Research Article
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Quantitative structure–activity relationship (QSAR) studies on a series of benzylidene oxazolidinedione and thiazolidinedione derivatives as 17β-HSD3 inhibitors

Abstract

A promising family of 17β-HSD3 inhibitors with potential uses in treating androgen-dependent disorders includes benzylidene oxazolidinedione and thiazolidinedione derivatives. As possible inhibitors of 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD3), an enzyme involved in the manufacture of androgens, these substances have drawn a lot of interest. A prospective therapeutic approach for the management of androgen-dependent illnesses, such as prostate cancer and hirsutism, is the inhibition of 17β-HSD3. 49 benzylidene oxazolidinedione and thiazolidinedione derivative having inhibitory action against 17-HSD3 were modelled using QSAR approach. The GA-MLR analysis reveals that the three variable model is most suitable for forecasting the inhibitory activity of novel 17-HSD3 inhibitors.

Keywords: quantitative structure–activity relationship, benzylidene oxazolidinedione, thiazolidinedione derivatives, 17β-HSD3 inhibitors

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Abbreviations: 17β-HSD3,17β-hydroxysteroid dehydrogenase type 3; DRE, digital rectal exam; PSA, prostate-specific antigen; LHRH, luteinizing hormone to suppress androgenic activity

Introduction

One of the most often diagnosed tumors in males, prostate cancer is a major global cause of illness and mortality. It originates from the prostate gland's cells, a walnut-sized gland that is situated in front of the rectum and beneath the bladder. Although prostate cancer normally develops slowly and may not initially show any signs, it can eventually become more aggressive and spread to other body organs. Although there is no known cause for prostate cancer, there are several risk factors that have been discovered, including age, family history, ethnicity, and lifestyle elements including diet and exercise. Prostate cancer is more common in men over the age of 65, and incidence rises with age. Prostate cancer is more common in African-American males than in men of other ethnicities, and a family history of the disease is a major risk factor.

Prostate-specific antigen (PSA) blood levels and a digital rectal exam (DRE) are frequently used to make the diagnosis of prostate cancer. To confirm the diagnosis and to ascertain the degree and severity of the cancer, other diagnostic procedures, such as a prostate biopsy, may be required. The stage and severity of the tumor, as well as the patient's general health influence the treatment options for prostate cancer. Watchful waiting, active surveillance, surgery, radiation therapy, hormone therapy, and chemotherapy are all possible forms of treatment. Curing cancer or reducing its growth while managing symptoms are the two main objectives of treatment.

The causes, prevention, and treatment of prostate cancer are the subject of current research. The development of customized medicine and genetic testing may make it possible to identify individuals who are at a high risk of developing prostate cancer and allow for adjusting treatments to their specific needs. Furthermore, ongoing clinical trials are looking into new prostate cancer therapies and potential biomarkers. There are numerous risk factors for prostate cancer as well as a variety of treatment choices, making it a serious health problem for men all over the world. The diagnosis, management, and prevention of this disease may be improved with further study and clinical trials.[1,2]

The incidence of prostate cancer has been steadily rising over the past few decades. It is the second most common type of cancer in Western men and the most common among men over 50. Despite being highly treatable if caught early, prostate cancer still claims the lives of tens of thousands of men each year, making it a significant public health issue.[3,4]

Metastasis cases are treated with hormone therapy that uses analogues of luteinizing hormone to suppress androgenic activity (LHRH). But each method has major downsides and risks that affect the patient's quality of life. Since the prostate needs androgenic hormones to grow and develop properly, controlling androgenic receptor activity and/or stopping the production of androgenic hormones are important ways to treat disease.[4–6] The first mechanism of action is used by medications like flutamide, bicalutamide, enzalutamide, and apalutamide (ARN-509), while the second mechanism is used by abiraterone (Figure 1).[7]

The enzyme 17-hydroxysteroid dehydrogenase type 3 **17βHSD3**, which is overexpressed in hormone-dependent prostate cancer and converts androstenedione to active androgen testosterone, is one potential target for prostate cancer chemotherapy.[8–10]

Materials & methods

Using a series of forty-nine derivatives of benzylidene oxazolidinedione and thiazolidinedione, we attempted to create a quantitative structure activity relationship model in this current work. These compounds, which exhibit the capacity to block the **17βHSD3** enzyme, were taken from the literature.[7] The in vitro ability of each substance to inhibit the enzyme **17βHSD3** was tested. To achieve

symmetrically distributed data, the data originally presented as half-maximal inhibitory concentration (IC_{50}, in nM) were changed to -log IC_{50} (pIC_{50}). All forty-nine derivatives of benzylidene oxazolidinedione and thiazolidinedione and their inhibitory activities are reported in Table 1.

