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SYNTHESIS AND *IN SILICO* CHEMINFORMATIC STUDY OF NOVEL NAPHTHOFURAN C-2 COUPLED DIAMIDE AND 3, 4-DIHYDROPHTHALAZIN-1(2H)-ONE ANALOGUES

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ABSTRACT

A novel series of naphthofuran C-2 coupled diamide and 3, 4-dihydrophthalazin-1(2H)-one analogues (3-8) were synthesized by multi step reaction. The synthesized compounds were characterized by spectral analysis. Analogues were exposed to *in silico* ADMET studies were carried out to identify drug likeness. Molecular and pharmacokinetic properties of the entitled derivatives were calculated to predict the bioactivity score. The molecules exhibited acceptable range in ADMET prediction and bioactive score. The ADMET study exhibited a less toxic nature and it encourages us to taken up for further screening of different pharmacological assays.

KEYWORDS

Naphthofuran, Carbohydrazide, ADMET and Drug likeness.

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INTRODUCTON

Naphthofuran nuclei are key structural moieties found in a large number of biologically important natural products. Many of the natural naphthofurans, such as (±)-laevigatin[1], (+)-heritol[2,3] and balsaminone-A[4], possess interesting pharmacological and cytotoxic properties[5]. A large number of naphthofuran derivatives are endowed with various biological activities like anthelmintic, anticonvulsant, and antipyretic[6] and their plant extracts are being used for traditional medicines[7], while mansonone D and Dunnione[8] of naphthofuran family are vital biologically active agents. In addition, naphthofurans condensed with various

heterocycles exhibited wide spectrum of activities[9-11].

Phthalazin-1(2H)-one derivatives are of considerable interest due to their antidiabatic[12] antiallergicb[13], antiasthmatic[14], antihypertensive[15], vasorelaxant[16], aldose reductase inhibitor[17] and antimicrobial[18] activities. The diverse biological activities of these pharmacophores; naphthofuran and phthalazin-1(2H)-one, pharmacophores, encouraged us to discover a new lead compounds, which contains all these pharmocophores in a single molecules that may exhibit higher pharmacological activities. By combining these pharmacophore components in a single molecule, to give a compact system, we synthesized a series of naphthofuran coupled phthalazin-1(2H)-one derivatives. The synthesized new phthalazin-1(2H)-one derivatives were characterized by spectral analysis and drug likeness properties.

MATERIAL AND METHODS

Analysis and instruments

Chemicals used in the synthesis of compounds were purchased from Alfa Aesar and Spectrochem Pvt. Ltd. The solvents were of reagent grade and when necessary, they were purified and dried by the standard methods. Melting points (M. Pt.) of the synthesized compounds were determined with the help of Raga digital melting point apparatus and are uncorrected; Infrared data were recorded on a Bruker spectrophotometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVANCE II 400 and 100 MHz instruments using DMSO-d6/$CDCl_3$ as a solvent and TMS as an internal standard; chemical shifts are expressed as d values (ppm). The *J* values are expressed in Hertz (Hz). Mass spectra (MS) were recorded in JEOL GCMATE II LC–Mass spectrometer using electron impact ionization (EI) technique. Analytical thin-layer chromatography (TLC) was performed on precoated TLC sheets of silica gel 60 F254 (Merck, Darmstadt, Germany), visualized by long and short wavelength UV lamps. Column chromatographic purifications were performed on Merck silica gel (60-100 mesh).

General procedure for the synthesis of 2-{[2-(naphtha [2, 1-*b*] furan-2 yl carbonyl) hydrazinyl] carbonyl} benzoic acid derivatives (3-5)

The carbohydrazides are developed from ND satyanarayan, *et al*[11]. The hydrazide (2) (0.001 mol) and different anhydrides (0.004 mol) are taken in dry toluene, was stirred at room temperature for overnight. The solvent was evaporated under reduced pressure and the precipitate was recrystalized from ethanol to furnish pure (3-5).

General procedure for the synthesis of 2-(naphtha [2, 1-*b*] furan-2-yl carbonyl)-3, 4-dihydrophthalazin-1(2*H*)-one derivatives (6-8)

A mixture of 4-(2, 5-dimethylpyrrol-1-yl) benzoic acid hydrazide (0.01 mol) and appropriate aromatic anhydrides (0.01 mol) in 5 ml absolute ethanol and glacial acetic acid (0.005 mol) was refluxed for 4-6 hrs. The reaction mixture was poured into crushed ice. The solid obtained was filtered, washed with dilute sodium bicarbonate solution and recrystalized with suitable solvent.

