qsar

August 28, 2019

Load libraries.

[204]:
```
import pandas as pd
import numpy as np
from sklearn.model_selection import train_test_split
from sklearn.feature_selection import VarianceThreshold
from sklearn.preprocessing import StandardScaler
from sklearn.ensemble import RandomForestClassifier
from sklearn.model_selection import RandomizedSearchCV
from sklearn import metrics
from sklearn.metrics import confusion_matrix
from sklearn.svm import SVC
from sklearn.linear_model import LogisticRegression
from sklearn.naive_bayes import GaussianNB
from sklearn.decomposition import PCA
from sklearn.manifold import TSNE
from sklearn.manifold import MDS
from rdkit import Chem
from rdkit.Chem import Descriptors
from rdkit.Chem import Scaffolds
from rdkit.Chem.Scaffolds import MurckoScaffold
from rdkit.ML.Descriptors import MoleculeDescriptors
from scipy import stats
from statsmodels import robust
from pprint import pprint
import matplotlib.pyplot as plt
import seaborn as sns
color = sns.color_palette()
# ... to draw molecules in the notebook
from rdkit.Chem import Draw
from rdkit.Chem.Draw import IPythonConsole
```

Read data.

[162]:
```
df = pd.read_csv('data/ReadyBiodegradability.csv', header = 0)
df = df.drop(['Unnamed: 0', 'SMILESbeta'], axis=1)
df.sample(5).head()
```

[162]:

	SMILES	EndPt	ReadyBiodeg
1128	OC(=O)c1cccnc1	RB	1
1777	CCC1CCCCC1	NRB	0
389	CCOC(=O)c1ccc2c(c1)C(=O)OC2(c1ccc(cc1OCC)N(CC)...	NRB	0
22	OC(=O)\C=C/C(O)=O	RB	1
181	CCCCCCCC\C=C/CCCCCCCCCCCC(N)=O	RB	1

Calculate Murcko frameworks.

[163]:
```
for i in range(len(df)):
    df.at[i, 'core'] = MurckoScaffold.MurckoScaffoldSmilesFromSmiles(df.loc[i,␣
↪'SMILES'])
```

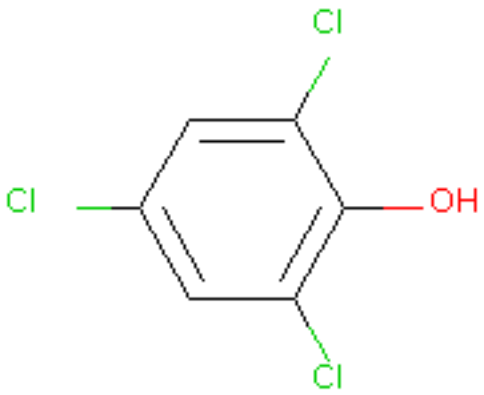
[199]:
```
df.sample(5).head()
```

[199]:

	SMILES	EndPt	ReadyBiodeg	core
1592	CCCCCCCCO	RB	1	
634	N[C@@H](CCC(=O)O)C(=O)O	RB	1	
1867	Oc1c(Cl)cc(Cl)cc1Cl	RB	1	c1ccccc1
539	CC(=NNC(=S)N)C	NRB	0	
407	N#Cc1cc(C)cc(c1/N=N/c1ccc(cc1NS(=O)(=O)C)N(CC)...	NRB	0	c1ccc(N=Nc2ccccc2)cc1

[202]:
```
Draw.MolToImage(Chem.MolFromSmiles(df.loc[1867, 'SMILES']))
```

[202]:



[203]:
```
Draw.MolToImage(Chem.MolFromSmiles(df.loc[1867, 'core']))
```

[203]:

Examine the N most frequent frameworks.

[168]:
```
cores_df = pd.DataFrame(cores['core'].value_counts().head(7))
```

[169]:
```
cores_df.reset_index(inplace=True)
```

[170]:
```
cores_df.columns = ['core_SMILES', 'count']
```

Note that frameworks are not returned for acyclic systems.

[171]:
```
cores_df
```

[171]:

	core_SMILES	count
0		666
1	c1ccccc1	512
2	c1ccc2ccccc2c1	43
3	c1ccc(Cc2ccccc2)cc1	36
4	c1ccc(-c2ccccc2)cc1	34
5	c1ccncc1	34
6	c1ccc(N=Nc2ccccc2)cc1	28

Remove the acyclic 'frameworks'.