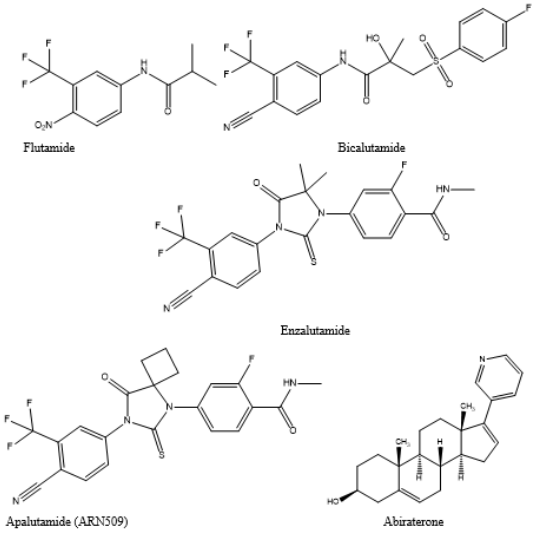


Figure 1 Various structure of chemical compounds.

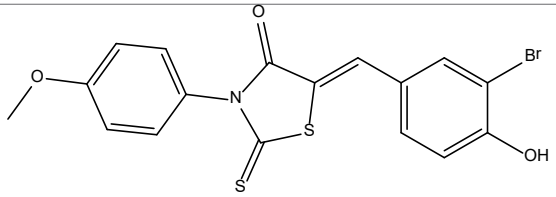
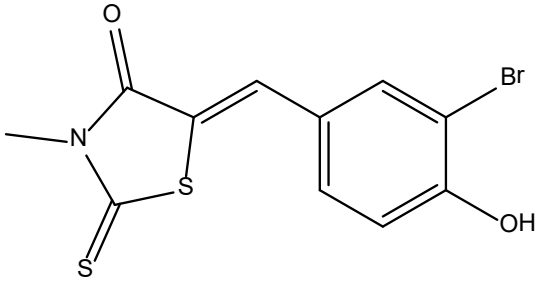
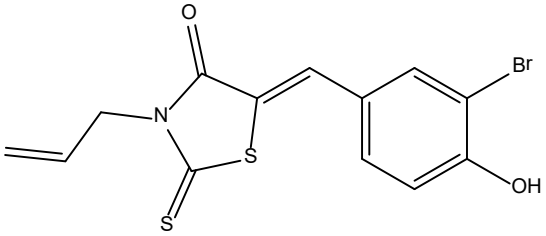
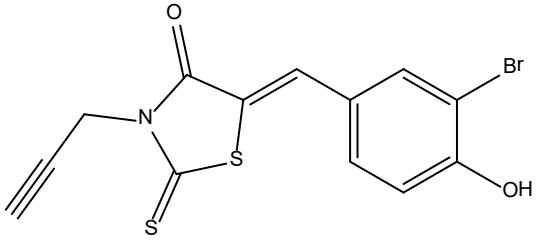
The molecular structures of these 49 compounds were drawn using ACD Chemsketch Software[11] and these molecular structures were minimized using the MM994X force field(Figure 3).

A total of 5666 molecular descriptors, including physicochemical and topological descriptors, were calculated using the Alva descriptor software (alvaDesc).[12] The Alva descriptor software was used to remove constant, near constant, and descriptors with pair absolute correlation bigger than 0.95 from hundreds of calculated descriptors2 only includes the descriptors with a significant relationship to the activity. The QSAR analysis was further developed using these descriptors.

Results and discussion

The current dataset was constructed from literature[7] which include benzylidene oxazolidinedione and thiazolidinedione compounds that inhibit 17**βHSD3**. A training set and a test set have been created from the data set. 37 compounds, or 75% of the total of 49 compounds, were chosen as the training set by random selection and were utilized to create the QSAR model. The test set for assessing the predictability of the constructed model was the remaining 25% of compounds, or 12 compounds. The test set compounds are indicated with a "*" mark in Table 1, and the compounds presented with a "#" mark are outliers and these compounds were not included in QSAR model development.

Table 1 A series of benzylidene oxazolidinedione and thiazolidinedione and their activity values

Compd no	Molecular structure	pIC_{50}
1.		7.85
2		6.05
3*		6.92
4		6.52

Citation: Vishwakarma S, Parihar SS, Shaik B, et al. Quantitative structure–activity relationship (QSAR) studies on a series of benzylidene oxazolidinedione and thiazolidinedione derivatives as 17β-HSD3 inhibitors. *MOJ Toxicol.* 2023;7(1):27–36. DOI: 10.15406/mojt.2023.07.00175

Table 1 Continued.....

