functionalized nicotinamide hybrids have been efficiently synthesized by a one-pot methodology under clement conditions. The use of water as a non-toxic, non-flammable, readily available and efficient reaction media is another remarkable feature of this protocol. The DFT profiling, molecular docking, *in vitro* biological evaluation and ADMET prediction of nicotinamide derivatives reflect their adequacy in developing efficient drug candidates. The synthesized nicotinamide hybrids showed excellent antioxidant potency and appreciable antibacterial strength against the chosen bacterial strains. The title compounds displayed promising bioavailability and efficient oral administration propensities with low toxicity risks in ADMET analysis.

TABLE-7
PHARMACOKINETICS FOR THE NICOTINAMIDE HYBRIDS (**3a-j**)

| Compd. | GI absorption | BBB permeation | P-gp substrate | CYP1A2 inhibitor | CYP2C19 inhibitor | CYP2C9 inhibitor | CYP2D6 inhibitor | CYP3A4 inhibitor | Skin permeation (cm/s) | Bioavailability score |
|---|---|---|---|---|---|---|---|---|---|---|
| **3a** | High | No | No | No | No | No | No | No | -7.48 | 0.55 |
| **3b** | High | No | No | No | No | No | No | No | -7.28 | 0.55 |
| **3c** | High | No | No | No | No | No | No | No | -7.14 | 0.55 |
| **3d** | High | No | No | No | No | No | No | No | -6.9 | 0.55 |
| **3e** | High | Yes | No | No | No | No | No | No | -6.32 | 0.55 |
| **3f** | High | No | No | No | No | No | No | No | -7.15 | 0.55 |
| **3g** | High | No | No | No | No | No | No | No | -6.95 | 0.55 |
| **3h** | High | No | No | No | No | No | No | No | -6.82 | 0.55 |
| **3i** | High | No | No | Yes | No | No | No | No | -6.57 | 0.55 |
| **3j** | High | No | No | Yes | Yes | No | No | No | -5.99 | 0.55 |

TABLE-8
TOXICITY PREDICTION FOR THE NICOTINAMIDE HYBRIDS (**3a-j**)

| Compd. | Mutagenic risk | Tumorigenic risk | Irritant risk | Reproductive risk |
|---|---|---|---|---|
| **3a** | Orange | Orange | Green | Orange |
| **3b** | Green | Green | Green | Green |
| **3c** | Green | Green | Green | Green |
| **3d** | Orange | Green | Green | Green |
| **3e** | Green | Green | Green | Green |
| **3f** | Green | Green | Green | Green |
| **3g** | Red | Green | Green | Red |
| **3h** | Red | Red | Green | Red |
| **3i** | Orange | Green | Green | Red |
| **3j** | Green | Green | Green | Red |

Green indicates low toxicity; orange indicates moderate and red indicates high toxicity risk

## ACKNOWLEDGEMENTS

The authors gratefully acknowledge Maharshi Dayanand University, Rohtak, India for support and facilities. The authors also acknowledge SAIF, Punjab University, Chandigarh, India, for the spectral and elemental analysis. Two of the authors, J.R. and R.G. thank CSIR and UGC, New Delhi, respectively, for providing the financial support.