Spectral analysis of 2-{[2-(naphtha [2, 1-*b*] furan-2 yl carbonyl) hydrazinyl] carbonyl} benzoic acid (3)

Yield: 73 %, M. Pt: 178-180^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 11.03 (S, 1H, acid proton), 8.31-8.43 (d, 1H, J=4 Hz), 8.2-8.3 (d, 2h, J=8 Hz), 8.14-8.16 (d, 1H, J=0.8 Hz), 7.78-7.83 (t, 1H, J=4Hz), 7.6-7.7 (d, 5H, J=4 Hz), 7.42-7.44 (d, 3H, J=0.8 Hz): ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 169.8, 165.3, 159.1, 158.2, 157.3, 154.7, 141.3, 136.3, 134.1, 132.4, 131.3, 130.1, 129.3, 128.5, 126.9, 125.1, 123.7, 121.8, 120.3, 111.8, 109.7; Calculated mass: 374.3 g/mol; MS (m/z): 375.1 g/mol [M^{+}].

Spectral analysis of 2-(naphtha [2, 1-*b*] furan-2-yl carbonyl)-3, 4-dihydrophthalazin-1(2*H*)-one (6)

Yield: 65 %, M. Pt: 206-208^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.1 (S, 1H, -NH proton), 7.8-7.9 (d, 1H, J=4 Hz), 7.5-7.6 (d, 2h, J=4 Hz), 7.53 (s, 1H), 7.3-7.4 (m, 7H), 3.8 (s, 1H), 2.7 (s, 1H): ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 165.3, 159.9, 158.3, 155.4, 143.7, 141.9, 140.3, 139.3, 137.1, 135.0, 134.3, 132.7, 131.0, 129.9, 127.3, 126.9,

125.3, 121.9, 111.6, 109.8, 48.9; Calculated mass: 342.3 g/mol; MS (m/z): 343.7 g/mol [M^+].

***In silico* ADME-Toxicity study of title compounds**

The molecular descriptors of compounds (3-5 and 6-8) are predicted by pharmacokinetic parameters such as absorption, distribution, metabolism, excretion and toxicity (ADMET). The evaluation of biologically active molecules and to eliminate the poor once can be known by ADMET/SAR studies[19] wherein the active lead molecule which contains undesirable functional groups can be removed based on Lipinski rule. The lead molecules are statistically calculated for surface area, geometry and fingerprint properties to understand biologically important end points for the molecule(s). The aqueous solubility (PlogS), Blood brain barrier penetration (QlogBB), intestinal absorption (logHIA) and hepatotoxicity, Caco-2 cell permeability (QPPCaco) help in predicting the toxicity of lead molecules with different routes; intraperitoneal, oral, intravenous and subcutaneous toxic effects. The *in-silico* ADMET study helps us to determine the efficacy and safety of active molecules.

Calculation of pharmacokinetic parameters and **toxicity potential**

Chemical structures and SMILES notations of the title compounds were obtained by using ACD labs Chem sketch version 12.0. SMILES notations of the derivatives were then fed in the online Molinspiration software version 2011.06 to calculate various molecular properties and to predict bioactivity score for drug targets including enzymes and nuclear receptors, kinase inhibitors, GPCR ligands, and ion channel modulators. Molecular properties such as partition coefficient (Log P), Topological polar surface area (TPSA), hydrogen bond donors and acceptors, rotatable bonds, number of atoms, molecular weight, and violations of Lipinski's rule of five were calculated to evaluate the drug likeness of the synthesized compounds[20].

RESULTS AND DISCUSSION

Drug likeness score and bioactivity score of entitled compounds

The drug likeness and bioactivity screening of the synthesized compounds are represented in Table No.3 and No.4. Lipinski's rule of five is commonly used by pharmaceutical chemists in drug design and development to predict oral bioavailability of potential lead or drug molecules. According to Lipinski's rule of five, a candidate molecule will likely to be orally active, if: i) the molecular weight is under 500, ii) the calculated octanol/water partition coefficient (Log P) <5, iii) there were fewer than 5 hydrogen bond donors (OH and NH groups) and, iv) there are less than ten hydrogen bond acceptors (notably N and O)[19]. The molecular properties naphthofuran coupled carbonyl) hydrazinyl] carbonyl} benzoic acid and 3, 4-dihydrophthalazin-1(2*H*)-one derivatives (3-8) were calculated by using Molinspiration chemiformatics software and are presented in tables.

Number of hydrogen bond acceptors (O and N atoms) and number of hydrogen bond donors (NH and OH) in the synthesized compounds (3-8) were in accordance with the Lipinski's rule of five i.e. less than 10 and 5, respectively. It can be predicted that among all synthesized derivatives were likely to be orally active as they obeyed Lipinski's rule of five.

[a]Estimated LD_{50}-mouse value in mg / kg after Intraperitoneal, Oral, Intravenous and Subcutaneous administration.