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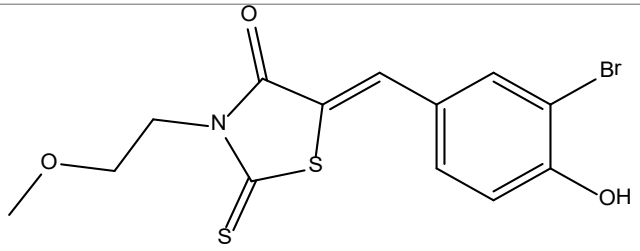
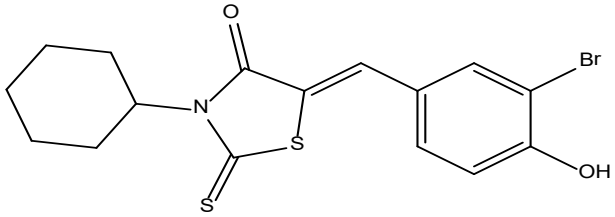
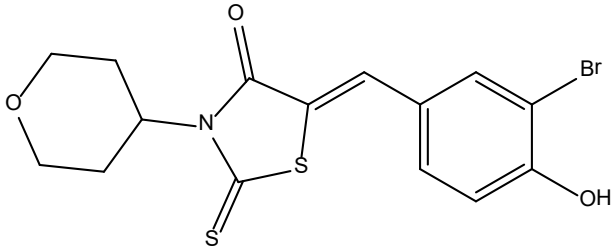
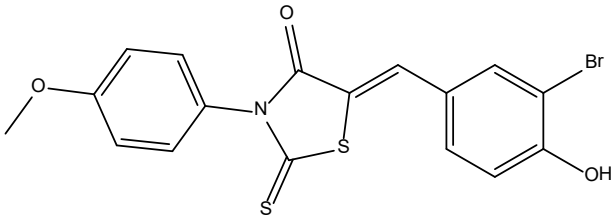
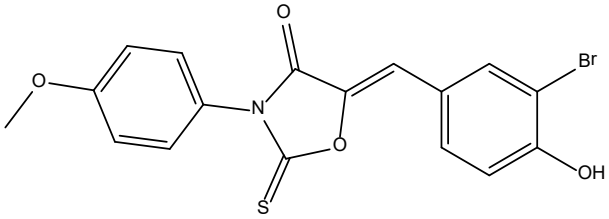
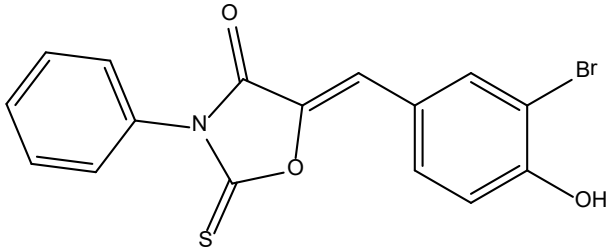
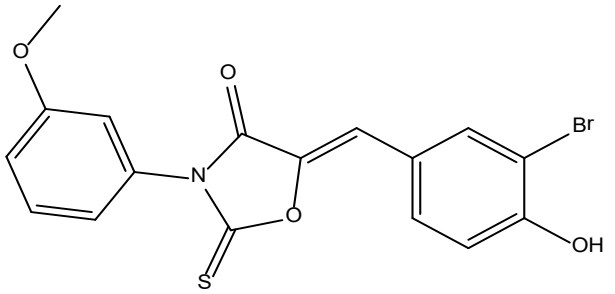
5		6.72
6		8.52
7		7.12
8*		7.05
9		7.89
10		8.22
11*		8.15

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Table 1 Continued.....

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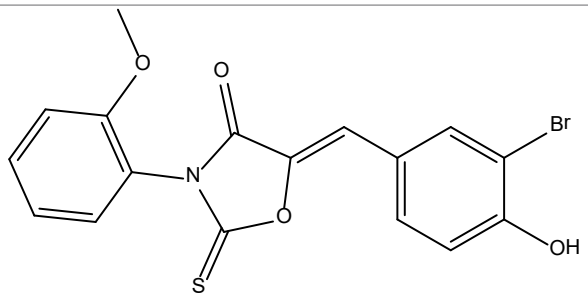
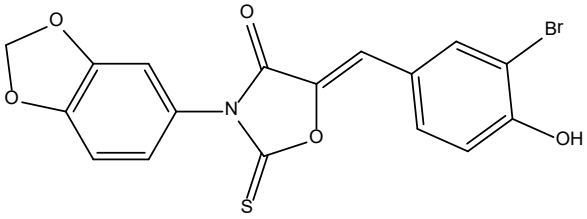
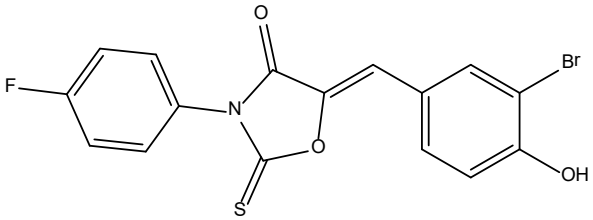
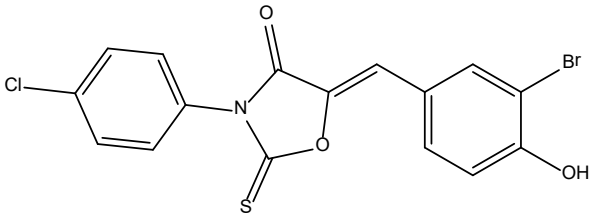
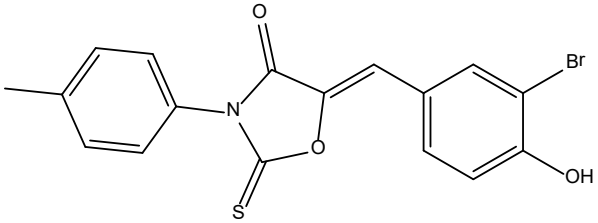
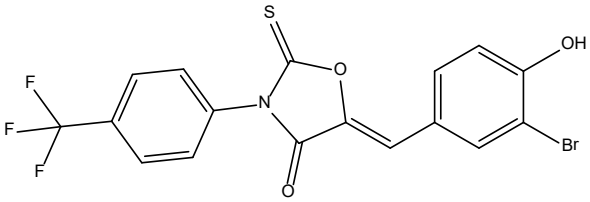
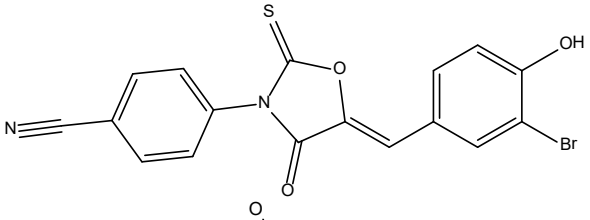
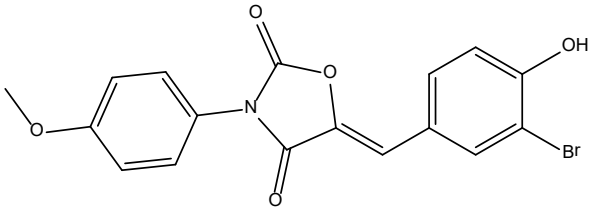
12*		7.22
13		8.10
14		8.70
15		8.22
16		8.70
17*		8.52
18		7.72
19		7.64

