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Antifungal Activity of Synthesized Benzothiazole Derivatives using Structure Activity Relationship

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In the field of drug discovery the benzothiazole is found to be a magical compound. Computational tools were used to predict their molecular property, drug likeness, overall drug score and toxicity risks which are essential parameter for a chemical to be qualified as a drug. As good results were observed by computational tools then novel series of 2-amino-6-substituted benzothiazoles with halo ketone have been synthesized by conventional method. All the synthesized compounds have been characterized by elemental analysis and IR, ^{1}H NMR data in full accordance with their expected (depicted) structures. The synthesized compounds were screened for their antifungal activity using standard drug ampicillin.

Keywords: Benzothiazole, Halo-ketone, Computational tool, Antifungal activity.

INTRODUCTION

Heterocyclic compounds containing N and S hetero atoms are useful material in drug research. Being a heterocyclic compound benzothiazole find use in research as a starting material for the synthesis of many bioactive structures. Several benzothiazole derivatives have been used against antiproliferative and DNA binding properties [1], anticancer and antioxidant activity against pancreatic cancer cell [2], antitumor and antiviral [3], antiinfective [4], human MCF-7cancer cell line [5], novel non-sulfamide NEDD8 activating enzyme inhibitors [6], antidepressant [7], hypoglycaemic and hypolipidemic [8], cervical cancer [9], anticonvulsant [10], anti-acetyl cholinesterase [11], kinase inhibitor [12], antituberculotic [13], antifungal [14], *Candida albicans* N-myristoyl transferase inhibition [15], antitumor [16], antimicrobial [17], diuretic activity [18], *etc*.

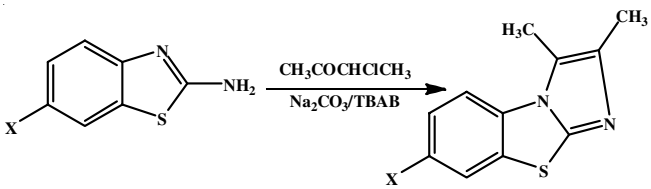
Considering the importance of this nuclei, we have reported synthesis of some new benzothiazole derivatives by conventional method. All synthesized compounds were tested for their antifungal activity using standard drug. QSAR models first summarize a supposed relationship between chemical structures and biological activity in a data-set of chemicals. In order to select the best drug candidates for the next level of research, imidazo-benzothiazoles derivative were subjected to predict toxicity risks, drug properties and bioactivity score using online OSIRIS property explorer and Molinspiration tools.

EXPERIMENTAL

The reagent grade chemicals were used with further purification. All the melting points were taken in open capillaries and are uncorrected. The purity and completion of reaction of synthesized compounds was checked by TLC studies. IR spectra were measured on FTIR Perkin Elmer Spectrophotometer using KBr disc. ^{1}H NMR was recorded in $CDCl_3$ and DMSO with tetramethylsilane (TMS) as internal standard at 400 MHz on a ECS (JEOL) NMR Spectrophotometer. The chemical shift are recorded as parts per million (ppm). Fast atom bombardment mass spectra (FABMS) were recorded at room temperature on a JEOL SX-102/DA-6000 Mass Spectrophotometer/data system using Argon/Xenon (6 kV, 10 mA) as the FAB gas. The accelerating potential was 10 kV. The elemental analysis of compound was performed on Elementar Vario EL III Carlo Erba-1108 elemental analyzer.

General procedures for the synthesis of 7/5-substituted 2,3-dimethylimidazo[1,3]benzothiazole: The required 2-

amino-6-substituted benzothiazole were synthesized by methods reported in literature [19,20]. A mixture of 2-amino-4/6-substituted benzothiazole (0.01 mol) and halo-ketone (0.01 mol) was refluxed in ethanol (20 mL). The reaction was monitored by silica gel TLC (hexane:acetone 60:40). After completion of the reaction, the reaction mixture was allowed to attain room temperature and solid separated was filtered. The crude product was recrystallized from distilled ethanol (**Scheme-I**).



Scheme-I: Synthesis of 7-substituted-2,3-dimethylimidazo[1,3]benzothiazole

7-Chloro-2,3-dimethylimidazo{2,1-b}[1,3]benzothiazole: Yield: 50 %; m.p. 135 ºC; IR (KBr, ν_{max}, cm^{-1}): 1560 (C=N), 1110 (C-N), 856 (C-Cl), 1305(C-S); ^{1}H NMR (400 MHz): 7.01-7.39 (m, 3H, Ar-H), 1.64 (s, 6H, CH_3); EI-MS *m/z*: 236.72. Elemental anal. calcd. (found) %: C 55.81 (55.79); H 3.83 (3.82); N 11.83 (11.84); S 13.54 (13.56); Cl 14.98 (14.97).

