BIOLOGICAL FEATURES, DRUG LIKENESS, PHYSICAL PROPERTIES AND DOCKING STUDIES ON METHYLPHENYLTHIAZOLYLNAPHTHYLMETHANONE ANALOGS

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ABSTRACT

Nature is one of the maximum critical resources of pharmacologically energetic compounds in the look for capsules against existence threatening diseases. The methylphenylthiazolylnaphthylmethanone were synthesized and characterized by different physicochemical techniques such as IR, ^{1}H NMR, ^{13}C NMR and Mass spectra. Marine organisms also have the potential to turn into destiny tablets towards critical illnesses, such as most cancers, a variety of bacterial and viral illnesses, malaria and inflammations. In addition, the Lipinski rule of five, molecular docking was used to calculate binding affinities and predict binding locations for the various receptors. All the compounds exhibited good docking scores against 107G cancer

protein. The antioxidant looks at also evaluated wonderful IC_{50} value. Among the methylphenylthiazolylnaphthylmethanone, compound 3b was highly active on the SKMEL cell line (Human Skin Cancer).

Keywords: physicochemical technique, Lipinski rule of five, molecular docking, antioxidant, SKMEL

INTRODUCTION

Natural products represent major strategy for the development and discovery of new drugs. Their structure elucidation, stereochemistry, chemical modification, synthesis and pharmacology have received a great deal of interdisciplinary attention from areas of research other than chemistry and include pharmacology and medicine[1]. Thiazole ring system has become an important structural component in many pharmaceutical agents. Some of its derivatives are marked as anti-biotic, anti-tubercular, anti-cancer and anti-hypertensive agents[2,3]. The emergence of anticancer drug resistance, which results in the failure of the majority of chemotherapeutic anticancer treatments, has significantly reduced the clinical efficacy of the most commonly prescribed anticancer drug[4]. As a result, there is an urgent need for effective cancer prevention and treatment strategies to be implemented[5]. Structure activity relationship studies of thiazole-based drugs/leads revealed that substituents on specific positions, specifically positions 2 and 4 of the 1,3-thiazole ring, have a significant impact on biological outcomes[6]. As a result, molecular docking can be regarded as a first-line technique for identifying pharmaceutical leads[7].

MATERIAL AND METHODS

Experimental

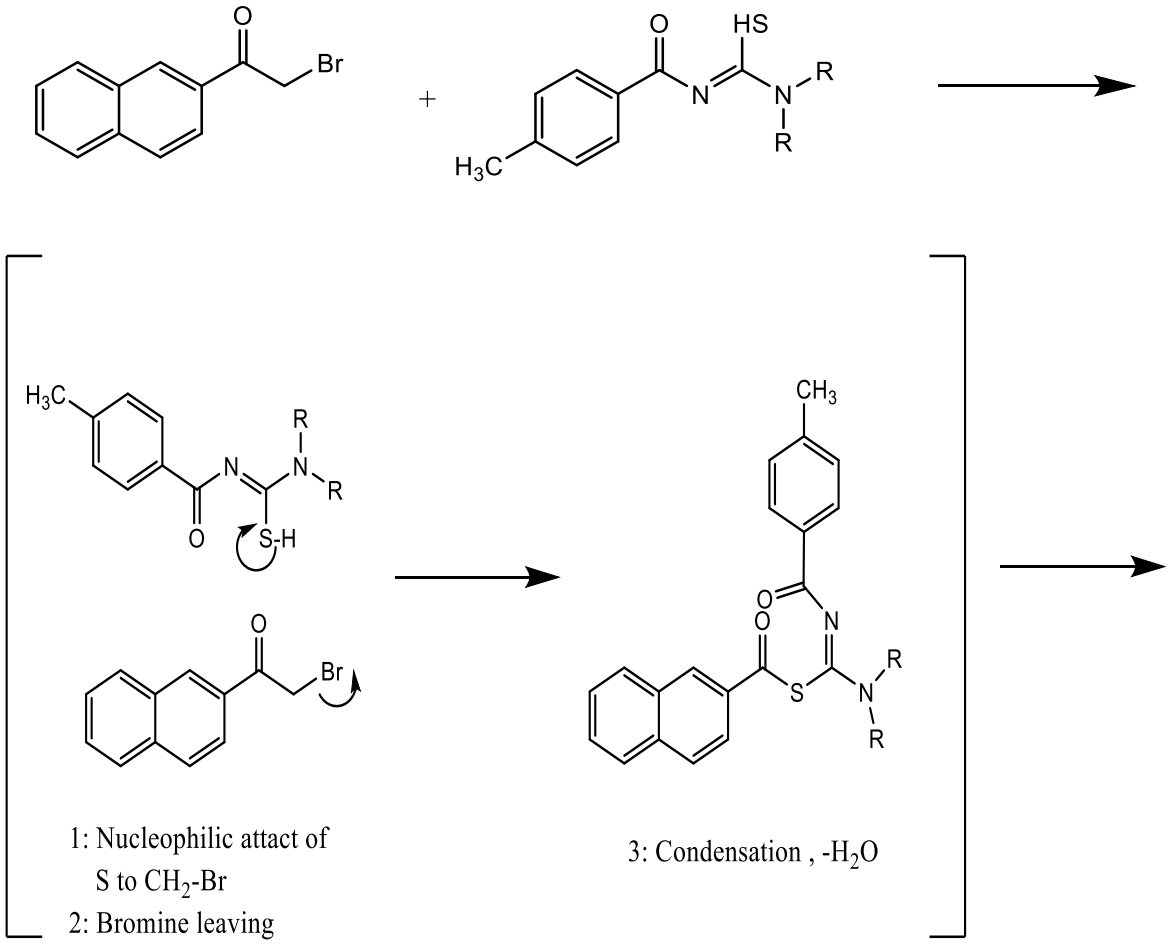
The reagents and solvents utilized were bought from Sigma Aldrich, Hi-media research centers pvt. Ltd. The IR spectra were recorded on a Perkin-Elmer Spectrum in 4000-400 cm^{-1} range using the KBr pellet technique. The ^{1}H, ^{13}C NMR and Mass spectra were recorded on Bruker Avance III, 400MHz instrument utilizing DMSO-d_6 as the internal reference. And a basic analysis was performed. Athmic Biotech Solutions pvt. Ltd. Thiruvananthapuram for the biological studies of my research work.