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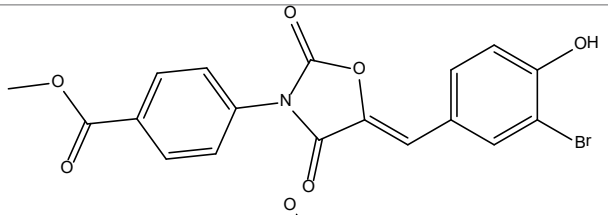
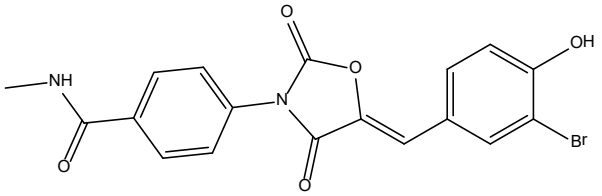
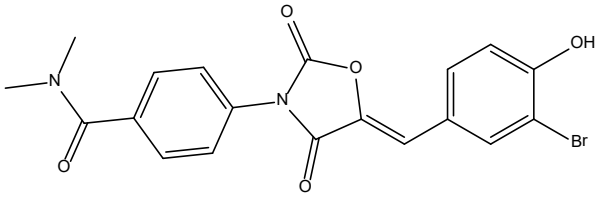
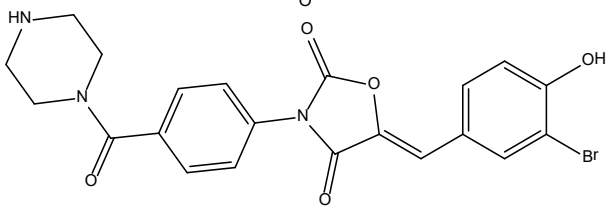
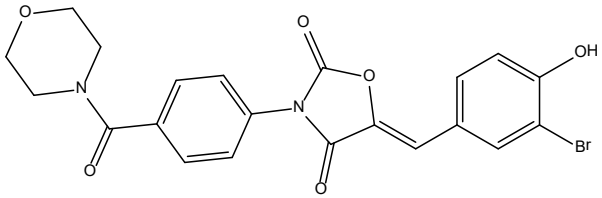
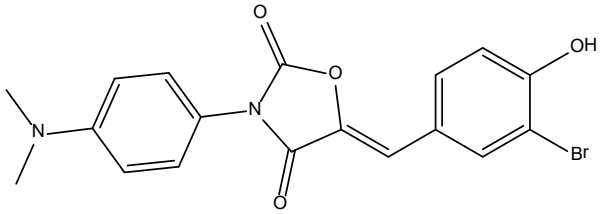
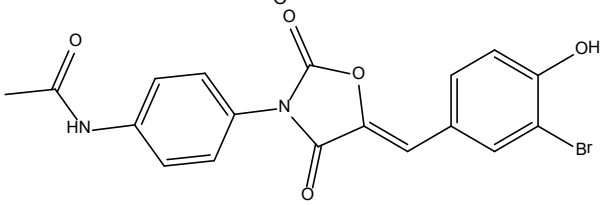
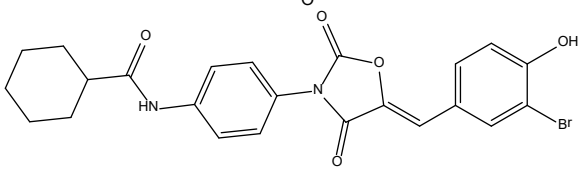
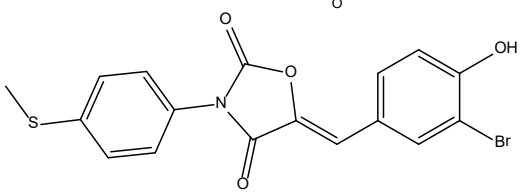
20		7.62
21*		7.25
22*		7.60
23*		7.38
24		6.52
25		7.60
26		7.24
27		7.68
28*		7.05

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Table 1 Continued....

