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QSAR studies on a series of biphenyl carboxamide analogues for analgesic activity

Abstract

Anti-inflammatory medicines are frequently used to treat inflammation-related conditions such as rheumatoid arthritis and osteoarthritis as well as pain, fever, and other symptoms. In the present case quantitative structure activity relationship studies have been performed on a series of biphenyl carboxamide analogs acting as anti-inflammatory drugs. The biological activity in terms of logBA has been modeled for the twenty-five biphenyl carboxamide derivatives. Multiple linear regression analysis revealed a statistically significant model comprising of two variables to be the best. The R^2 value for the training set model comes out to be 0.800. The predicted R^2 comes out to be 0.7217 suggesting that the two variable model is good. The model will help to design some novel biphenyl carboxamides with potent analgesic activity.

Keywords: biphenyl carboxamide derivatives, analgesic activity, QSAR studies, topological descriptors

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Introduction

Analgesics, which work on the peripheral or central nerve systems to relieve pain, include paracetamol (acetaminophen), nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, aryl acetic acids, anthranilic acid derivatives, and propionic acid derivatives. When choosing analgesics, the degree and type of pain, such as neuropathic pain, are taken into account. The WHO pain ladder, which was primarily created for pain due to cancer, is frequently used to locate suitable analgesics in a stepwise manner.[1]

Although the exact mechanism of action of paracetamol/acetaminophen is uncertain, it appears that it acts on the brain's nerve terminals rather than the peripheral nervous system. By inhibiting cyclooxygenases, aspirin and other nonsteroidal anti-inflammatory medications (NSAIDs) reduce the generation of prostaglandins. This reduces inflammation and pain. Both paracetamol and aspirin have one aromatic center and one carboxyl group center as a pharmacophoric characteristics.[2-5]

Overdosing on paracetamol can result in serious, potentially fatal liver and kidney damage despite the drug's generally low risk of side effects.[6-8] Non-steroidal anti-inflammatory drugs can raise the risk of hemorrhage by impairing platelet function, which increases the risk of hemorrhage as well as peptic ulcers, renal failure, allergic reactions, and hearing loss. It had been postulated that the ulceration was brought on by the presence of carboxyl group function.[9,10]

There are two biphenyl analgesics on the market: flurbiprofen and diflunisal. Diflunisal inhibits the synthesis of prostaglandins,[11] whilst flurbiprofen lessens the hormone that fuels the body's inflammatory and pain-producing processes. The anti-inflammatory, antimicrobial, insecticidal, antidiabetic, cytotoxic, leishmanicidal, trypanocidal, and antimycobacterial activities of biphenyl-4-carboxylic acid have been demonstrated.[12-17]

In the past, pharmacophore modelling, docking, and 3D QSARs[9,10] have all been used to study biphenyl drugs. The typical structure seen in the majority of non-steroidal anti-inflammatory drugs included one acidity center and two aromatic ring centers as a pharmacophoric component. The cause of non-steroidal anti-inflammatory drugs ulcerogenic was also shown to be a carboxyl group or any other sour center. Recently, it has been found that nonacidic compounds, such as carboxyl groups, are potent NSAIDs.

COX-2 inhibitors have been created as a result of the addition of a third aromatic center for almost 20 years. Recently, rofecoxib and valdecoxib were taken off the market due to reports of adverse cardiovascular consequences. As a result, the molecule interacted with additional biological receptors as a result of the inclusion of a third aromatic core, having negative side effects. Prasanna Datar et al.[18] have synthesized and assessed the analgesic effect of biphenyl carboxamide in order to examine the analgesic activity of compounds containing a biphenyl nucleus replaced with a carboxamide linkage at position 2.

Materials and methods

Shah et al.[19] reported twenty-five substituted significant analogues of flurbiprofen [4'-methylbiphenyl-2-(substituted phenyl) carboxamide derivatives] for anti-inflammatory properties were selected for this study. The activity of these molecules was reported by Shah et al.,[19] as the percent inhibition required to inhibit carrageenan-induced rat paw edema. The activity was transformed into a logarithmic value (logBA).

