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Original Article

In silico screening of additional analogs of 6-substituted benzyloxy benzimidazole-2-carbamates in search of potent antitumor agents

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ABSTRACT

The objective of this study was to investigate the series of 6-substituted benzyloxy benzimidazole-2-carbamates fully for carrying out further structural modification and lead optimization in search of potent antitumor agents. A range of additional analogs of 6-substituted benzyloxy benzimidazole-2-carbamates were designed and were subjected to molecular properties prediction and drug-likeness. The molecular properties and bioactivity scores of these additional analogs were predicted through molinspiration software and chemdraw ultra *v* 7.0. The solubility and drug-likeness score was predicted through molsoft 2007 software. The drug likeness was also evaluated on basis of Lipinski's rule of five. The compounds fulfilled Lipinski's rule except those bearing $-C_6H_5$, $-CF_3$, 1-naphthyl and 2-naphthyl benzyloxy substituent at 6-position which were found to be lipophilic. All compounds showed good bioactivity scores for drug targets. Compounds 5a-b and 12a-b containing electron donating methoxy substituents in the aromatic side chain at 6-position of benzimidazole ring are likely to be orally active and expected to have enhanced antitumor activity. Thus they can be considered to be potential candidates for further development and optimization in the series of 6-substituted benzyloxy benzimidazole-2-carbamates.

Key words: antitumor activity, molecular properties, oral bioavailability, benzimidazole-2-carbamates.

INTRODUCTION

Benzimidazole-2-carbamate, a privileged structural motif is endowed with diverse pharmacological activities such as antifungal, anthelmintic, anticancer, antiviral and vascular damaging properties [1-11]. Due to their synthetic accessibility, extensive research work has been carried out which has led to synthesis and evaluation of a vast number of benzimidazole-2-carbamates. The anthelmintic benzimidazole-2-carbamates have been screened for their antitumor activity [12]. However factors such as low oral bioavailability due to poor aqueous solubility and rapid metabolism have precluded their use as antitumor agents [13]. A recent study carried out on anthelmintic albendazole has suggested a marked improvement in its solubility when encapsulated with cucurbit[n]uril [14]. Such studies have demonstrated that there is further scope to pursue research in the field of benzimidazole-2-carbamates in order to discover compounds possessing outstanding antitumor properties. A set of ten 6-substituted benzyloxy benzimidazole-2-carbamates have been designed, synthesized and reported to possess favorable drug-like properties and significant anti-tumor activity [15, 16].

The objective of the present study was to screen additional analogs of 6-substituted benzyloxy benzimidazole-2-carbamates to determine molecular properties, drug-likeness, lipophilicity and solubility in order to investigate the series fully using virtual screening softwares such as molinspiration, molsoft and chemdraw ultra *v* 7.0. Such studies are useful for development and optimization of series of compounds as potential lead and/or drug candidates. This further reduces the need for expensive lab work as only those molecules which possess favorable molecular properties can be taken up for further research.

MATERIALS AND METHODS

The structures of all selected 6-substituted benzimidazole-2-carbamates were drawn using

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chemdraw ultra *v* 7.0 (Fig.1). Their SMILES notations were generated and were used in online molinspiration software version 2011.06 for calculation of molecular properties and prediction of bioactivity score for drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, enzymes and nuclear receptors) [17]. The log solubility and drug-likeness scores were predicted using molsoft 2007 online software.

RESULTS

The IUPAC name of twenty six analogs of 6-substituted benzyloxy benzimidazole-2-carbamates (1a-13b) studied is represented in Table 1. The calculated values of various parameters for additional analogs of 6-substituted benzyloxy benzimidazole-2-carbamates to assess drug-likeness have been represented in Table 2. The predicted bioactivity scores of screened compounds for GPCR ligand, ion-channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor and enzyme inhibitory activity is represented in Table 3. Drug likeness model score and solubility data computed by molsoft 2007 for all the twenty six molecules is represented by a numerical value as shown in Table 4.