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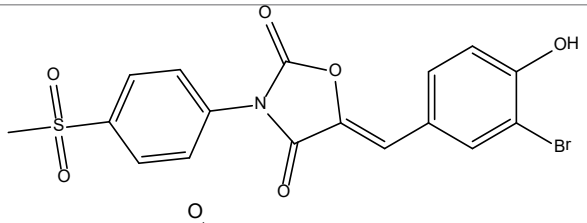
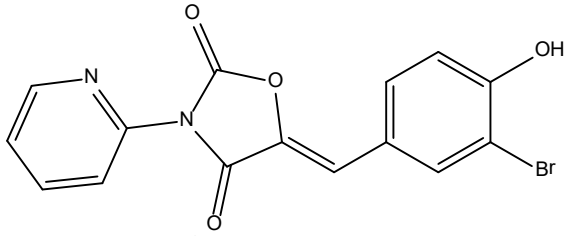
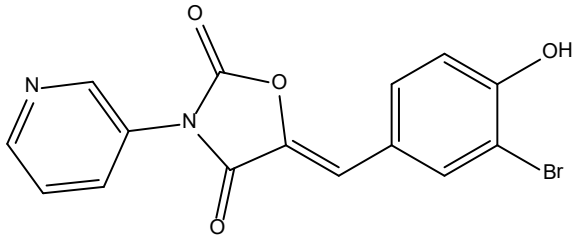
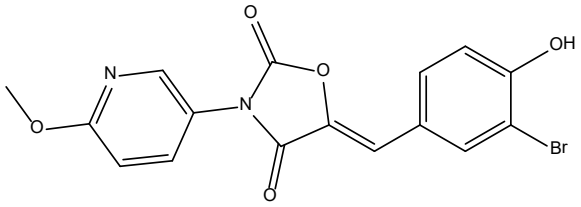
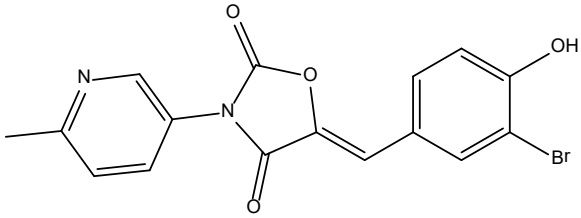
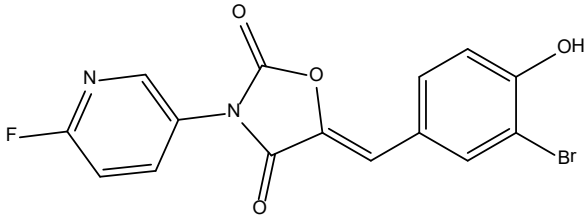
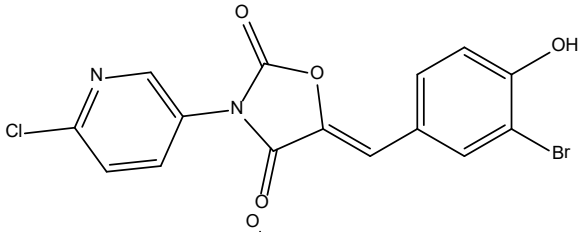
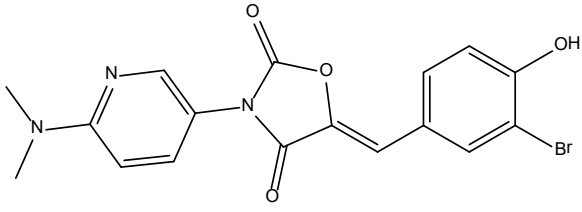
29		6.05
30		7.13
31*		7.67
32*		8.40
33#		7.17
34		7.68
35		7.70
36		8.40