7-Bromo-2, 3-dimethylimidazo{2,1-b}[1,3]benzothiazole: Yield: 45 %; m.p. 130 ºC; IR (KBr, ν_{max}, cm^{-1}): 1529 (C=N), 1103 (C-N), 810 (C-Br), 1304 (C-S); ^{1}H NMR (400 MHz): 6.90-7.14 (m, 3H, Ar-H), 2.1 (s, 6H, CH_3); EI-MS *m/z*: 281.17. Elemental anal. calcd. (found) %: C 46.99 (46.98); H 3.23 (3.24); N 9.96 (9.95); S 11.40 (11.42); Br 28.42 (28.41).

7-Nitro-2,3-dimethylimidazo{2,1-b}[1,3]benzothiazole: Yield: 35 %; m.p. 190 ºC; IR (KBr, ν_{max}, cm^{-1}): 1580 (C=N), 1119 (C-N), 1520 (NO_2), 1319 (C-S); ^{1}H NMR (400 MHz): 7.10-7.42 (m, 3H, Ar-H), 2.2 (s, 6H, CH_3); EI-MS *m/z*: 247.27. Elemental anal. calcd. (found) %: C 53.43 (53.45); H 3.67 (3.68); N 16.99 (16.98); S 12.97 (12.99); O 12.94 (12.91).

7-Ethoxy-2,3-dimethylimidazo{2,1-b}[1,3] benzothiazole: Yield: 60 %; m.p. 210 ºC; IR (KBr, ν_{max}, cm^{-1}): 1068 (C-O-C sym.), 1270 (C-O-C asym.), 1625 (C=N), 1111 (C-N), 1325 (C-S); ^{1}H NMR (400 MHz): 6.90-7.21 (m, 3H, Ar-H), 1.78 (s, 6H, CH_3), 3.32 (q, 2H, CH_2), 2.98 (t, 3H, CH_3); EI-MS *m/z*: 247.27. Elemental anal. calcd. (found) %: C 63.39 (63.35) ; H 5.73 (5.74); N 11.37 (10.97); S 13.02 (12.87); O 6.49 (6.44).

5-Methyl-2,3-dimethylimidazo{2,1-b}[1,3]benzothiazole: Yield: 65 %; m.p. 225 ºC; IR (KBr, ν_{max}, cm^{-1}): 1536 (C=N), 1106 (C-N), 1324 (C-S); ^{1}H NMR (400 MHz): 6.99-7.30 (m, 3H, Ar-H), 2.1 (s, 6H, CH_3), 2.53 (s, 3H, Ar-CH_3); EI-MS *m/z*: 217.28. Elemental anal. calcd. (found) %: C 66.63 (66.59); H 5.59 (5.60); N 12.95 (12.88); S 14.82 (14.84).

Antifungal activity: The antifungal activity of these compounds was tested by agar diffusion method using two concentrations of the test compound, *viz*. 50 and 100 µg/mL against *Aspergillus flavus* and *Aspergillus niger*. Each compound (1 mL) was poured into a petri-dish having about 20-25 mL of molten potato-dextrose agar medium. As the medium gets solidify, petri dishes were inoculated separately with the fungal isolates and kept at 26 ºC for 96 h in incubator. The % inhibition of these compounds was calculated by using following expression:

$$\text{Inhibition (\%)} = \frac{C - T}{C} \times 100$$

where C = diameter of fungus in control and T = diameter of fungus in test compound.

RESULTS AND DISCUSSION

The synthesis of compounds 7/5-substituted-2,3-dimethylimidazo{2,1-*b*}[1,3]benzothiazole starting from 2-amino-6-substituted benzothiazole carried out by conventional method. It is noteworthy that the reaction takes time of 6-12 h in conventional methods. All the synthesized compounds have been characterized on the basis of their spectral data.

Antifungal activity: Standard drug ampicillin was used for comparison. The synthesized compounds were tested at 50 and 100 µg/mL.The results (Table-1) show that compounds **b**, **c** and **e** were highly active against *Aspergillus flavus*, while compounds **a** and **d** were active highly against *Aspergillus niger* at lower concentration 50 µg/mL.

in silico Studies on drug-like properties and bioactivity score on different human targets like GPCR, ion channel, kinase, nuclear receptor, protease and enzyme were predicted for newly proposed imadazole benzothiazole derivatives using OSIRIS Property Explorer and Molinspiration online tools to select best possible drug candidates [21-24]. They were subjected to predict the mutagenic, tumorigenic, irritant, reproductive risks, and drug-relevant properties and bioactivity score. In addition, to recognize the relationship between the physico-chemical properties and bioactivity observed for these compounds the drug likeness and bioactivity are calculated using Molinspiration software. The excellent results (Tables 2-4) further indicates the probable potentiality of these compounds as future drugs.

Conclusion

Computational tools predicted that all the synthesized compounds shows excellent drug like properties, bioactivity score and no toxicity risk. All the compounds shows remarkable antifungal activity so these compounds would be of better use in drug development against fungal infection.