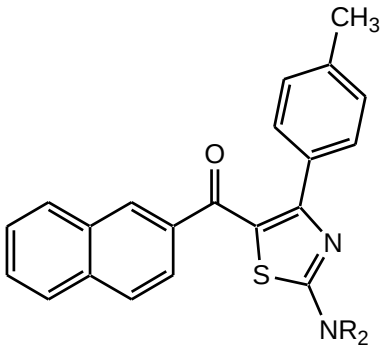
General procedure for synthesis of methylphenylthiazolylnaphthylmethanone (3a-3e)

The reaction between 4-methylbenzoyl thiourea (20 mmol) using a distinct ring closure method of methylene-carbonyl condensation and (2-bromoacetyl)naphthalene (20 mmol) were mixed and heated ethyl alcohol. After the reaction gets completed the mixture is left for cooling. When the mixture reached in 20^{0} it was poured into cool water (50 mL) and added water and neutralization of $NaHCO_{3.}$ The target compound was recrystallized using ethyl alcohol **(Fig: 1)**.

Figure: 1

Methylphenylthiazolylnaphthylmethanone (3a-3e)





Analytical data

(2-dimethylamino-4-methylphenylthiazol-5-yl-2-naphthyl)methanone (3a): Yellow solid, Yield (63%), Anal. Found: C, 74.13, H, 5.39, N, 7.51%. Calculated for $C_{23}H_{20}N_2OS$ (372.48): C, 74.16, H, 5.41, N, 7.52%. IR (KBr, ν_{max}, cm^{-1}): 3056 (C-H str., aromatic), 2926 (C-H str., aliphatic), 1688 (C=O str), 1594 (C-C str), 1395 (C-N str), 730 (C-S str); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 2.488 (3H, s, CH_3), 2.512 (6H, s, $N(CH_3)_2$), 7.615-7.704 (3H, m, 2ArH, H-1 of naphthalene), 7.962-8.052 (6H, m, 2ArH, H-3, H-5, H-6, H-7 of naphthalene), 8.069-8.130 (2H, m, H-4, H-8 of naphthalene) **(Fig: 2 & 3)**;

^{13}C-NMR (400 MHz, DMSO-d_6, ppm) δ: 39.29, 39.50, 39.71, 39.92, 40.12, 40.33, 40.54, 41.60, 126.72, 127.41, 127.78, 127.95, 128.17, 128.70, 129.53, 132.70, 132.92, 133.10, 133.13, 133.39, 135.01, 139.50, 164.82; MS (ESI-MS) m/ʒ: 373(MH^+) **(Fig: 4 & 5)**.