DISCUSSION

Drug-likeness is a virtual screening methodology that efficiently identifies molecules with highest chance to become drugs. Lipinski's rule of five is a widely used criterion to evaluate drug-likeness and provides insight in to ADME properties of synthesized compounds [18]. Additional molecular properties such as polar surface area, volume and flexibility also influence pharmacokinetics *in vivo* [19]. Octanol-water partition coefficient or log P determines hydrophobicity of a molecule and affects drug absorption, bioavailability, drug-receptor interactions, metabolism and toxicity. Compounds having log P value less than 5 are likely to exhibit good oral bioavailability. Log P values of compounds screened were found to be in the range of 2.90-4.87 with the exception of 2b which was found to be most lipophilic (log P: 5.43). Thus incorporation of 2-phenyl benzyloxy at 6-position was found to be least favorable. Compounds 2a, 9b, 11b and 13b had log P values just below 5. Compound 5a bearing 2, 3, 4, 5-tetramethoxy benzyloxy group at 6-position was found to be least lipophilic as it had a log P value of 2.90.

Molecular weight is a parameter which governs transportation across cell membranes. Drugs with molecular weight < 500 are easily transported across cell membranes. All compounds screened had molecular weight < 500. An orally active drug candidate should have not more than 5 hydrogen bond donors and 10 hydrogen bond acceptors. The number of hydrogen bond acceptors and donors of all tested compounds were found to be less than 10 and 5 respectively. But compounds 5a and 5b were found to possess considerable number of hydrogen bond acceptors. Molecular polar surface area (TPSA) is the sum of surfaces of polar atoms in a molecule and predicts drug transport properties [21]. To improve the prediction of drug-likeness; a compound should have polar surface area not greater than 140 $Å^2$. TPSA of all compounds was found to be in range of 76.25 to 113.19 (< 140 $Å^2$). Number of rotatable bonds is a measure of molecular flexibility and a determinant of oral bioavailability of drugs. Compounds having 10 or fewer rotatable bonds are predicted to have good oral bioavailability. Of all molecules investigated, compound 6b was found to be most rigid with only two rotatable bonds while 5b was most flexible. All the compounds studied had number of atoms in range of 23-31 and were found to be within limits of 20-70 atoms.

A molecule with a bioactivity score more than 0 is likely to be biologically active, a score of -0.50 to 0.00 indicates moderate activity while a score < -0.50 indicates that it will be inactive [21]. The bioactivity scores of screened compounds were found to be in range of -0.50 to 0.00 which demonstrated that investigated compounds are likely to show biological activity. The bioactivity scores of compounds screened for GPCR ligand and kinase inhibitor activity was found to be > 0.00 with the highest score observed for compound 2a. The bioactivity scores for kinase inhibitor suggested the highly bioactive nature of molecules. Bioactivity scores for nuclear receptor ligand, protease inhibitor and enzyme inhibition was found to be in range of -0.050-0.20, -0.01-0.23 and -0.03-0.26 respectively.

Drug-likeness can be further assessed by a score which can be assigned to a molecule and is a real value ranging from 0 to 1. It is a useful parameter to distinguish between drug-like and non-drug like compounds. Compounds 5a, 5b, 7a and 12a had maximum drug-likeness score of 0.83, 0.72, 0.73 and 0.70 respectively while compounds 1b and 2b had lowest drug-like scores of -0.02 and 0.07. Solubility in water can be predicted to determine the absorption and rate of action of molecules. Compounds 5a and 12a were found to have good aqueous solubility of 21.29 mg/L and 16.24 mg/L respectively whereas compounds 2b, 11a-b and 13a-b were found to have lowest aqueous solubility. Thus increasing number of methoxy groups on aromatic side chain and substitution of

methoxy groups at 2, 6-position gave compounds having desired molecular properties, solubility, and good bioactivity and drug-likeness scores. The ethyl esters 5b and 12b were also found to be most promising. Therefore, compounds 5a, 5b, 12a and 12b having methoxy groups in aromatic side chain are worth pursuing for further research to obtain molecules with better antitumor activity and desired pharmacokinetic characteristics. Thus in general, compounds with electron donating groups such as –OMe and Me in the aromatic side chain at 6-position exhibited better molecular properties over those containing electron withdrawing groups (-Cl, -CF_3). Compounds 3a and 6a are also likely to be better drug candidates whereas those containing 2-phenyl, 1-naphthyl and 2-naphthyl benzyloxy substituent are likely to be poor drug candidates.