## CONFLICT OF INTEREST

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

## REFERENCES

1. S. Kumari, A.V. Carmona, A.K. Tiwari and P.C. Trippier, *J. Med. Chem.*, **63**, 12290 (2020); https://doi.org/10.1021/acs.jmedchem.0c00530
2. M.B. Andrus, W. Li and R.F. Keyes, *Tetrahedron Lett.*, **39**, 5465 (1998); https://doi.org/10.1016/S0040-4039(98)01112-5
3. J.C. Vázquez-Ucha, J. Arca-Suárez, G. Bou and A. Beceiro, *Int. J. Mol. Sci.*, **21**, 9308 (2020); https://doi.org/10.3390/ijms21239308.
4. D. Glynn, D. Bernier and S. Woodward, *Tetrahedron Lett.*, **49**, 5687 (2008); https://doi.org/10.1016/j.tetlet.2008.07.090
5. Y.C. Boo, *Antioxidants*, **10**, 1315 (2021); https://doi.org/10.3390/antiox10081315
6. V.A. Snaidr, D.L. Damian and G.M. Halliday, *Exp. Dermatol.*, **28**, 15 (2019); https://doi.org/10.1111/exd.13819
7. G. Moustafa, H. Khalaf, A. Naglah, A. Al-Wasidi, N. Al-Jafshar and H. Awad, *Molecules*, **23**, 761 (2018); https://doi.org/10.3390/molecules23040761
8. M. Lappas and M. Permezel, *J. Nutr. Biochem.*, **22**, 1195 (2011); https://doi.org/10.1016/j.jnutbio.2010.10.009
9. D. Surjana, G.M. Halliday and D.L. Damian, *J. Nucleic Acids*, **2010**, 157591 (2010); https://doi.org/10.4061/2010/157591
10. M. Peng, L. Shi and S. Ke, *Chem. Cent. J.*, **11**, 109 (2017); https://doi.org/10.1186/s13065-017-0338-5
11. B. Özgeris, *J. Antibiot.*, **74**, 233 (2021); https://doi.org/10.1038/s41429-020-00399-7
12. R. Singh and K. Jakhar, *Der Pharma Chem.*, **8**, 175 (2016).
13. R. Singh, K. Jakhar, P. Sharma and G.V. Kumar, *Der Pharma Chem.*, **8**, 261 (2016).
14. R. Ronchetti, G. Moroni, A. Carotti, A. Gioiello and E. Camaioni, *RSC Med. Chem.*, **12**, 1046 (2021); https://doi.org/10.1039/D1MD00058F
15. V.R. Katla, R. Syed, M. Golla, A. Shaik and N.R. Chamarthi, *J. Serb. Chem. Soc.*, **79**, 283 (2014); https://doi.org/10.2298/JSC120716095K
16. R. Gavadia, J. Rasgania and K. Jakhar, *Asian J. Chem.*, **34**, 3231 (2022); https://doi.org/10.14233/ajchem.2022.24042
17. R. Gavadia, J. Rasgania, M.V. Basil, V. Chauhan, S. Kumar and K. Jakhar, *J. Mol. Struct.*, **1283**, 135325 (2023); https://doi.org/10.1016/j.molstruc.2023.135325
18. H.M. Faidallah, M.M. Al-Mohammadi, K.A. Alamry and K.A. Khan, *J. Enzyme Inhib. Med. Chem.*, **31(S1)**, 157 (2016); https://doi.org/10.1080/14756366.2016.1180594
19. K.C. Gulipalli, P. Ravula, S. Bodige, S. Endoori, P.K.R. Cherukumalli, J.N.N.S. Chandra and N. Seelam, *Russ. J. Gen. Chem.*, **90**, 1336 (2020); https://doi.org/10.1134/S1070363220070221
20. T.O. Brito, A.X. Souza, Y.C.C. Mota, V.S.S. Morais, L.T. de Souza, Â. de Fátima, F. Macedo and L.V. Modolo, *RSC Adv.*, **5**, 44507 (2015); https://doi.org/10.1039/C5RA07886E