(2-diethylamino-4-methylphenylthiazol-5-yl-2-naphthyl)methanone (3b): Yellow solid, Yield (61%), Anal. Found: C, 74.95, H, 6.03, N, 6.97%. Calculated for $C_{25}H_{24}N_2OS$ (400.54): C, 74.97, H, 6.04, N, 6.99%. IR (KBr, ν_{max}, cm^{-1}): 3055 (C-H str., aromatic), 2927 (C-H str.,

aliphatic), 1669 (C=O str), 1539 (C-C str), 1358 (C-N str), 688 (C-S str); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.041-1.417 (6H, m, 2CH_3), 1.914 (3H, s, CH_3), 2.393 (4H, *J*= 3.5 Hz, q, N(CH_2)$_2$), 6.708 (2H, *J*= 10 Hz, d, ArH), 7.182 (3H, *J*= 10 Hz, d, 2ArH, H-1 of naphthalene) 7.256-7.894 (4H, m, H-3, H-5, H-6, H-7 of naphthalene), 7.931-8.116 (2H, m, H-4, H-8 of naphthalene).

(4-methylphenyl-2-pyrrolidin-1-ylthiazol-5-yl-2-naphthyl)methanone (3c): Yellow solid, Yield (62%), Anal. Found: C, 75.34, H, 5.54, N, 7.01%. Calculated for $C_{25}H_{22}N_2OS$ (398.52): C, 75.35, H, 5.56, N, 7.03%. IR (KBr, ν_{max}, cm^{-1}): 3056 (C-H str., aromatic), 2920 (C-H str., aliphatic), 1688 (C=O str), 1595 (C-C str), 1393 (C-N str), 681 (C-S str); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 2.488-2.512 (8H, m, pyrrolidine), 3.549 (3H, s, CH_3), 7.610-7.723 (5H, m, ArH, H-1 of naphthalene), 7.964-8.055 (4H, m, H-3, H-5, H-6, H-7 of naphthalene), 8.071-8.123 (2H, m, H-4, H-8 of naphthalene).

(4-methylphenyl-2-piperidin-1-ylthiazol-5-yl-2-naphthyl)methanone (3d): Yellow solid, Yield (60%), Anal. Found: C, 75.69, H, 5.84, N, 6.77%. Calculated for $C_{26}H_{24}N_2OS$ (412.55): C, 75.70, H, 5.86, N, 6.79%. IR (KBr, ν_{max}, cm^{-1}): 3056 (C-H str., aromatic), 2938 (C-H str., aliphatic), 1688 (C=O str), 1594 (C-C str), 1392 (C-N str), 730 (C-S str); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.647 (3H, s, CH_3), 2.364 (4H, *J*= 14.8 Hz, t, N(CH_2)$_2$), 2.495-2.609 (6H, m, 3CH_2), 6.757 (5H, *J*= 10.4 Hz, d, ArH, H-1 of naphthalene), 7.536-7.756 (4H, m, H-3, H-5, H-6, H-7 of naphthalene), 7.953-8.071 (2H, m, H-4, H-8 of naphthalene).

(4-methylphenyl-2-morpholin-1-ylthiazol-5-yl-2-naphthyl)methanone (3e): Yellow solid, Yield (60%), Anal. Found: C, 72.42, H, 5.34, N, 6.75%. Calculated for $C_{25}H_{22}N_2O_2S$ (414.52): C, 72.44, H, 5.35, N, 6.79%. IR (KBr, ν_{max}, cm^{-1}): 3053 (C-H str., aromatic), 2854 (C-H str.,

aliphatic), 1677 (C=O str), 1596 (C-C str), 1352 (C-N str), 690 (C-S str); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 2.516 (8H, s, morpholine), 2.716 (3H, s, CH_3), 7.641-7.768 (5H, m, ArH, H-1 of naphthalene), 7.982-8.089 (4H, m, H-3, H-5, H-6, H-7 of naphthalene), 8.119-8.253 (2H, m, H-4, H-8 of naphthalene).