CONCLUSION

A set of twenty-six 6-substituted benzyloxy benzimidazole-2-carbamates were designed by modifying groups on the aromatic portion of side chain at 6-position and alkyl group such as methyl and ethyl at 2-carbamate position. From the study carried out it can be concluded that the additional analogs of 6-substituted benzyloxy benzimidazole-2-carbamates possess desirable molecular properties for drug-likeness. The molecules exhibited moderate to good bioactivity scores. The compounds screened were found to be compatible with Lipinski's rule of five with the exception of compounds containing phenyl, trifluoromethyl and naphthyl benzyloxy substituent in aromatic side chain at position 6 of benzimidazole ring. Compounds 5a-b and 12a-b emerged as most promising molecules and are worth pursuing for further development.

Table 1: IUPAC names of compounds 1a-13b investigated

Cmpd No.	IUPAC name
1a	Methyl [6-(2-methyl benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
1b	Ethyl [6-(2-methyl benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
2a	Methyl [6-(2-phenyl benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
2b	Ethyl [6-(2-phenyl benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
3a	Methyl [6-(3-methoxy benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
3b	Ethyl [6-(3-methoxy benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
4a	Methyl [6-(3,5-dimethoxy benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
4b	Ethyl [6-(3,5-dimethoxy benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
5a	Methyl [6-(2, 3, 4, 5-tetramethoxy benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
5b	Ethyl [6-(2, 3, 4, 5-tetramethoxy benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
6a	Methyl [6-(3-methyl benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
6b	Ethyl [6-(3-methyl benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
7a	Methyl [6-(3-chloro benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
7b	Ethyl [6-(3-chloro benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
8a	Methyl [(6-benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
8b	Ethyl [(6-benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
9a	Methyl [6-(3-trifluoromethyl benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
9b	Ethyl [6-(3-trifluoromethyl benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
10a	Methyl [6-(4-methoxy benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
10b	Ethyl [6-(4-methoxy benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
11a	Methyl [6-(Naphthalen-2-yl methoxy)-1H-benzoimidazol-2-yl]-2-carbamate
11b	Ethyl [6-(Naphthalen-2-yl methoxy)-1H-benzoimidazol-2-yl]-2-carbamate
12a	Methyl [6-(2, 6-dimethoxy benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
12b	Ethyl [6-(2, 6-dimethoxy benzyloxy)-1H-benzoimidazol-2-yl]-2-carbamate
13a	Methyl [6-(Naphthalen-1-yl methoxy)-1H-benzoimidazol-2-yl]-2-carbamate
13b	Ethyl [6-(Naphthalen-1-yl methoxy)-1H-benzoimidazol-2-yl]-2-carbamate

Table 2: Results of molecular properties prediction of compounds 1a-13b

Cmpd No.	Log P	TPSA[1]	nAtoms[2]	Volume	MW[3]	nrotb[4]
1a	3.48	76.25	23	279.55	311.34	5
1b	4.08	76.25	24	296.35	325.37	6
2a	4.83	76.25	28	334.40	373.41	6
2b	5.43	76.25	29	351.20	387.44	7
3a	3.12	85.48	24	288.54	327.34	6
3b	3.72	85.48	25	305.34	341.37	7
4a	3.13	94.72	26	314.08	357.37	7
4b	3.73	94.72	27	330.88	371.39	8
5a	2.90	113.19	30	365.17	417.42	9
5b	3.50	113.19	31	381.98	431.44	10
6a	3.51	76.25	23	279.55	311.34	5
6b	4.11	76.25	24	296.35	325.37	2
7a	3.74	76.25	23	276.53	331.76	5
7b	4.34	76.25	24	293.33	345.79	6
8a	3.08	76.25	22	262.99	297.31	5
8b	3.69	76.25	23	279.79	311.34	6
9a	4.17	76.25	27	311.09	379.34	7
9b	4.76	76.25	28	327.89	393.37	8
10a	3.14	85.48	24	288.54	327.34	6
10b	3.74	85.48	25	305.34	341.37	7
11a	4.27	76.25	26	306.98	347.37	5
11b	4.87	76.25	27	323.79	361.40	6
12a	3.10	94.72	26	314.08	357.37	7
12b	3.70	94.72	27	330.98	371.39	8
13a	4.24	76.25	26	306.98	341.37	5
13b	4.84	76.25	27	323.79	361.40	6

1= molecular polar surface area, 2= no of atoms, 3=molecular weight, 4=no. of rotatable bonds.

