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In silico ADMET, Drug Likeness Properties and Rapid one pot Microwave Assisted Synthesis of Novel 2, 6-di (furan-2-yl)-4-phenylpyridine Analogues

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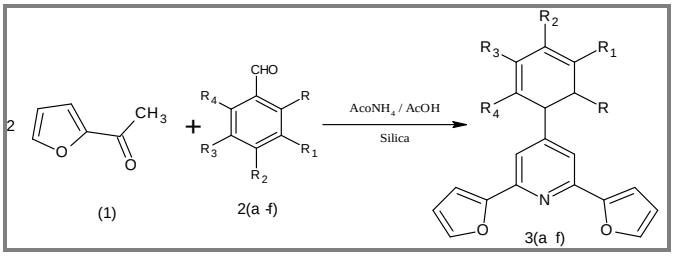
ABSTRACT

A rapid one pot synthesis of title compounds was achieved by microwave irradiation of 2-acetyl furan and substituted aromatic aldehydes in the presence of acetic acid. The structures of synthesized molecules were confirmed by spectral characterization using ^{1}H NMR, ^{13}C NMR and mass spectra. The in silico ADMET (absorption, distribution, metabolism, excretion and toxicity) studies were carried out to predict the safety, efficacy of the molecules based on the physicochemical properties. The molecules exhibited acceptable range in ADMET prediction and bioactive score. The ADMET study exhibited a less toxic nature and it encourages us to look into the preliminary screening of different pharmacological assays.

Graphical Abstract



Keywords: Furan, aldehydes, drug likeness and ADMET.

INTRODUCTION

The drug development process from the target identification to the final product being marketed is a time and money consuming process, with the total research and development costs reported as being up to 800 million dollars and an average of 10 years [1]. Drug candidate to be sufficiently bioavailable and ultimately a commercial success, its pharmacodynamic activity needs to be in consistent with its structural, physicochemical and biological properties [2].

Drug like properties are characteristics of compounds, which need to be in balance to make compounds suitable to act as drugs. Structural properties, such as molecular size and hydrogen

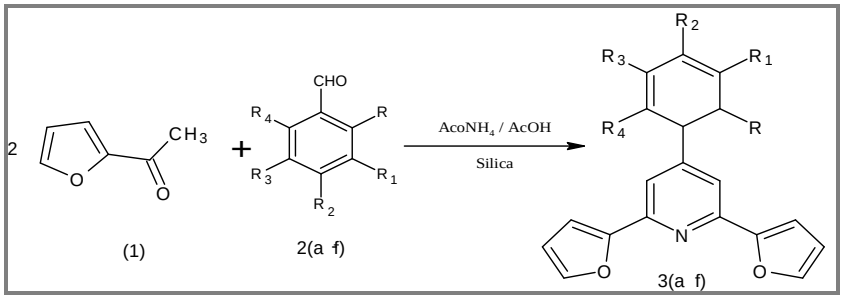
bonding capacity affect the physicochemical properties, such as solubility and lipophilicity and are contributes to the unique biological properties of each compound to discover the lead or drug [3].

Use of microwave ovens for rapid organic synthesis was demonstrated for the first time, they studied the utilization and advantages of microwave irradiation for organic synthesis involving hydrolysis of benzamide to benzoic acid under acidic conditions [4]. Rate of reaction increased considerably (5-1000 fold) for the transformations compared to classical thermal reflux conditions. The advantages of using microwave dielectric heating for performing organic reactions were realized thereafter by many different groups and as a consequence the amount of articles describing high-speed chemical synthesis promoted by microwave irradiation has grown quickly [5].

Terpyridine derivatives showed various biological activities [6]. Some of the researcher also reported that terthiophene derivatives, which are bioisosteres of terpyridine, showed considerable inhibitory activity on PKC and an antitumor cytotoxicity against several human cell lines. Although the cytotoxicity of terpyridine derivatives has long been reported, a systematic study on the effects of substituted pyridines and of the substituents on the pyridine nucleus has not yet been pursued. Such previous studies prompted us to design 2,4,6-trisubstitutedpyridine derivatives as a topoisomerase-inhibitors. We reasoned that the substituents at 2, 4, and/or 6-position may affect the conformation of the whole molecule to retain a preferably planar conformation for better conjugation with the central pyridine anchor, thus interacting with topoisomerase-I effectively [7]. In this study, we described the synthesis of 2,4,6-trisubstitutedpyridine derivatives as bioisosteres of terpyridine/terthiophene and cheminformatic studies was also determined.