Figure: 2

IR (KBr) Spectrum of (2-dimethylamino-4-methylphenylthiazol-5-yl-2-naphthyl)methanone 3a

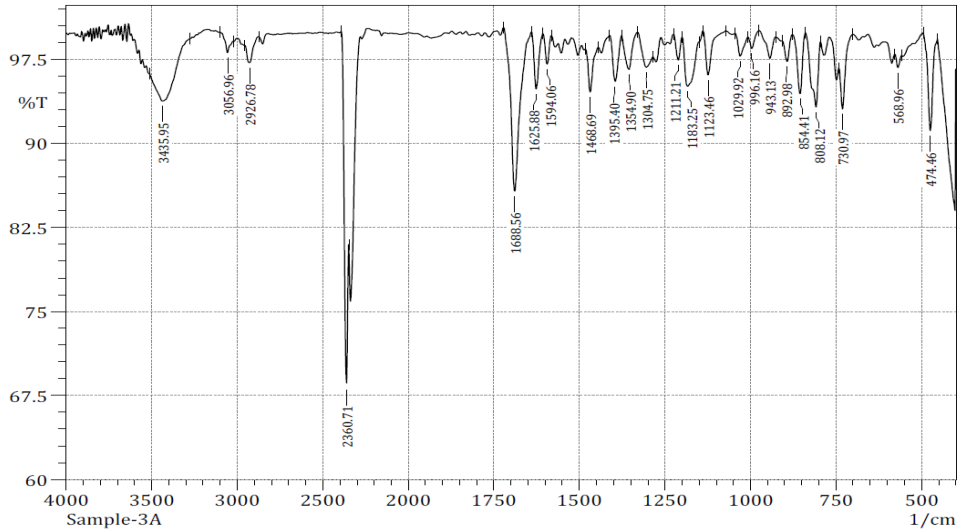


Figure: 3

H[1] NMR Spectrum of (2-dimethylamino-4-methylphenylthiazol-5-yl-2-naphthyl)methanone 3a