A Series of twenty-five biphenyl carboxamide derivatives were taken from the literature.[19] The molecular structures of all 25 compounds were drawn using Chem sketch software developed by Advance chemistry development[20] and these structures were reported in Table 1. The energy minimization of these structures was done using the MM994X force field. Table 1 also records the logBA values of these compounds. Five thousand six hundred sixty-five descriptors, including 0D, 1D, 2D, and 3D, were calculated using Alva descriptor software.21 Among thousands of descriptors, only those descriptors are listed in Table 1, which are found to be suitable and to govern the activity of the compounds are as below:

H0e = H autocorrelation of lag0 / weighted by Sanderson electronegativity

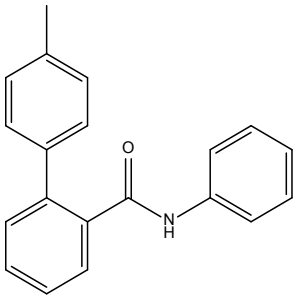
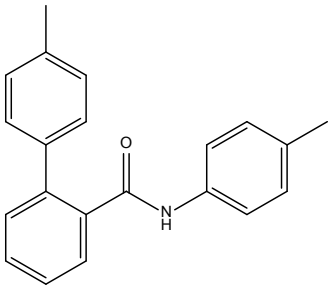
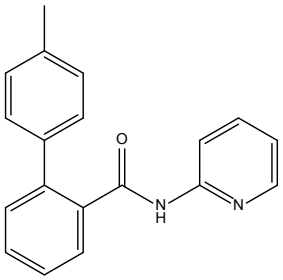
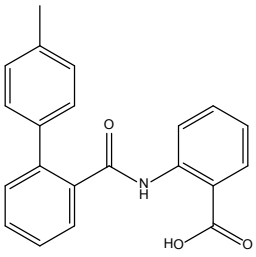
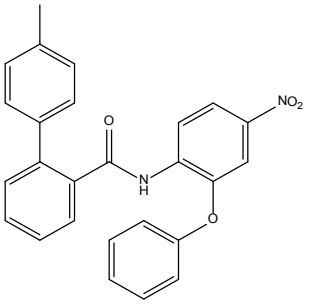
DISPs = displacement value / weighted by I-state

Depressant-80 (IP1) = Ghose-Viswanadhan-Wendoloski antidepressant-like index at 80%

Results and discussion

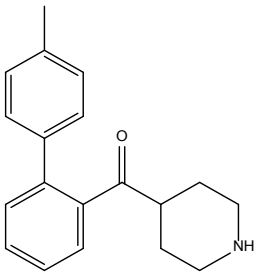
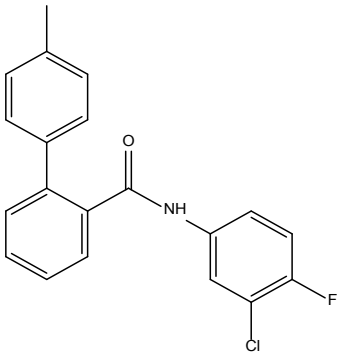
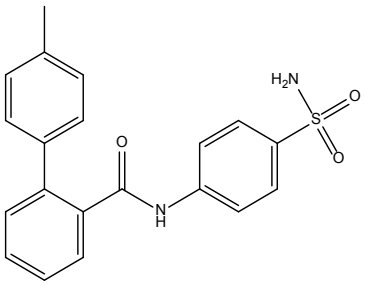
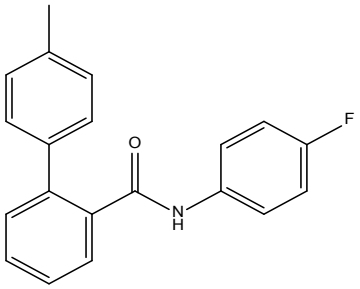
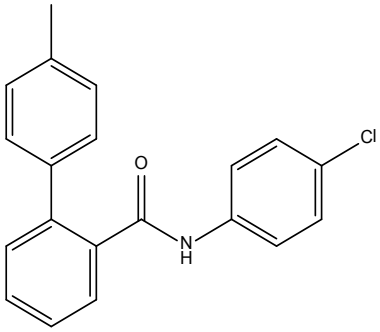
For QSAR studies, 80 percent of the compounds (20 compounds) were randomly selected as the training set from a total data set of 25 compounds, and these compounds were used for QSAR model development. The remaining 20% (5 compounds) were used to estimate the predictability of the developed QSAR model. The test set compounds are marked with a "*" in Table 1.