Table 3: Bioactivity scores of compounds 1a-13b

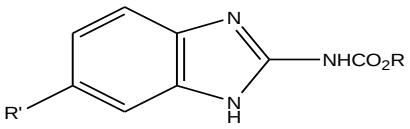
Cmpd No.	GPCR* ligand	Ion channel modulator	Kinase inhibitor	Nuclear Receptor ligand	Protease inhibitor	Enzyme Inhibitor
1a	0.14	0.03	0.36	-0.19	0.03	0.07
1b	0.11	0.04	0.27	-0.16	0.02	0.01
2a	0.29	0.23	0.50	0.03	0.20	0.26
2b	0.25	0.23	0.42	0.04	0.17	0.20
3a	0.15	0.07	0.38	-0.19	0.08	0.08
3b	0.10	0.06	0.28	-0.18	0.05	0.02
4a	0.13	0.06	0.36	-0.16	0.07	0.08
4b	0.09	0.05	0.27	-0.15	0.03	0.02
5a	0.06	0.00	0.26	-0.26	-0.02	0.02
5b	0.03	-0.01	0.18	-0.25	-0.05	-0.03
6a	0.14	0.04	0.37	-0.20	0.05	0.05
6b	0.11	0.05	0.28	-0.18	0.04	-0.00
7a	0.17	0.12	0.38	-0.21	0.06	0.08
7b	0.15	0.12	0.29	-0.19	0.05	0.02
8a	0.16	0.12	0.42	-0.21	0.08	0.12
8b	0.14	0.12	0.34	-0.17	0.08	0.06
9a	0.25	0.13	0.35	0.13	0.19	0.21
9b	0.22	0.13	0.27	0.13	0.16	0.15
10a	0.15	0.09	0.40	-0.19	0.09	0.09
10b	0.11	0.07	0.30	-0.19	0.06	0.02
11a	0.19	0.11	0.40	-0.12	0.15	0.14
11b	0.16	0.11	0.32	-0.11	0.12	0.08
12a	0.16	0.06	0.35	-0.18	0.05	0.06
12b	0.12	0.05	0.26	-0.17	0.01	0.00
13a	0.33	0.10	0.46	-0.15	0.18	0.23
13b	0.29	0.10	0.37	-0.14	0.15	0.18

** GPCR: G-protein coupled receptor*

Table 4: Predicted aqueous solubility, drug likeness scores and Lipinski's parameters