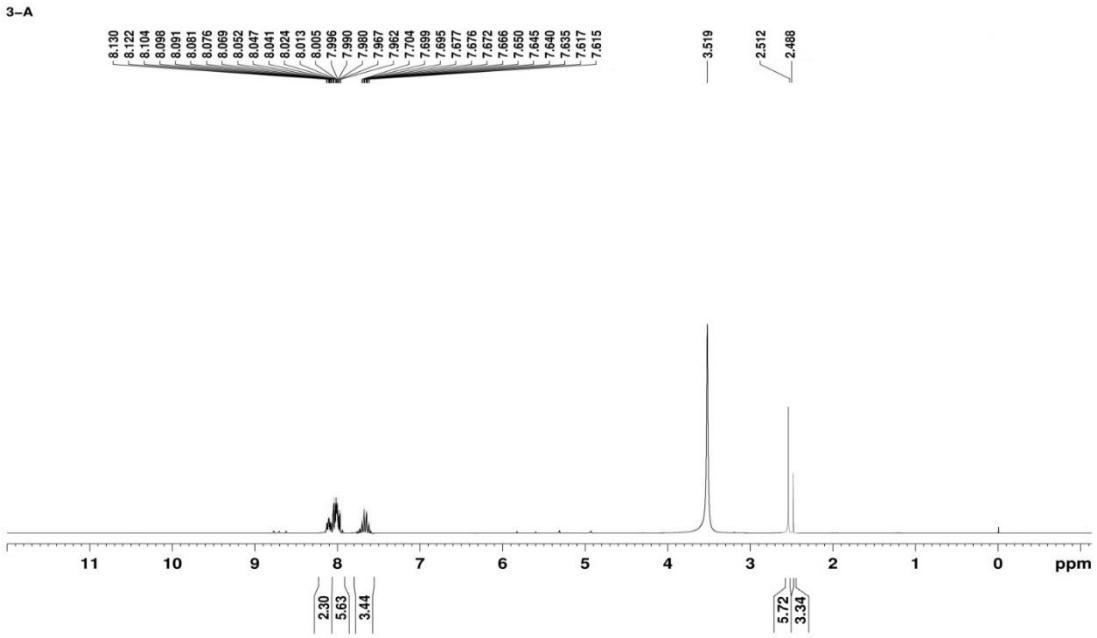


Figure: 4

C[13] NMR Spectrum of (2-dimethylamino-4-methylphenylthiazol-5-yl-2-

naphthyl)methanone 3a

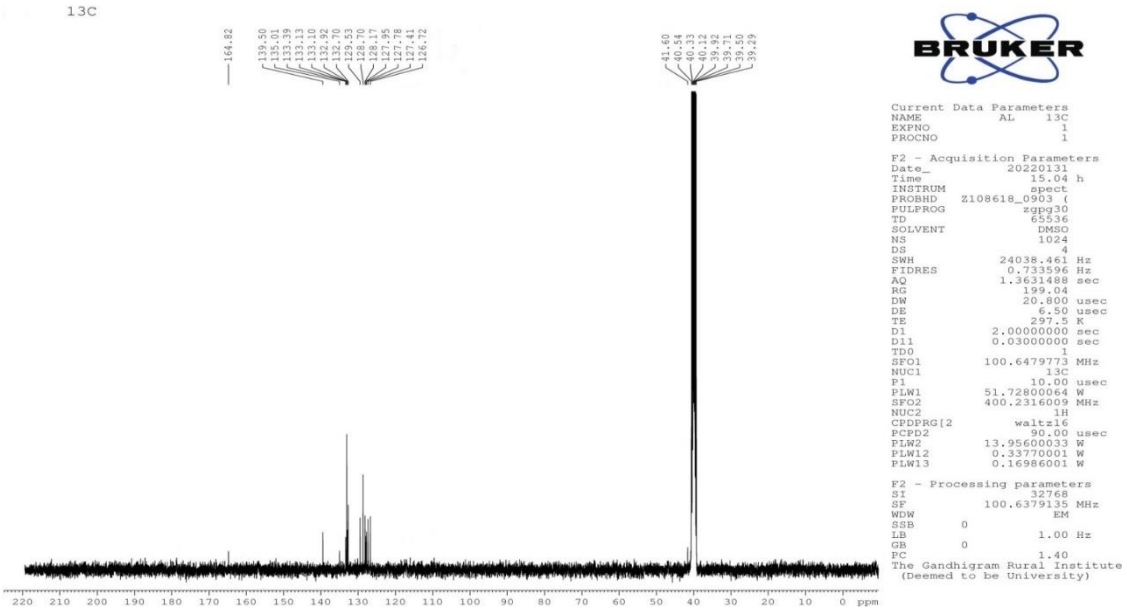
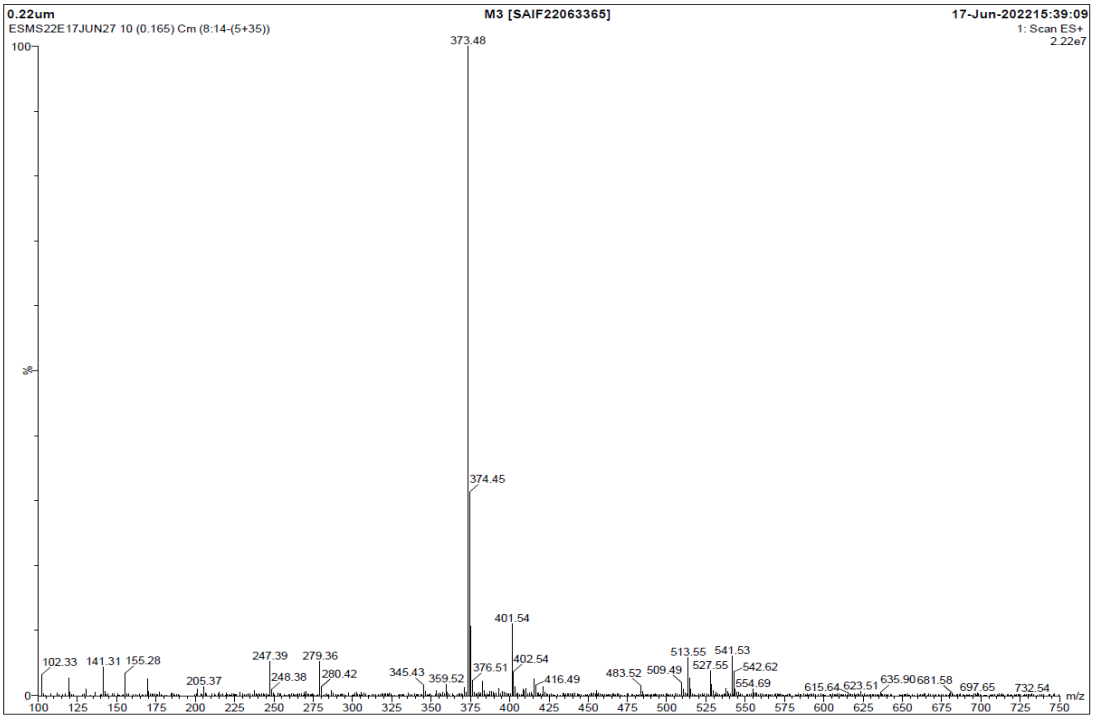


Figure: 5

ESI Mass Spectrum of (2-dimethylamino-4-methylphenylthiazol-5-yl-2-naphthyl)methanone 3a



Molecular docking studies

Molecular docking is a computer-assisted drug design (CADD) method for predicting the favourable orientation of a ligand (i.e. drug) to a target (i.e. receptor) when they are bound to form a stable complex. Understanding the preferred orientation can then be used to determine the strength of binding affinity between ligand and target site, for example, by docking score[8]. Furthermore, docking studies can be used to determine the type of interactions that exist between ligand and receptor, namely hydrogen bonding and hydrophobic interactions. The three-dimensional structure of Naphthalene 1,2-Dioxygenase with Naphthalene bound in the active site (PDB code: 107G) was obtained from RCSB Protein Data Bank[9] for docking purposes. Hydrogen atoms were introduced into the structure to allow for proper ionization at

physiological pH. Furthermore, the protein structure was prepared by removing the repeated chains, water molecules, and any surfactants, hydrogen was added to the receptor's atom, and partial charges were calculated.