Table 1 A series of biphenyl carboxamide analogues and their biological activities

Compd. No.	Structure	H0e	DISPs	IP_I	logBA Obsd.	logBA Pred. by eq. I	Δ	Pred. LOO
1		2.85	0.37	1	1.21	1.35	0.14	1.36
2		2.84	0.36	0	1.50	1.46	-0.04	1.45
3		2.88	0.36	1	1.29	1.35	0.06	1.35
4*		3.03	0.34	1	1.55	1.34	-0.22	-
5		3.07	0.76	0	1.57	1.67	0.10	1.71

Citation: Chouhan A, Shaik B, Ahmad I, et al. QSAR studies on a series of biphenyl carboxamide analogues for analgesic activity. *J Anal Pharm Res.* 2023;12(1):51–58. DOI: 10.15406/japlr.2023.12.00423

Table Continued...

Compd. No.	Structure	H0e	DISPs	IP_I	logBA			Pred. LOO
					Obsd.	Pred. by eq. I	Δ	
6		2.81	0.15	I	1.20	1.24	0.04	1.25
7		3.16	0.75	0	1.64	1.66	0.02	1.67
8		3.08	0.86	I	1.61	1.61	-0.01	1.61
9		3.02	0.66	I	1.60	1.50	-0.10	1.49
10		2.95	0.31	0	1.55	1.44	-0.11	1.41

Citation: Chouhan A, Shaik B, Ahmad I, et al. QSAR studies on a series of biphenyl carboxamide analogues for analgesic activity. *J Anal Pharm Res.* 2023;12(1):51–58. DOI: 10.15406/japlr.2023.12.00423

Table Continued...

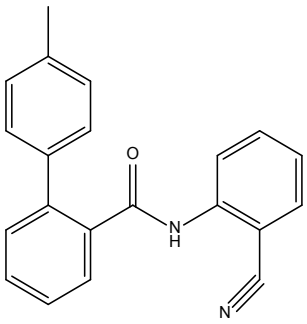
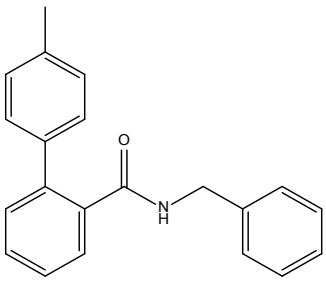
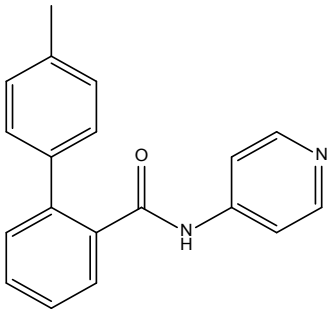
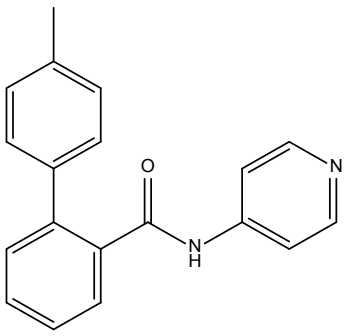
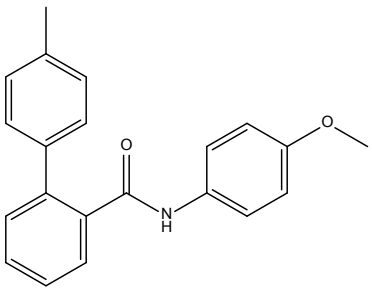
Compd. No.	Structure	H0e	DISPs	IP_I	logBA			Pred. LOO
					Obsd.	Pred. by eq. I	Δ	
11		2.93	0.28	I	1.25	1.30	0.06	1.31
12		2.92	0.34	I	1.34	1.34	-0.01	1.34
13		2.90	0.40	I	1.47	1.37	-0.10	1.36
14		2.90	0.40	I	1.40	1.37	-0.03	1.37
15		2.89	0.32	I	1.34	1.32	-0.02	1.32

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Table Continued...