21. B.A. Lanman, J.R. Allen, J.G. Allen, A.K. Amegadzie, K.S. Ashton, S.K. Booker, J.J. Chen, N. Chen, M.J. Frohn, G. Goodman, D.J. Kopecky, L. Liu, P. Lopez, J.D. Low, V. Ma, A.E. Minatti, T.T. Nguyen, A.B. Reed, N. Nishimura, A.J. Pickrell, Y. Shin, A.C. Siegmund, N.A. Tamayo, C.M. Tegley, M.C. Walton, H.-L. Wang, R.P. Wurz, M. Xue, K.C. Yang, P. Achanta, M.D. Bartberger, J. Canon, L.S. Hollis, J.D. McCarter, C. Mohr, K. Rex, A.Y. Saiki, T. San Miguel, L.P. Volak, K.H. Wang, D.A. Whittington, S.G. Zech, J.R. Lipford and V.J. Cee, *J. Med. Chem.*, **63**, 52 (2020); https://doi.org/10.1021/acs.jmedchem.9b01180
22. F. Azam, I.A. Alkskas and M.A. Ahmed, *Eur. J. Med. Chem.*, **44**, 3889 (2009); https://doi.org/10.1016/j.ejmech.2009.04.007
23. L.D. Pennington, K.K.C. Sham, A.J. Pickrell, P.E. Harrington, M.J. Frohn, B.A. Lanman, A.B. Reed, M.D. Croghan, M.R. Lee, H. Xu, M. McElvain, Y. Xu, X. Zhang, M. Fiorino, M. Horner, H.G. Morrison, H.A. Arnett, C. Fotsch, M. Wong and V.J. Cee, *ACS Med. Chem. Lett.*, **2**, 752 (2011); https://doi.org/10.1021/ml2001399
24. J. Rasgania, R. Gavadia and K. Jakhar, *J. Mol. Struct.*, **1274**, 134424 (2023); https://doi.org/10.1016/j.molstruc.2022.134424
25. P.-P. Zhang, Q. Wang, L.-J. Min, H.-K. Wu, J.-Q. Weng, C.-X. Tan, Y.-G. Zhang and X.-H. Liu, *J. Mol. Struct.*, **1205**, 127485 (2020); https://doi.org/10.1016/j.molstruc.2019.127485
26. D.R. Park, H. Kim, J.C. Jung, M.S. Shin, S.J. Han and I.K. Song, *Korean J. Chem. Eng.*, **26**, 990 (2009); https://doi.org/10.1007/s11814-009-0164-0
27. G.D. Wagh, S.P. Pathare and K.G. Akamanchi, *ChemistrySelect*, **3**, 7049 (2018); https://doi.org/10.1002/slct.201800954
28. S. Dhawan, P.S. Girase, V. Kumar and R. Karpoormath, *Synth. Commun.*, **51**, 3729 (2021); https://doi.org/10.1080/00397911.2021.1989597
29. D. Dallinger and C.O. Kappe, *Chem. Rev.*, **107**, 2563 (2007); https://doi.org/10.1021/cr0509410
30. A.M. Naglah, H.M. Awad, M.A. Bhat, M.A. Al-Omar and A.E.-G.E. Amr, *J. Chem.*, **2015**, 364841 (2015); https://doi.org/10.1155/2015/364841
31. V.R. Shah, M. Vadodaria and A.R. Parikh, *Indian J. Chem.*, **36B**, 101 (1997).
32. Z. Popovic, N. Smreèki, O. Jovic, K. Miškovic Špoljaric, D. Gašo-Sokaè, V. Bušic, S. Roca and B. Markovic, *Inorg. Chim. Acta*, **516**, 120131 (2021); https://doi.org/10.1016/j.ica.2020.120131
33. O. Trott and A.J. Olson, *J. Comput. Chem.*, **31**, 455 (2009); https://doi.org/10.1002/jcc.21334
34. S.D. Dogan, M.G. Gündüz, H. Dogan, V.S. Krishna, C. Lherbet and D. Sriram, *Eur. J. Med. Chem.*, **199**, 112402 (2020); https://doi.org/10.1016/j.ejmech.2020.112402
35. M.M. Ghorab, M.S.A. El-Gaby, A.M. Soliman, M.S. Alsaid, M.M. Abdel-Aziz and M.M. Elaasser, *Chem. Cent. J.*, **11**, 42 (2017); https://doi.org/10.1186/s13065-017-0271-7