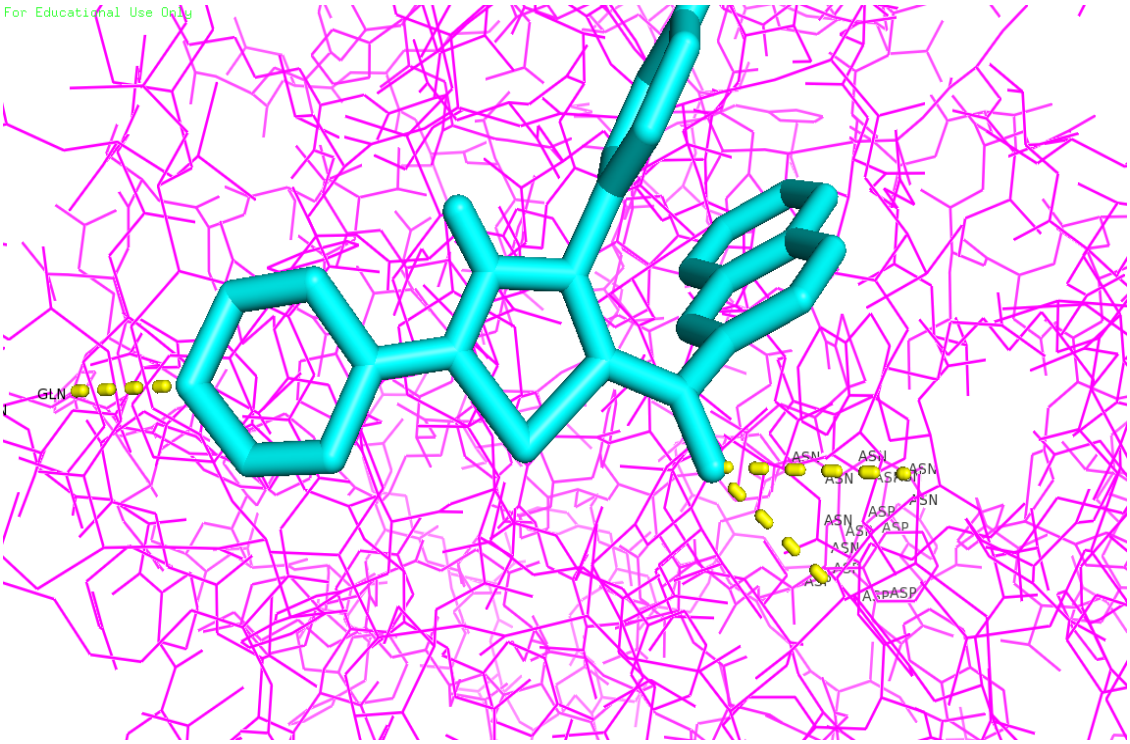
Table: 2

Docking score of methylphenylthiazolylnaphthylmethanone 3

Compound	Docking Score (Kcal/mol)	Residue involved in Hydrogen bonding
3a	-7.5	MET-242, ARG-577
3b	-7.1	ASN-365, THR-212
3c	-8.3	ARG-577
3d	-7.9	ASN-365, THR-212
3e	-8.9	ASN-201, ASP-205, GLN-115

Fig: 7

Docking Image of (4-methylphenyl-2-morpholin-1-ylthiazol-5-yl-2-naphthyl)methanone(3e)



Theoretically all the synthesized compounds showed very good binding scores ranging from -7.1 to -8.9 Kcal/mol as the nitro group at *para* position in these compounds is making hydrogen bonding interaction with MET-242, ARG-577, ASN-201, ASP-205, ASN-365, THR-212 and GLN-115. (4-methylphenyl-2-morpholin-1-ylthiazol-5-yl-2-naphthyl)methanone**(3e)** showed lowest interaction energy that is -8.9 Kcal/mol for 107G. The amino acid residues such ASN-201, ASP-205 and GLN-115 form hydrogen bonding interactions with the **3e Fig: 7**. Hydrogen bonding interactions and docking scores of methylphenylthiazolylnaphthylmethanone outflow are summarized in **(Table: 2)**.