MATERIALS AND METHODS

Analysis and instruments: Chemicals used in the synthesis of compounds were purchased from Alfa Aesarand 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).



R	R_1	R_2	R_3	R_4
-H-	-H-	-OH-	-H-	-H-
$-CF_3-$	-H-	-H-	-H-	-H-
-H-	-OH-	-H-	-H-	-H-
-F-	-H-	-H-	-H-	-F-
-H-	-H-	-Cl-	-H-	-H-

Scheme 1. 2, 6 di-furan 4 phenyl pyridine analogues

Table 1. Physicochemical properties of 2, 6 di-furan 4 phenyl pyridine analogues

Samples code	R	R_1	R_2	R_3	R_4	Molecular Formula	Molecular weight	(%) Yield	Melting point(°C)
3a	-H-	-H-	OH	H-	H-	$C_{19}H_{13}NO_3$	303.31	74	146-148°
3b	CF_3	-H-	-H-	H-	H-	$C_{20}H_{12}F_3NO_2$	355.309	88	162-164°
3c	-H-	OH	-H-	H-	H-	$C_{19}H_{13}NO3$	303.311	72	180-182°
3d	-F-	-H-	-H-	H-	F-	$C_{19}H_{11}F_2NO_2$	323.29	75	110-112°
3e	-H-	-H-	-Cl	H-	H-	$C_{19}H_{13}ClNO_2$	321.75	83	90-92°

General procedure for the synthesis of 2, 6 di-furan 4 phenyl pyridine 3(a-e): The rapid green synthesis of novel furan analogs by reacting 2-acetyl furan (0.5g, 2 mole), substituents of benzaldehyde (0.63, 1 mole) and ammonium acetate (0.5g,1.5 mole), together with the adding of glacial acetic acid (1 mL) and silica gel (60-120 mesh) as matrix (adsorbent). The thoroughly mixed above mixture was subjected to microwave irradiation for 10-12 min at a temperature of 180°C. The completion of the reaction was monitored occasion by subjecting the reaction mixture for TLC using 6:4 v/v (n-hexane: ethyl acetate).

Spectral analysis of 4-(4-chlorocyclohexa-2,4-dien-1-yl)-2,6-di(furan-2-yl)pyridine 3(e): Yield:83 %, M. Pt: 90-92^{o}C; IR(KBr), cm^{-1} 1368 (C-N), 1080 (C=N), 1658 (C-O), 1596 (C=C), 2851 (C-H), 811.14 (C-Cl); ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm):8.41 (S, 1H), 8.03 (s, 1H), 7.81-7.83 (d, 4H, J=8Hz), 7.69 (s, 2H), 7.627-7.608 (d, 2H, J=7.6 Hz), 7.54 (s, 1H), 7.462-7.48 (d, 2H, J=7.2 Hz), 7.41-7.44 (d, 2H, J=12 Hz), 7.36-7.34 (d, 2H, J=20 Hz), 7.26 (s, 1H), 7.12 (s.1H), 6.93(s, 1H), 6.81 (s, 1H), 6.75 (s, 1H), 6.63-6.65 (d, 2H, J=8); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm):186.0, 176.9, 160.8, 153.3, 148.8, 148.3, 141.7, 153.5, 133.8, 131.5, 131.4, 130.8, 129.7, 128.8, 123.1, 120.1, 119.5, 113.1, 112.9.

***In silico* ADME-Toxicity study of title compounds:** The molecular descriptors of compounds 3(a-e) 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 [**8**] 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 [**9**].

RESULTS AND DISCUSSION

***In silico* ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiles:** The compounds with poor bioavailability show less effectiveness against disease. To solve this problem,

predicting bioavailability properties will be of great advantage for drug development. Hence, using computer-based methods like ADMET and SAR tools the molecular descriptors and drug likeliness properties were studied. The pharmacokinetic properties are represented in table 2 and 3. The coefficient of blood/brain barrier penetration (logB/B) was computed and assessed with central nervous system (CNS). The CNS activity was computed on -2 (inactive) to +2 (active) scales which show all the molecules are displayed within acceptable range.

