Toxicity prediction of anti tuberculosis active molecules

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Abstract

The aim of the work was to understand the toxicity, physically significant descriptors and pharmaceutically relevant properties of some imidazoles obtained from the open sources that may found to be active against tuberculosis. At present five azoles were modeled for the prediction and calculation of descriptors that were carried out by means of computational approach [1].

Introduction

Current treatment of tuberculosis (TB) is based on drugs that are more than 40 years old. Drugs that are active against resistant forms of TB are less potent, more toxic, and need to be taken for a long time (18 months). The recent emergence of virtually untreatable extensively drug-resistant TB (XDR-TB) poses a new threat to TB control worldwide. Furthermore, effective treatment of TB in persons co infected with HIV is complicated due to drug–drug interactions.

Shorter and simpler regimens that are safe, well tolerated, effective against drug-susceptible and drug-resistant TB, appropriate for joint HIV–TB treatment, and amenable to routine programmatic conditions are needed urgently.

The recent treatment of tuberculosis

WHO recommends the universal use of the 6-month rifampin throughout Short Course Chemotherapy (SCC) regimen for the treatment of drug-susceptible TB. For MDR-TB and XDR-TB are, however, complicated due to long duration, high toxicity, poor tolerance, and high cost, resulting in poor outcomes. But found that some of the nitroimidazoles belonging to a novel class of

antimicrobacterial agents are active against drug susceptible and drug resistant organism for the treatment of MDRTB [2].

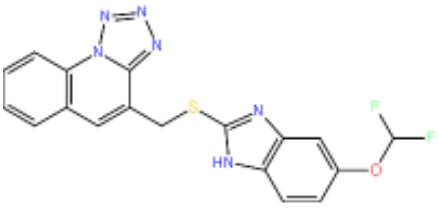
At present a study of ADME (Absorption Distribution Metabolism Elimination) of certain azoles was analyzed for predicting the ADME properties prior to expensive experimental procedures, such as HTS, can eliminate unnecessary testing on compounds that are doomed to fail, it can also focus lead optimization efforts to enhance the desired ADME properties. Finally, incorporating ADME predictions as a part of the development process will result in lead compounds that are more likely to exhibit satisfactory ADME performances during clinical trials

Nearly 40% of drug candidates fail in clinical trials due to poor ADME properties. These late-stage failures contribute significantly to the skyrocketing cost of new drug development. The ability to detect problematic candidates early will dramatically reduce the amount of wasted time and resources, and streamline the overall development process.

Materials and methods

We used the following molecules for the toxicity prediction.

1



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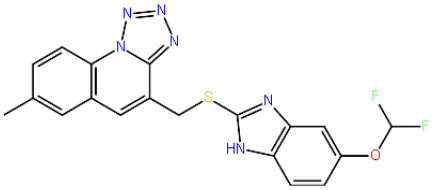

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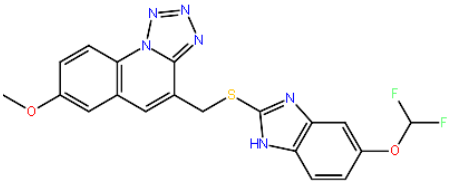

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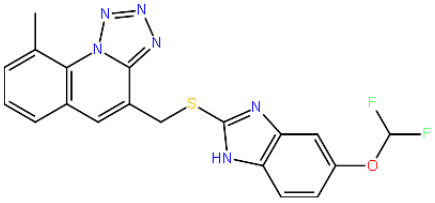

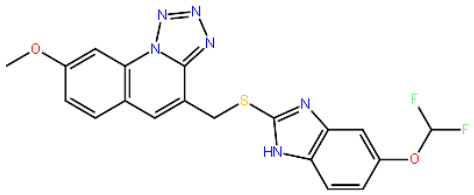

Method

The molecules obtained from the open source was modeled, minimized and were uploaded for the descriptor and toxicity prediction and the results were tabulated in the respective tables 1, 2 and 3.

Results and Discussions

The results for the each molecule are tabulated.

Table 1.