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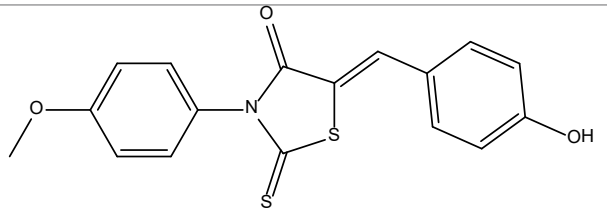
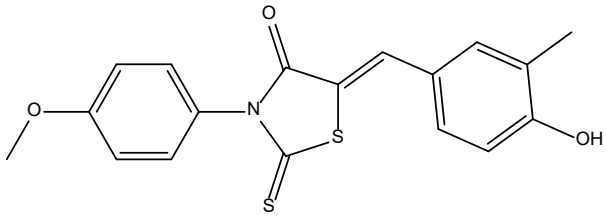
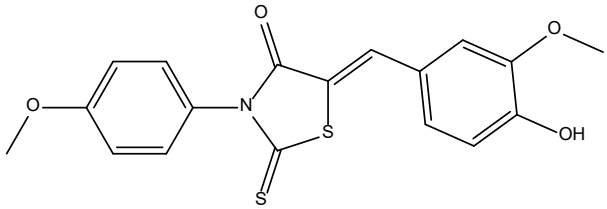
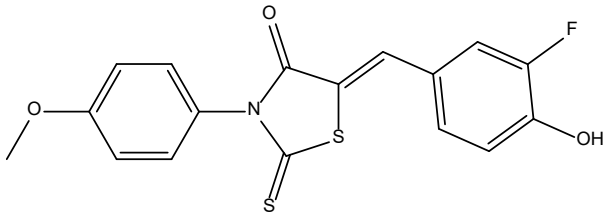
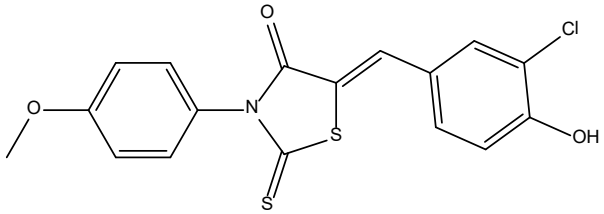
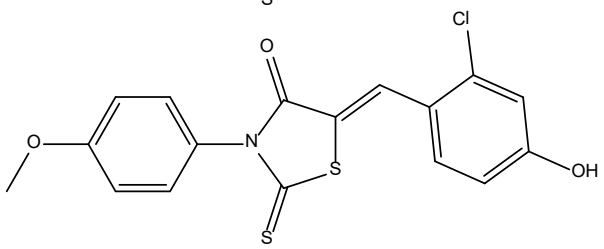
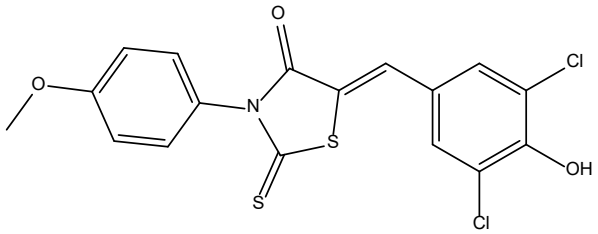
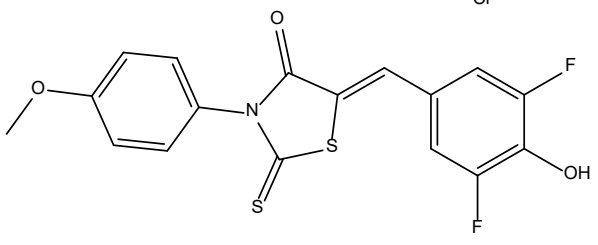
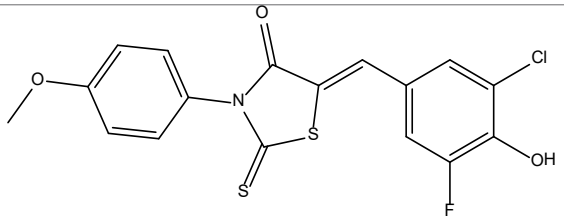
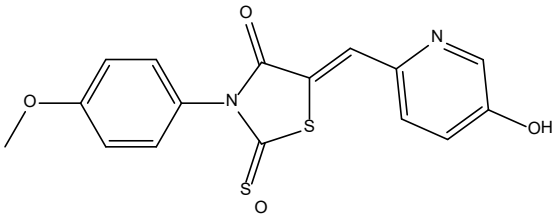
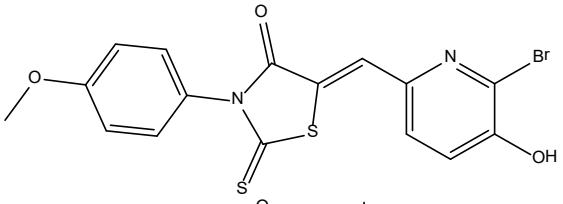
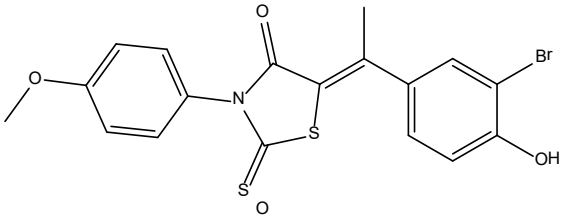
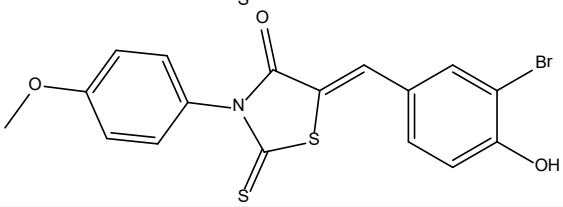
37		6.91
38		7.70
39		6.60
40		8.70
41		8.40
42		8.30
43		7.92
44		8.30

Table 1 Continued....