Lipinski's rule of five

The analysis of Lipinski's rule of five depicted that methylphenylthiazolylnaphthylmethanone obey the five rules[10]. The data obtained from Lipinski rule of five of methylphenylthiazolylnaphthylmethanone is listed in **Table: 3**. The docking of

receptor cell division protein Naphthalene 1,2-Dioxygenase with Naphthalene bound in the active site (PDB code: 107G) with newly synthesized methylphenylthiazolylnaphthylmethanone exhibited well established bonds with amino acids in the receptor.

Table: 3

Lipinski rule of methylphenylthiazolylnaphthylmethanone 3

Compound	Molecular Weight <500 Dalton	HB Donar <5	HB Acceptor <10	Log P <5	Molecular Refractivity 40-130
3a	372	1	3	3.42	113.33
3b	400	1	3	3.73	122.56
3c	398	1	3	3.71	120.45
3d	412	1	3	4.68	125.07
3e	414	1	4	4.71	122.03

Antioxidant Activity

The simple, quick, and inexpensive method to assess the antioxidant extent of food involves the use of 2,2-Diphenyl-1-picrylhydrazyl (DPPH) which is commonly used to test the ability of compounds to act as hydrogen donors and free radical scavengers and to estimate antioxidant activity. Hence, the DPPH radicals are broadly used to analyze the radical scavenging activity of compounds. Thus, the assessment of antioxidant ability was executed *in vitro* by DPPH scavenging assay. The free radical DPPH and the odd electron provide maximum absorption at 517 nm (purple colour). The radical is scavenged by the antioxidants, the

absorbance decreases resulting in colour change from purple to pale yellow. The absorbance of DPPH at 517 nm was determined using ultraviolet spectra after 30 minutes. The DPPH concentration in the reaction solution was calculated from the calibration curve plotted at 517 nm at different concentrations and inhibition percentages[11]. Ascorbic acid was used as a standard in our study **(Fig: 8)**.

$$\% \text{ inhibition} = \frac{\text{Control absorbance-Sample absorbance}}{\text{Control absorbance}} \times 100$$

The antioxidant activity of methylphenylthiazolylnaphthylmethanone shows good antioxidant activities. The compound (2-diethylamino-4-methylphenylthiazol-5-yl-2-naphthyl)methanone **3b** shows excellent antioxidant activity have IC_{50} values 51 µM, respectively, and hence they exhibit show uncontrolled cell growth, good antioxidant activities **(Table: 4).**

Figure: 8

% Inhibition Vs concentration of (2-diethylamino-4-methylphenylthiazol-5-yl-2-naphthyl)methanone 3b

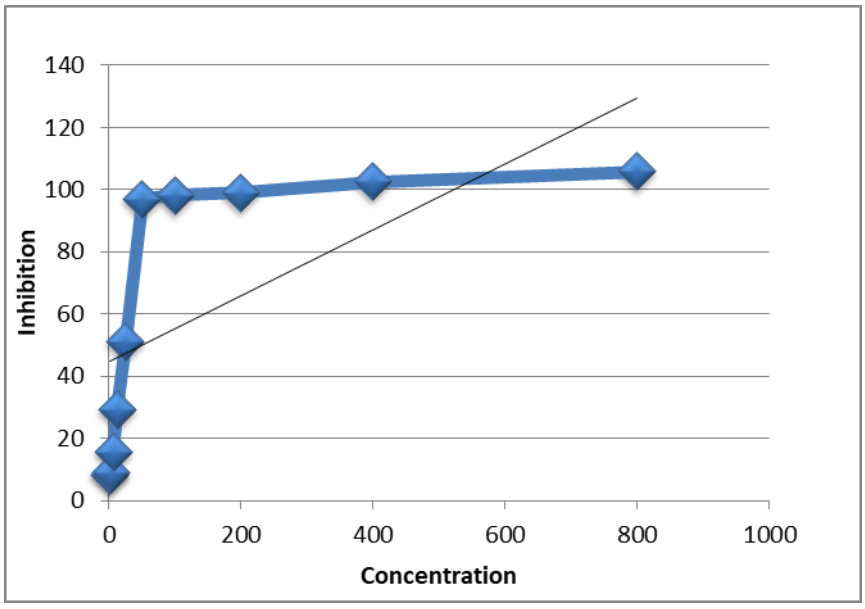


Table: 4

Antioxidant potential of methylphenylthiazolylnaphthylmethanone 3

Compound	IC_{50} Value (µM)
3a	84
3b	51
3c	110
3d	151
3e	90
Ascorbic acid (Std)	90