Principal descriptors:

S.No.	Descriptors	Molecule 1	Molecule2	Molecule 3	Molecule 4	Molecule 5	Range
1	mol MW	398.389	412.416	428.415	412.416	428.415	103.0/725.0
2	dipole	11.646	12.18	12.395	11.838	11.447	1.0/12.5
3	SASA	650.293	683.244	687.03	672.599	686.944	300.0/1000.0
4	FOSA	51.524	140.243	143.359	124.598	143.892	0.0/750.0
5	FISA	131.926	131.99	131.761	119.372	131.651	7.0/330.0
6	PISA	342.267	286.469	287.093	303.779	286.675	0.0/450.0
7	WPSA	124.576	124.542	124.817	124.85	124.727	0.0/175.0
8	volume	1117.714	1178.377	1192.293	1166.266	1192.173	500.0/2000.0
9	PSA	84.097	84.108	92.34	81.341	92.235	7.0 / 200.0
10	Rotatable bonds	4	4	5	4	5	0.0 / 15.0
11	donorHB	1	1	1	1	1	0.0 / 6.0

12	accptHB	4.5	4.5	5.25	4.5	5.25	2.0 / 20.0
13	glob	0.800958	0.789669	0.791489	0.796662	0.791535	0.75 / 0.95
14	IP(eV)	9.034	9.025	9.006	9.026	9.003	7.9 / 10.5
15	EA(eV)	1.878*	1.835*	1.873*	1.824*	1.794*	-0.9 / 1.7

Table 2.

Predictions for Properties:

S.No.	Descriptors	Molecule 1	Molecule 2	Molecule 3	Molecule 4	Molecule 5	Range
1	QPpolrz	39.277	41.172	41.093	40.853	41.084	13.0/70.0
2	QPlogPC16	11.795	12.013	12.15	11.918	12.144	4.0 / 18.0
3	QPlogPoct	19.164	19.767	20.164	19.57	19.899	8.0 / 35.0
4	QPlogPw	9.568	9.268	9.798	9.275	9.794	4.0 / 45.0
5	QPlogPo/w	4.366	4.681	4.456	4.715	4.456	-2.0 / 6.5
6	QPlogS	-6.366	-6.957*	-6.58*	-6.767*	-6.578*	-6.5 / 0.5
7	CIQPlogS	-6.836	-7.124	-7.149	-7.124	-7.149	-6.5 / 0.5
8	QPlogKhsa	0.604	0.766	0.609	0.735	0.609	-1.5 / 1.5
9	QPlogBB	-0.743	-0.783	-0.834	-0.625	-0.833	-3.0 / 1.2
10	Primary metabolites	2	3	3	3	3	1.0 / 8.0
11	CNS	-1	-1	-1	0	-1	(-- to ++)
12	QPlog HERG	-6.385	-6.302	-6.275	-6.271	-6.272	concern below -5
13	QPPCaco	555.71	554.937	557.709	730.963	559.058	<25 poor, >500
14	QPPMDCK	1261.799	1259.362	1270.561	1702.802	1272.43	<25 poor, >500
15	QPlogKp	-2.361	-2.559	-2.456	-2.265	-2.456	Kp in cm/hr

16	Rule Of Five	0	0	0	0	0	Maximum is 4
17	Rule Of Three	1	1	1	1	1	maximum is 3
18	Percent Human Oral Absorption	100	100	100	100	100	100

* indicates the violation of the rules.

Table 3.

Similarity search:

S.No.	Molecules	Name	Percentage %
1	Molecule 1	Timiperone, Benperidol, Quinestradol Talniflumate, Metergoline	86.33, 85.32, 85.22, 84.63, 84.45
2	Molecule 2 and molecule 4	Talniflumate ,Metergoline, Tioclomarol Quinestradol, Estramustine	87.58, 86.37, 84.76, 84.71, 84.26
3	Molecule 3 and molecule 5	Talniflumate, Losartan, Tioclomarol Perospirone, Timiperone	88.20, 86.42, 85.77, 85.24, 84.30

From the above results the azoles have been analyzed in such a way that the molecule 2 to5 were violating two of the parameter in the principal descriptors and predictions for properties as mentioned in the tables. Also, molecule 1 was violating the parameter solute Electron Affinity in principal descriptors. The molecules similar to the known compounds were also tabulated. These molecules are showing more drug like properties with less toxicity, for which they can be screened against any of the targets in Mycobacterium Tuberculosis in designing the future TB drug.

References

1. QikProp, version 3.3, Schrödinger, LLC, New York, NY, 2010.
2. Christian L., Andrew V., and Mario C. R., New drugs and new regimens for the treatment of tuberculosis, review of the drug development pipeline and implications for national programmes, 2010, 16,186–193.