Compd no	Molecular structure	pIC_{50}
45		9.00
46*		7.05
47		7.40
48#		7.05
49		7.05

Multiple regression analysis was carried out using NCSS statistical software[13] on the compounds in the training set in order to create a significant relationship between pIC_{50} and the calculated descriptors of the molecules. Table 2 is a list of all potential and statistically significant models obtained from multiple linear regression analysis. This table makes it obvious that nine correlations with one variable, seven correlations with two variables and six correlations with three variables were obtained.

The following provides the three variables' most significant correlation.

Equation 1 (Eq.1)

$$pIC_{50} = -28.1319(\pm 6.6477)\ GATS2m - 4.9467(\pm 1.3559)\ MATS8i - 1.3098(\pm 0.9328)\ MATS8i + 22.3189 \quad (1)$$

$$N = 35, r^2 = 0.7807, r^2_{adj} = 0.7594, S = 0.3783, F = 36.7789, r^2_{cv} = 0.7053, r^2_{pred} = 0.5722$$

In the above Eq. (1) the symbols n denotes the number of data points used in the correlation, r^2 is the square of the correlation coefficient, r^2_{cv} is the square of cross-validated correlation coefficient obtained by the leave-one-out (LOO) jackknife procedure, and r^2_{pred} is the square of correlation coefficient obtained for test set compounds to judge the external validity of the correlation.

The correlation is supposed to be valid and has a good internal predictive ability if $r^2_{cv} > 0.60$. Similarly, the external predictive ability of the model is supposed to be good if it's $r^2_{pred} > 0.5$. The above three-variable model Eq.1 fulfills the requirement of both parameters, so the correlation expressed by Eq. 1 is found to be extremely valid. Among the remaining two statistical parameters, s and F, s is the standard deviation, and F is the Fischer-ratio between the variances of the calculated and observed activities. Thus, the three variables used in this correlation are found to be quite significant, and if they are removed one by one, the significance of the correlation is appreciably dropped (Eqs. 2 to 3).

Equation 2 (Eq.2)

$$pIC_{50} = -29.0131(\pm 7.3156)\ GATS2m - 4.8894(\pm 1.4982) + 1.3098(\pm 0.9328)\ Mor24p + 22.9204 \quad (2)$$

$$N = 35, r^2 = 0.7226, r^2_{adj} = 0.7053, S = 0.4187, F = 41.6866, r^2_{cv} = 0.6906, r^2_{pred} = 0.4936$$

Equation 3 (Eq.3)

$$pIC_{50} = 1.3495(\pm 0.6269)\ gmax - 9.3919 \quad (3)$$

$$N = 35, r^2 = 0.3675, r^2_{adj} = 0.3484, S = 0.6226, F = 19.1778, r^2_{cv} = 0.3132, r^2_{pred} = 0.0241$$

Thus, from the above results, Eq. 1, 2, and 3 have a significant correlation between the inhibitory activity values and the structural descriptors of the compounds. The internal and external validation parameters r^2_{CV}, r^2_{pred}, $average\, r^2\, m, \Delta r^2\, m$ were also determined and recorded in Table 2.

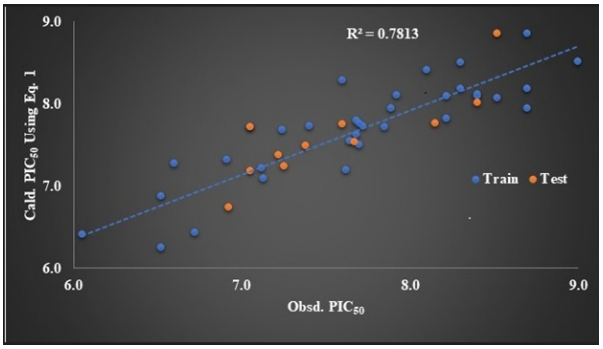


Figure 2 Correlation Between Observed and Calculated pIC_{50} Using eq. 1.

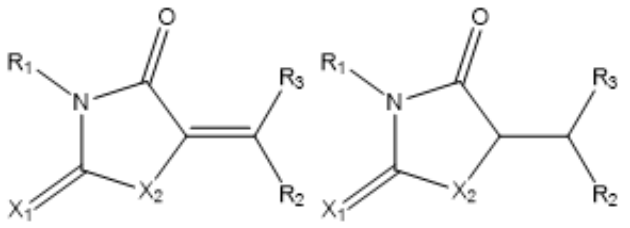


Figure 3 Basic molecular structure of the benzylidene oxazolidinedione and thiazolidinedione used in the present study.