Table 2. LD_{50} ADME-TOX Parameters of substituted 2, 6-di (furan-2-yl)-4-phenylpyridine using ACD/ I-Lab 2.0 3(a-e)

Ligands	Intraperitoneal	Oral	Intravenous	Subcutaneous
3a	490 (0.37)	490 (0.31)	43 (0.31)	390 (0.23)
3b	450 (0.35)	430 (0.34)	34 (0.32)	230 (0.24)
3c	540 (0.34)	1000 (0.35)	45 (0.38)	420 (0.24)
3d	620 (0.24)	570 (0.35)	43 (0.26)	830 (0.28)
3e	410 (0.4)	510 (0.27)	28 (0.4)	330 (0.33)

Estimated LD_{50}-mouse value was in mg kg^{-1} after Intraperitoneal, Oral, Intravenous and Subcutaneous administration.

Table 3. ADME and pharmacological parameters prediction for the ligands substituted 2, 6-di (furan-2-yl) -4-phenylpyridine using ADMET/SAR 3(a-e)

Ligands	miLog P[a]	TPSA[b]	n-Atoms	n-ON[c]	n-OHNH[d]	n-Violation	n-rotb [e]	MW[f]
3a	4.51	39.17	22	3	0	0	3	287.32
3b	5.36	39.17	26	3	0	1	4	355.31
3c	4.01	59.40	23	4	1	0	3	303.32
3d	4.74	39.17	24	3	0	0	3	323.30
3e	5.36	42.41	27	4	0	1	6	358.44

[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^{-1} (acceptable range -1 is poor, +1 is great). [c]predicted human intestinal absorption in nm s^{-1} (acceptable range 0 is poor, >1 is great). [d]predicted P-glycoprotein Substrate in nm s^{-1} (acceptable range of -5 is poor, 1 is great). [e]predicted P-glycoprotein inhibitor in nm s^{-1} (acceptable range 0-1).[f]predicted aqueous solubility, (Concern value is 0-2 highly soluble). [g]predicted Caco-2 cell Permeability in cm s^{-1}(Concern value is -1 to 1).

Drug likeness score and bioactivity score of entitled compounds: The drug likeness and bioactivity screening of the synthesized compounds are represented in table 4 and 5. 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) [**8**]. The molecular properties furan C-2 coupled pyridine and its analogues 3(a-e) were calculated by using molinspiration chemiformatics software.

Table 4. Drug likeness score for the synthesized 2, 6-di (furan-2-yl)-4-phenylpyridine derivatives 3(a-e)

Ligands	PlogBB[a]	PCaco[b]	logHIA[c]	logpGI (Non-substrate)[d]	logpGI (Non-inhibitor)[e]	PlogS[f]	logpapp[g]
3a	0.9885	0.5362	0.9748	0.8574	0.8271	-2.6396	1.4733
3b	0.9950	0.5959	1.0000	0.8172	0.9081	-4.7051	1.5863
3c	0.9513	0.7090	1.0000	0.7787	0.8625	-2.9340	1.0630
3d	0.9955	0.6473	1.0000	0.8436	0.9159	-4.3281	1.6680
3e	0.9766	0.6611	1.0000	0.7632	0.5602	-3.3019	1.4915

[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).

Number of hydrogen bond acceptors (O and N atoms) and number of hydrogen bond donors (NH and OH) in the synthesized compounds 3(a-e) 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.

Table 5. Bioactive score of the synthesized 2, 6-di (furan-2-yl)-4-phenylpyridine derivatives with the help of mol inspiration chemiformatics software 3(a-e)

Ligands	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
3a	0.06	-0.10	0.02	-0.08	-0.30	0.06
3b	0.20	0.08	0.11	0.17	-0.10	0.15
3c	0.12	-0.05	0.11	0.10	-0.27	0.12
3d	0.08	-0.11	0.12	-0.01	-0.25	0.12
3e	0.09	-0.12	0.03	-0.06	-0.26	-0.02

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 39.1-59.17Å 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 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 [**9, 10**].

The results clearly reveal that the physiological actions of furan C-2 coupled pyridine analogues 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.

APPLICATION

Pyridine coupled furans can be used as DNA intercalators.

CONCLUSION

The present research, reports the successful prediction of cheminformatic study of new furan; C-2 coupled pyridine derivatives. 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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