[a]Predicted blood / brain barrier partion coefficient (1-high penetration, 2- medium penetration and 3-low penetration). [b]predicted Caco-2 cell permeability in nm / s (acceptable range -1 is poor, +1 is great). [c]predicted human intestinal absorption in nm / s (acceptable range 0 is poor, >1 is great). [d]predicted P-glycoprotein Substrate in nm / s (acceptable range of -5 is poor, 1 is great). [e]predicted P-glycoprotein inhibitor in nm / s (acceptable range 0-1). [f]predicted aqueous solubility, (Concern value is 0-2 highly soluble). [g]predicted Caco-2 cell Permeability in cm / s (Concern value is -1 to 1).

[a]Logarithm of partition coefficient between n-octanol and water (miLogP), [b] Topological polar surface area (TPSA), [c] Number of hydrogen bond acceptors (n-ON), [d] Number of hydrogen bond donors (n-OHNH), [e] Number of rotatable bonds (n-rotb), [f] Molecular weight (MW).

G-protein coupled receptors (GPCR). A molecule having bioactivity score more than 0.00 is likely to exhibit considerable biological activities, while values -0.50 to 0.00 are expected to be moderately active and if the score is less than -0.50 it is presumed to be inactive.

Topological polar surface area is very much correlated with the hydrogen bonding of a molecule and is a very good indicator of the bioavailability of drug molecule. TPSA of synthesized derivatives was observed in the range of 79.62-108.64 Å and is well below the limit of 160 Å.

The bioactivity scores of title compounds for drug targets were also predicted by Molinspiration chemiformatics and are presented in Table No.4. A molecule having bioactivity score more than 0.00 is most likely to exhibit considerable biological activities, while values -0.50 to 0.00 are expected to be moderately active and if score is less than -0.50 it is presumed to be inactive[20].

The results clearly reveal that the physiological actions of naphthofuran coupled carbonyl) hydrazinyl] carbonyl} benzoic acid and 3, 4-dihydrophthalazin-1(2*H*)-one derivatives (3-8) might involve multiple mechanisms and could be due to the interactions with GPCR ligands, nuclear receptor ligands, inhibit protease and other enzymes. The bioactivity score of compounds is suggestive of significant interaction with all the drug targets. The identified compounds showed better bioactivity score.

Table No.1: LD_{50} ADME-TOX Parameters and probability of health effects of substituted carbonyl} benzoic acid and 3, 4-dihydrophthalazin-1(2*H*)-one derivatives (3-8) using ACD/ I-Lab 2.0

Ligands	Intraperitoneal[a]	Oral[a]	Intravenous[a]	Subcutaneous[a]
1	700 (0.14)	1600 (0.46)	430 (0.4)	2000 (0.22)
2	470 (0.47)	1500 (0.53)	450 (0.31)	3600 (0.29)
3	720 (0.47)	1300 (0.41)	520 (0.32)	3900 (0.31)
4	820 (0.13)	1600 (0.42)	190 (0.42)	1500 (0.48)
5	350 (0.09)	2000 (0.44)	460 (0.3)	2100 (0.32)
6	640 (0.27)	2400 (0.48)	330 (0.26)	700 (0.45)
Pyrazinamide	2000(0.83)	540(0.28)	170(0.56)	1000(0.71)
Ciprofloxacin	930(0.72)	3500(0.78)	120(0.86)	1400(0.58)
Streptomycin	310(0.76)	880(0.53)	110(0.67)	400(0.52)

Table No.2: ADME and pharmacological parameters prediction for the ligands of substituted carbonyl} benzoic acid and 3, 4-dihydrophthalazin-1(2*H*)-one derivatives (3-8) using ADMET/SAR