TABLE-1
ANTIFUNGAL ACTIVITY OF SYNTHESIZED BENZOTHIAZOLE DERIVATIVES AT DIFFERENT CONCENTRATIONS

Compounds	Concentration (50 µg/mL)				Concentration (100 µg/mL)			
	Aspergillus flavus (mm)	Inhibition (%)	*Aspergillus flavus* (mm)	Inhibition (%)	*Aspergillus flavus* (mm)	Inhibition (%)	*Aspergillus flavus* (mm)	Inhibition (%)
a	0.7	76.6	0.6	70.0	0.1	96.7	0.4	80.0
b	0.2	93.3	0.7	65.0	0.2	93.3	0.3	75.0
c	0.2	93.3	0.7	65.0	0.2	93.3	0.1	95.0
d	0.5	83.3	0.4	80.0	0.1	96.7	0.1	95.0
e	0.2	93.3	0.7	65.0	0.4	86.7	0.2	90.0
Control	3.0	–	2.0	–	3.0	–	2.0	–

TABLE-2
COMPARISON OF MOLECULAR PROPERTIES OF 7-SUBSTITUTED 2,3-DIMETHYLIMIDAZO{2,1-b}[1,3]BENZOTHIAZOLE

Substituents at position7	Mi Log P	TPSA	N atoms	MW	n ON	n OHNH	N violation	N rotb	Volume
OCH_3	3.02	26.54	16	232.31	3	0	0	1	202.62
Br	3.77	17.31	15	281.18	2	0	0	0	194.96
F	3.12	17.31	15	220.27	2	0	0	0	182.00
Cl	3.64	17.31	15	236.73	2	0	0	0	190.61
NO_2	2.92	63.13	17	247.28	5	0	0	1	200.41
CH_3	3.41	17.31	15	216.31	2	0	0	0	193.63
C_2H_5	3.87	17.31	16	230.34	2	0	0	1	210.43
OC_2H_5	3.39	26.54	17	246.34	3	0	0	2	219.42
CH_3CO	2.86	34.38	17	244.32	3	0	0	1	212.62
COOH	2.87	54.61	17	246.29	4	1	0	1	204.07

TABLE-3
COMPARISON OF BIOACTIVITY SCORE OF 7-SUBSTITUTED 2,3-DIMETHYLIMIDAZO {2,1-b}[1,3]BENZOTHIAZOLE

Substituents at position 7	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
OCH_3	-0.70	-0.32	-0.49	-1.49	-1.41	-0.56
Br	-0.87	-0.46	-0.70	-2.01	-1.70	-0.71
F	-0.70	-0.25	-0.62	-1.84	-1.54	-0.65
Cl	-0.71	-0.26	-0.68	-1.75	-1.49	-0.66
NO_2	-0.78	-0.26	-0.52	-1.69	-1.42	-0.60
CH_3	-0.76	-0.33	-0.56	-1.81	-1.59	-0.65
C_2H_5	-0.58	-0.18	-0.50	-1.53	-1.53	-0.49
OC_2H_5	-0.65	-0.30	-0.48	-1.30	-1.30	-0.54
CH_3CO	-0.62	-0.29	-0.56	-1.54	-1.34	-0.54
COOH	-0.49	-0.20	-0.39	-1.21	-1.18	-0.35

>0- active, -5.0-0.0- moderately active, < -5.0- inactive

TABLE-4
COMPARISON OF TOXICITY RISKS AND DRUG SCORE OF 7-SUBSTITUTED 2,3-DIMETHYLIMIDAZO{2,1-b}[1,3]BENZOTHIAZOLE USING OSIRIS PROPERTY EXPLORER

Substituents at position 7	Toxicity risks				Bioavailability and Drug-Score					
	MUT	TUM	IRRIT	RE	clog p	Solubility	MW	TPSA	Drug likness	Drug Score
OCH_3	G	G	G	G	2.64	-2.36	232	54.77	-0.34	-0.64
Br	G	G	G	G	3.43	-3.17	280	45.54	-2.34	0.45
F	G	G	G	G	2.81	-2.65	220	45.54	-1.89	.51
Cl	G	G	G	G	3.31	-3.07	236	45.54	-0.02	0.62
CH_3	G	G	G	G	3.05	-2.68	216	45.54	-1.62	0.51
C_2H_5	G	G	G	G	3.47	-2.84	230	45.54	-0.59	0.58
OC_2H_5	G	G	G	G	3.04	-2.66	246	54.77	-1.88	0.5
CH_3CO	G	G	G	G	2.58	-3.02	244	62.61	-0.39	0.62
COOH	G	G	G	G	2.02	-2.35	246	82.84	-1.65	0.54

G: green (nontoxic); R: red (toxic), MUT: mutagenic; TUM: tumorigenicity; IRRIT: irritant; RE: reproductive effective.

CONFLICT OF INTEREST

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

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