Anticancer Activity

SKMEL (Human Skin Cancer) cells (2500 cells/well) were seeded on 96 well plates and allowed to acclimatize to the culture conditions of 37 °C and 5% CO_2 in the incubator for 24 hours. The test samples were prepared in DMEM media at a concentration of 100 mg/mL and filter sterilized with a 0.2 m Millipore syringe filter. The samples were diluted further in DMEM media before being added to the wells containing cultured cells at final concentrations of 6.25, 12.5, 25, 50, and 100 g/mL. As a control, untreated wells were kept. To minimise errors, all experiments were performed in triplicate and average values were taken. The plates were then

incubated for 24 hours after being treated with the test samples[12]. After incubation length, the media from the wells have been aspirated and discarded. A 100 μL of 0.5 mg/mL MTT answer in PBS become added to the wells. The plates had been in addition incubated for 2 h for the improvement of formazan crystals. The supernatant changed into eliminated and 100 μL DMSO (100%) have been introduced in line with nicely. The absorbance at 570 nm turned into measured with micro plate reader. Two wells consistent with plate without cells served as clean.

All experiments had been performed in triplicates. The mobile viability become expressed the usage of the subsequent system:

$$\textbf{Percentage of cell viability} = \frac{\textbf{Average absorbance of treated}}{\textbf{Average absorbance of control}} \times 100$$

The compound (2-diethylamino-4-methylphenylthiazol-5-yl-2-naphthyl)methanone **3b** was the most active anti-oxidant derivative. In anticancer study of (2-diethylamino-4-methylphenylthiazol-5-yl-2-naphthyl)methanone **3b** exhibited the highest anticancer activity against SKMEL cell lines (Human Skin Cancer) with IC_{50} values 65.91μM are very good anticancer compound (**Table: 5)** and **(Fig: 9)**.

Figure: 9

Percentage viability Vs concentration of (2-diethylamino-4-methylphenylthiazol-5-yl-2-naphthyl)methanone 3b

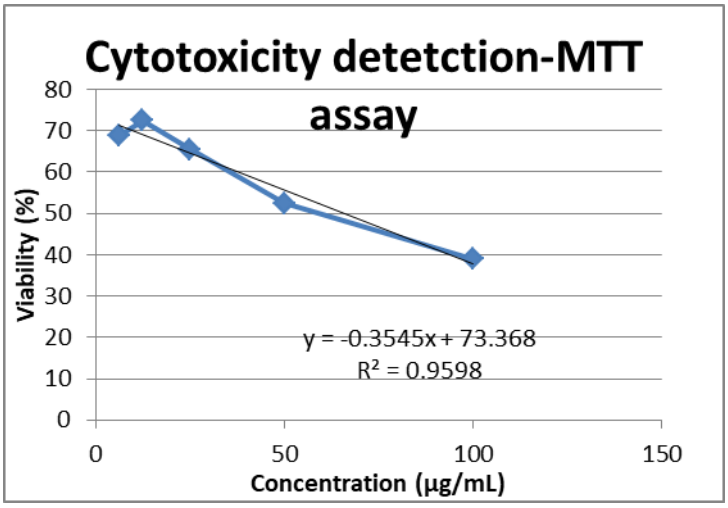


Table: 5

Concentration (µg/mL)	**Percentage Viability 3b**
6.25	68.76
12.5	72.45
25	65.54
50	52.43
100	38.98
IC_{50}	65.91

Conclusion

Chemical structures of synthesized compounds were ascertained on the basis of their spectral data (IR and ^{1}H NMR). Molecular docking studies revealed that compound (4-methylphenyl-2-morpholin-1-ylthiazol-5-yl-2-naphthyl)methanone**(3e)** is showing excellent binding score of – 8.9 Kcal/mol, respectively as the nitro head group at para position is making strong hydrogen bonding interaction with ASN-201, ASP-205 and GLN-115 amino acid residues. The antioxidant evaluation of the compounds showed that the (2-diethylamino-4-methylphenylthiazol-5-yl-2-naphthyl)methanone **3b** possess the highest antioxidant activity among the synthesized methylphenylthiazolylnaphthylmethanone **3.** The *in vitro* anti-cancer assay performed for the compounds revealed that (2-diethylamino-4-methylphenylthiazol-5-yl-2-naphthyl)methanone **3b** is the most active anti-cancer compound.

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