Using the obtained models suggested in Table 2, we have predicted the pIC_{50} values, which are recorded in Table 3. A graph is drawn between the predicted and observed activities for both the training and test sets using models Eq. 1, which are recorded Table 3 and same has been depicted in Figure 2. This figure demonstrates the models' strong ability to inhibit the 17**βHSD3.** Figure 3 representing the best three-variable model, shows that almost all the points, except a few, lie near the straight line. The three-variable model is therefore the most effective model for estimating the activity of the current collection of chemicals, as demonstrated by the above statistical results using Eq. 1.

Table 2 Regression parameters and quality of correlation

Model no	Variable names	R^2	R^2adj	S	F-ratio	Q^2loo	R^2 pred	Average □²□	Δ□²□
1.	gmax	0.3675	0.3484	0.6226	19.1778	0.3132	0.0241	-0.005	0.0447
2.	GATS2m Mor24p	0.7226	0.7053	0.4187	41.6866	0.6601	0.4186	0.244	0.3079
3.	GATS2m Mor24p MATS8i	0.7807	0.7594	0.3783	36.7789	0.7053	0.5722	0.4005	0.3281

Table 3 Observed and calculated pIC_{50} values of three variable model

S. No.	Status	pIC_{50}		ΔpIC_{50}	Pred loo
		Obsd	Cal by eq 1		
1	Training	7.85	7.72	-0.13	7.71
2	Training	6.05	6.41	0.36	6.53
3	Prediction	6.92	6.74	-0.18	-
4	Training	6.52	6.26	-0.26	6.21
5	Training	6.72	6.44	-0.28	6.31
6	Training	8.52	8.07	-0.45	7.93
7	Training	7.12	7.22	0.1	7.24
8	Prediction	7.05	7.72	0.67	-
9	Training	7.89	7.95	0.06	7.96
10	Training	8.22	8.1	-0.12	8.09
11	Prediction	8.15	7.76	-0.39	-
12	Prediction	7.22	7.38	0.16	-
13	Training	8.1	8.41	0.31	8.44
14	Training	8.7	8.19	-0.51	8.15
15	Training	8.22	7.82	-0.4	7.8
16	Training	8.7	8.86	0.16	8.9
17	Prediction	8.52	8.86	0.34	-
18	Training	7.72	7.73	0.01	7.73
19	Training	7.64	7.55	-0.09	7.54
20	Training	7.62	7.2	-0.42	7.09
21	Prediction	7.25	7.24	-0.01	-
22	Prediction	7.6	7.75	0.15	-
23	Prediction	7.38	7.49	0.11	-
24	Training	6.52	6.88	0.36	6.97
25	Training	7.6	8.29	0.69	8.36
26	Training	7.24	7.68	0.44	7.71
27	Training	7.68	7.8	0.12	7.8
28	Prediction	7.05	5.76	-1.29	-

Citation: Vishwakarma S, Parihar SS, Shaik B, et al. Quantitative structure–activity relationship (QSAR) studies on a series of benzylidene oxazolidinedione and thiazolidinedione derivatives as 17β-HSD3 inhibitors. *MOJ Toxicol.* 2023;7(1):27–36. DOI: 10.15406/mojt.2023.07.00175

Table 3 Continued.....

S. No.	Status	pIC_{50}		ΔpIC_{50}	Pred loo
		Obsd	Cal by eq 1		
29	Training	6.05	5.78	-0.27	5.49
30	Training	7.13	7.1	-0.03	7.1
31	Prediction	7.67	7.54	-0.13	-
32	Prediction	8.4	8.02	-0.38	-
33	Excluded	7.17	-	-	-
34	Training	7.68	7.63	-0.05	7.62
35	Training	7.7	7.5	-0.2	7.49
36	Training	8.4	8.1	-0.3	8.05
37	Training	6.91	7.32	0.41	7.36
38	Training	7.7	7.76	0.06	7.76
39	Training	6.6	7.28	0.68	7.45
40	Training	8.7	7.95	-0.75	7.9
41	Training	8.4	8.12	-0.28	8.11
42	Training	8.3	8.18	-0.12	8.17
43	Training	7.92	8.11	0.19	8.12
44	Training	8.3	8.5	0.2	8.53
45	Training	9	8.52	-0.48	8.47
46	Prediction	7.05	7.19	0.14	-
47	Training	7.4	7.73	0.33	7.75
48	Excluded	7.05	-	-	-
49	Training	7.05	7.72	0.67	7.74

Conclusion

49 benzylidene oxazolidinedione and thiazolidinedione derivative having inhibitory action against 17**βHSD3** were used to create a QSAR model in this investigation. The models obtained through Multiple linear regression (MLR)analysis validated by internal and external validation, demonstrating that it is substantial, devoid of chance correlation, and capable of making accurate predictions. The model is sufficiently reliable to predict the inhibition of novel, 17**βHSD3** inhibitors of the target enzyme. The Eq. 1, also suggests that 2D autocorrelation weighted by mass and ionization potential and 3D-MoRSE descriptors weighted by polarizability will play a vital role while designing the novel molecules of 17**βHSD3** inhibitors.

Acknowledgments

None.

Conflicts of interests

The authors declare there are no conflicts of interest.

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