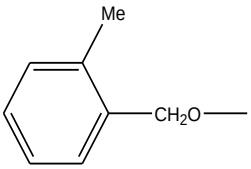
Cmpd No.	Molecular formula	Aq. solubility mg/L	Drug-likeness	nON*	nOHNH**	nviolation
1a	$C_{17}H_{17}N_3O_3$	2.94	0.23	6	2	0
1b	$C_{18}H_{19}N_3O_3$	1.29	-0.02	6	2	0
2a	$C_{22}H_{19}N_3O_3$	0.14	0.23	6	2	0
2b	$C_{23}H_{21}N_3O_3$	0.06	0.07	6	2	1
3a	$C_{17}H_{17}N_3O_4$	4.56	0.45	7	2	0
3b	$C_{18}H_{19}N_3O_4$	2.00	0.26	7	2	0
4a	$C_{18}H_{19}N_3O_5$	6.02	0.47	8	2	0
4b	$C_{19}H_{21}N_3O_5$	2.63	0.27	8	2	0
5a	$C_{20}H_{23}N_3O_7$	21.29	0.83	10	2	0
5b	$C_{21}H_{25}N_3O_7$	9.26	0.72	10	2	0
6a	$C_{17}H_{17}N_3O_3$	2.88	0.56	6	2	0
6b	$C_{18}H_{19}N_3O_3$	1.27	0.30	6	2	0
7a	$C_{16}H_{14}ClN_3O_3$	0.83	0.73	6	2	0
7b	$C_{17}H_{16}ClN_3O_3$	0.36	0.48	6	2	0
8a	$C_{16}H_{15}N_3O_3$	5.66	0.45	6	2	0
8b	$C_{17}H_{17}N_3O_3$	2.50	0.15	6	2	0
9a	$C_{17}H_{14}F_3N_3O_3$	0.65	0.54	6	2	0
9b	$C_{18}H_{16}F_3N_3O_3$	0.29	0.32	6	2	0
10a	$C_{17}H_{17}N_3O_4$	3.43	0.36	7	2	0
10b	$C_{18}H_{19}N_3O_4$	1.50	0.16	7	2	0
11a	$C_{20}H_{17}N_3O_3$	0.07	0.55	6	2	0
11b	$C_{21}H_{19}N_3O_3$	0.03	0.27	6	2	0
12a	$C_{18}H_{19}N_3O_5$	16.24	0.70	8	2	0
12b	$C_{19}H_{21}N_3O_5$	7.11	0.55	8	2	0
13a	$C_{20}H_{17}N_3O_3$	0.07	0.55	6	2	0
13b	$C_{21}H_{19}N_3O_3$	0.03	0.27	6	2	0

**nON= number of H-bond receptors, **nOHNH= number of H-bond donors*



R= -$NHCO_2Me$, -$NHCO_2Et$

R’



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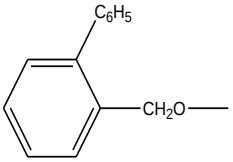

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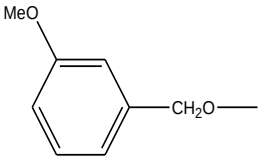
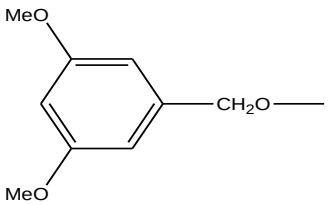


3-methoxy benzyloxy



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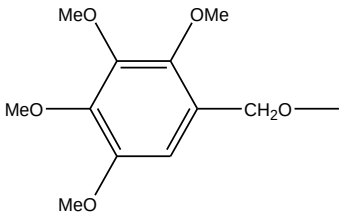
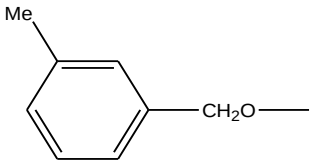


2, 3, 4, 5-tetramethoxy benzyloxy



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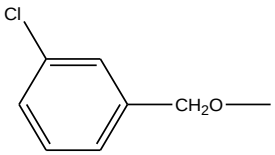

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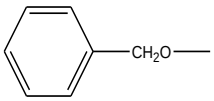
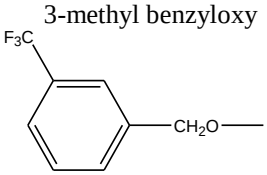


benzyloxy



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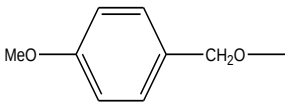
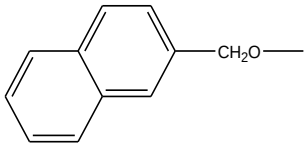


4-methoxy benzyloxy



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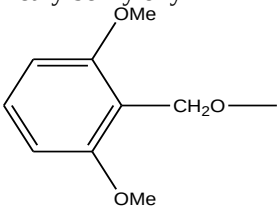
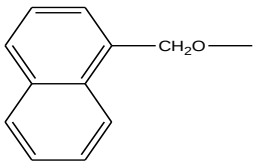


2, 6-dimethoxy benzyloxy



1-naphthyl benzyloxy

Fig.1: Structures of 6-substituted benzyloxy benzimidazole-2-carbamates designed and investigated for molecular properties prediction

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