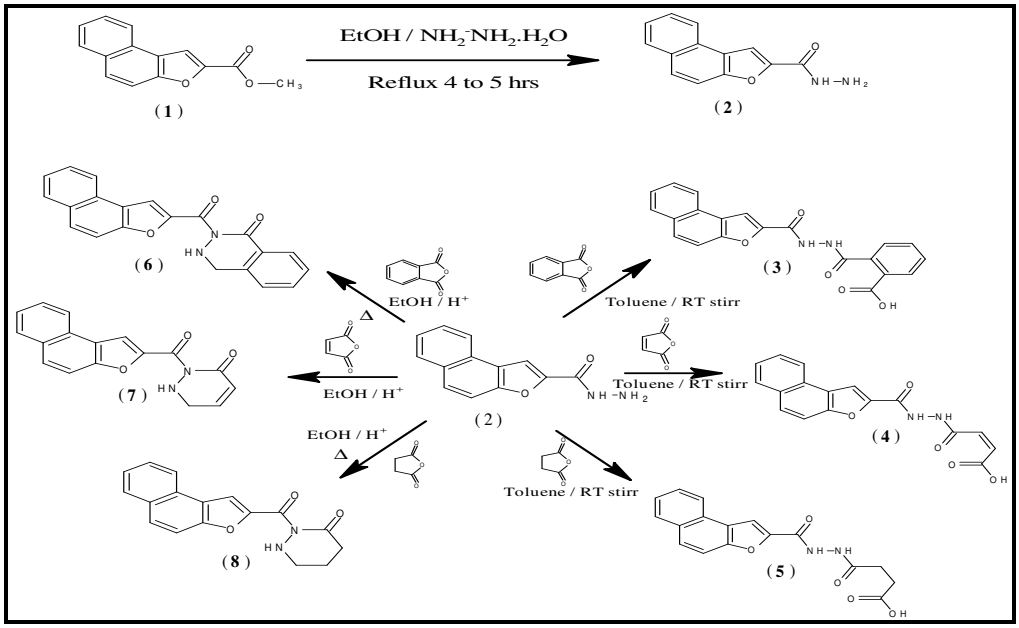
Ligands	PlogBB[a]	PCaco[b]	logHIA[c]	logpGI (Non substrate)[d]	logpGI (Non inhibitor)[e]	PlogS[f]	logpapp[g]
1	0.7912	0.6343	0.9572	0.8427	0.8801	-3.6933	0.4958
2	0.8699	0.6330	0.9808	0.8319	0.9142	-3.6858	0.4220
3	0.8823	0.7303	0.8995	0.8223	0.8931	-2.9351	-0.0926
4	0.9822	0.5424	0.9906	0.8555	0.8821	-3.3050	0.8717
5	0.9822	0.5424	0.9906	0.8555	0.8821	-3.3050	0.8717
6	0.9672	0.6176	0.9842	0.8550	0.8900	-2.7298	0.4162
Pyrazinamide	0.9745	0.7222	0.9813	0.8760	0.9731	-0.8476	1.3021
Ciprofloxacin	0.9655	0.8956	0.9795	0.9116	0.9231	-3.4638	0.8090
Streptomycin	0.9712	0.6968	0.8824	0.8177	0.9230	-2.0122	-0.5128

Table No.3: Drug likeness score for the synthesized substituted carbonyl} benzoic acid and 3, 4-dihydrophthalazin-1(2*H*)-one derivatives (3-8)

Compounds	miLog P[a]	TPSA[b]	n-Atoms	n-ON[c]	n-OHNH[d]	n-Violation	n-rotb[e]	MW[f]
1	3.17	108.68	28	7	3	0	4	374.35
2	1.70	108.64	24	7	3	0	4	324.29
3	1.72	108.64	24	7	3	0	5	326.31
4	3.89	85.08	27	6	1	0	1	356.34
5	2.78	85.08	23	6	1	0	1	306.28
6	1.90	79.62	23	6	1	0	1	308.29
Streptomycin	-4.87	324.42	40	18	15	3	9	580.59
Pyrazinamide	-0.71	68.88	9	4	2	0	1	123.11
Ciprofloxacin	-0.70	74.57	24	6	2	0	3	331.35

Table No.4: Bioactive score of the synthesized substituted carbonyl} benzoic acid and 3, 4-dihydrophthalazin-1(2*H*)-one derivatives (3-8) with the help of molinspiration chemiformatics software

Compounds	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	-0.14	-0.47	-0.22	-0.29	-0.16	-0.15
2	-0.17	-0.54	-0.32	-0.42	-0.14	-0.24
3	-0.10	-0.62	-0.38	-0.54	-0.08	-0.14
4	-0.23	-0.28	-0.19	-0.22	-0.20	-0.10
5	-0.23	-0.47	-0.28	-0.25	-0.29	-0.15
6	-0.19	-0.76	-0.38	-0.60	-0.19	-0.30
Streptomycin	0.15	-0.14	-0.15	-0.02	0.64	0.42
Pyrazinamide	-1.97	-1.45	-1.71	-2.87	-1.84	-1.43
Ciprofloxacin	0.12	-0.04	-0.07	-0.19	-0.21	0.28



Scheme No.1

CONCLUSION

The present research, reports the successful prediction of cheminformatic study of new naphthofuran coupled carbonyl) hydrazinyl] carbonyl} benzoic acid and 3, 4-dihydrophthalazin-1(2*H*)-one derivatives (3-8). Attempt is made to predict *in-silico* pharmacokinetic and bioactive score of synthesized molecules. All compounds are in acceptable range. The obtained results suggest that, these compounds may serve as lead chemical entities for further modification in the search for new classes of potential pharmacological agents.

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CONFLICT OF INTEREST

There is no any conflict of interest.

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