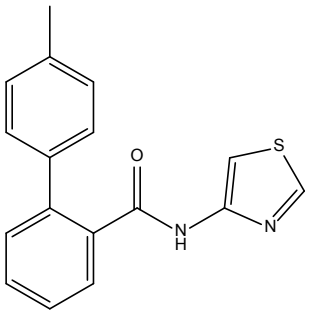
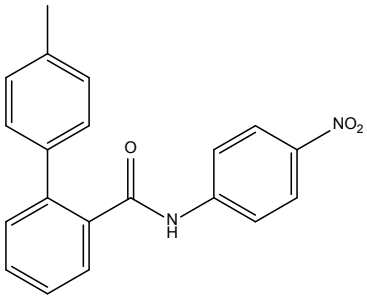
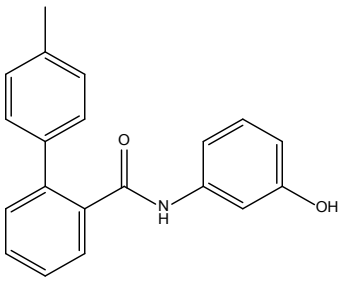
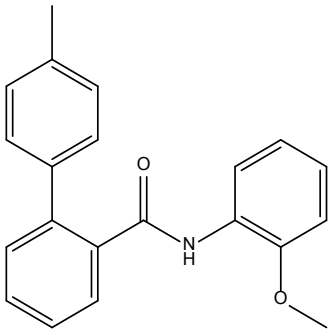
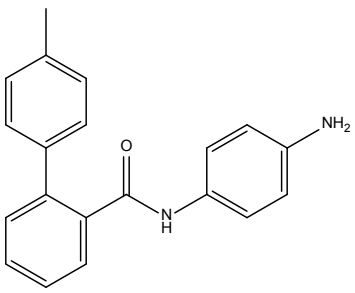
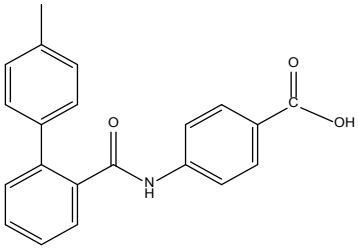
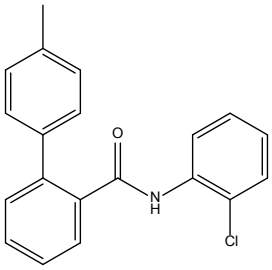
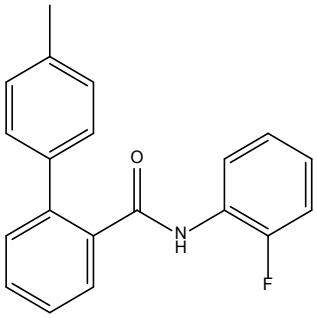
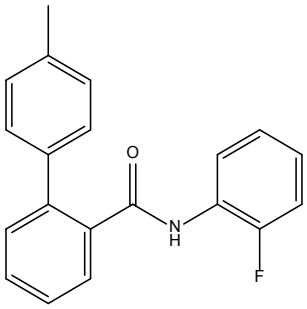
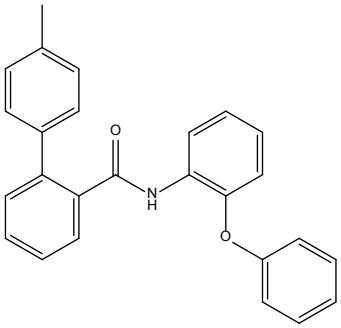
Compd. No.	Structure	H0e	DISPs	IP_I	logBA			Pred. LOO
					Obsd.	Pred. by eq. I	Δ	
16*		2.94	0.47	I	1.49	1.41	-0.08	-
17		3.11	0.93	I	1.61	1.64	0.03	1.65
18		2.97	0.34	I	1.38	1.34	-0.04	1.33
19		2.88	0.36	I	1.29	1.35	0.06	1.35
20		2.88	0.36	I	1.38	1.35	-0.03	1.35

Table Continued...

Compd. No.	Structure	H0e	DISPs	IP_1	logBA Obsd.	logBA Pred. by eq. I	Δ	Pred. LOO
21		3.04	0.78	I	1.62	1.56	-0.05	1.55
22		2.95	0.31	0	1.42	1.44	0.02	1.45
23*		2.98	0.31	I	1.60	1.32	-0.28	-
24*		2.98	0.31	I	1.52	1.32	-0.20	-
25*		2.87	0.28	0	1.41	1.42	0.01	-

IP_1, depressant-80; Δ, residual values

Citation: Chouhan A, Shaik B, Ahmad I, et al. QSAR studies on a series of biphenyl carboxamide analogues for analgesic activity. *J Anal Pharm Res.* 2023;12(1):51–58. DOI: 10.15406/japlr.2023.12.00423

Multiple linear regression analysis was performed using NCSS software[22] on the training set compounds to establish a correlation between observed logBA and the various calculated descriptors of the compounds. The most significant correlation consisting of two variables is given below.

logBA= -0.1158(±0.0758) DSIPs−0.1158(±0.0758) Depressant 80+ 1.2762 (1)

$N = 20, r^2 = 0.8000, r^2_{adj} = 0.7765, S = 0.0693, F = 34.0007, r^2_{cv} = 0.7217, r^2_{pred} = 0.7626,$

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 the 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. Using the equations (2) and (3), the values of r^2_{cv} and r^2_{pred} are calculated respectively, where $y_{i,obsd}$ in eq. (2) refers to the observed activity of compound i in the training set and that in eq.(3) to compound i in the test set. Similarly, $y_{i,pred}$ in eq.(2) refers to the predicted activity of compound i in the training set obtained in the leave-one-out Jackknife procedure and that in eq.(3) to that predicted for the test set compounds by the model obtained in the training set. However, $y_{av,obsd}$ in the equations refers to the average activity of the training set compound.

$$r^2_{cv} = 1 - [\Sigma_i (y_{i,obsd} - y_{i,pred})^2 / \Sigma_i (y_{i,obsd} - y_{av,obsd})^2] \quad (2)$$

$$r^2_{pred} = 1 - [\Sigma_i (y_{i,obsd} - y_{i,pred})^2 / \Sigma_i (y_{i,obsd} - y_{av,obsd})^2] \quad (3)$$

If $r^2_{cv} > 0.60$, the correlation is assumed to be valid and has a good internal predictive ability for an acceptable QSAR model. Likewise, $r^2_{pred} > 0.5$ indicates that the model's external predictive ability is good. The correlation stated by eq. (1) is found to be quite valid from both parameters. The remaining two statistical parameters, s and F, are the standard deviation and the Fischer-ratio of the variances of the calculated and observed activities, respectively. A higher value of *F* than this indicates a good correlation. Thus, all descriptors used in this correlation are found to be quite significant, and if we remove them one by one, the significance of the correlation is substantially dropped.

logBA = 1.2326(±0.4266) H0e-2.2040 1.2150 (4)

$N = 20, r^2 = 0.6719, r^2_{adj} = 0.6536, S = 0.0863, F = 36.8531, r^2_{cv} = 0.6034, r^2_{pred} = 0.7081$

Thus, from the above results, eq. (1) and eq. (4) have a significant correlation between the inhibitory activity values and the structural descriptors of the compounds.

The observed and predicted logBA values were calculated using model eq.1 are recorded in Table 1. A graph is drawn between the predicted and observed activities for both the training and test sets using models eq. 1 are recorded in Figure 1. The figure shows that the models have a good predictive ability. Figure 1 shows that almost all the points, except a few, lie near the straight line. Thus, using eq,1. From the above statistical values, it is clear that the two-variable model is the best suitable model for predicting the activity of the current set of compounds.

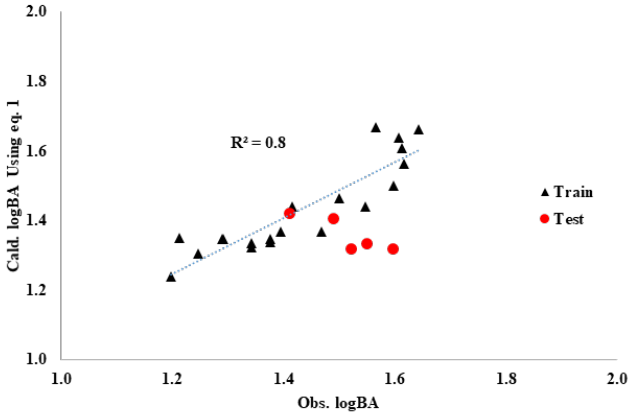


Figure 1 Correlation between observed and calculated logBA using eq. 1.

Conclusion

On the basis of above discussion it is concluded that the topological descriptors will play a vital role while designing novel biphenyl carboxamide analogues for analgesic activity. The obtained models are free from any kind of defect. The displacement value weighted by intrsinic state (DISPs) and Ghose-Viswanadhan-Wendoloski antidepressant-like index at 80% (Depressent-80) have a negative coefficient means that lowest values of these parameters will enhance the analgesic activity the present set of compounds.

Conflicts of interest

Authors declare that there is no conflict of interest.

Acknowledgements

None.

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