[172]:
```
cores_df = cores_df.iloc[1:]
```

[173]:
```
cores_df = cores_df.reset_index(drop=True)
```

[174]:
```
cores_df
```

[174]:
```
              core_SMILES  count
0               c1ccccc1    512
1         c1ccc2ccccc2c1     43
2    c1ccc(Cc2ccccc2)cc1     36
3    c1ccc(-c2ccccc2)cc1     34
4               c1ccncc1     34
5  c1ccc(N=Nc2ccccc2)cc1     28
```

Use the SMILES string associated with each framework to build a molecule for that framework.

[175]:
```
for i in range(len(cores_df)):
    cores_df.at[i, 'mol'] = Chem.MolFromSmiles(cores_df.loc[i, 'core_SMILES'])
```

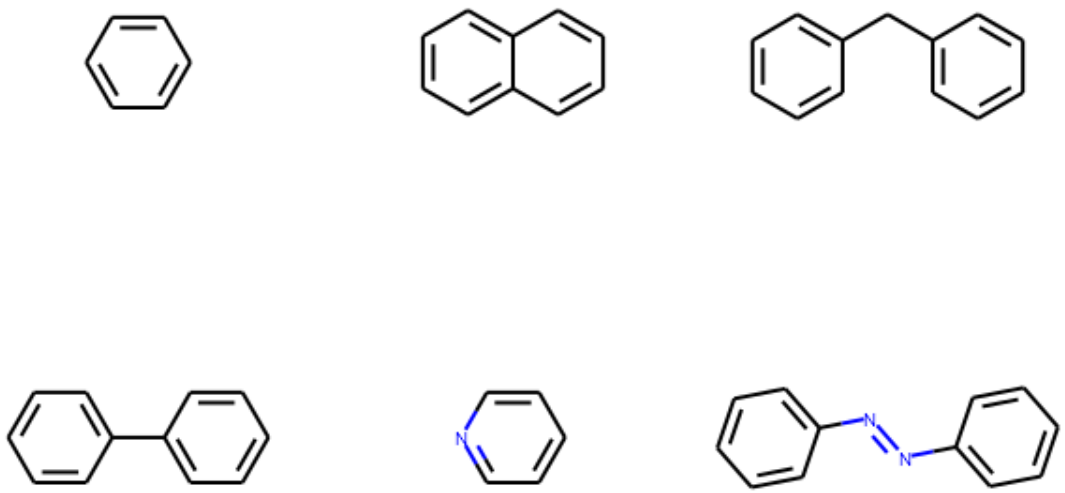
[176]:
```
cores_df.head(6)
```

[176]:
```
              core_SMILES  count  \
0               c1ccccc1    512
1         c1ccc2ccccc2c1     43
2    c1ccc(Cc2ccccc2)cc1     36
3    c1ccc(-c2ccccc2)cc1     34
4               c1ccncc1     34
5  c1ccc(N=Nc2ccccc2)cc1     28

                                                 mol
0  <rdkit.Chem.rdchem.Mol object at 0x00000000145...
1  <rdkit.Chem.rdchem.Mol object at 0x00000000145...
2  <rdkit.Chem.rdchem.Mol object at 0x00000000147...
3  <rdkit.Chem.rdchem.Mol object at 0x00000000147...
4  <rdkit.Chem.rdchem.Mol object at 0x00000000147...
5  <rdkit.Chem.rdchem.Mol object at 0x00000000147...
```

[205]:
```
Draw.MolsToGridImage([cores_df.iloc[i, 2] for i in range(len(cores_df))],
                     molsPerRow = 3)
```

[205]:



Calculate RDKit descriptors for molecules in the dataset.

[206]:
```
nms = [x[0] for x in Descriptors._descList]
calc = MoleculeDescriptors.MolecularDescriptorCalculator(nms)
for i in range(len(df)):
    try:
        descrs = calc.CalcDescriptors(Chem.MolFromSmiles(df.iloc[i, 0]))
        for x in range(len(descrs)):
            df.at[i, str(nms[x])] = descrs[x]
    except:
        for x in range(len(descrs)):
            df.at[i, str(nms[x])] = 'NaN'

df = df.replace([np.inf, -np.inf], np.nan)
df = df.dropna()
df = df.reset_index(drop=True)

df.sample(5).head()
```

[206]:

	SMILES	EndPt	ReadyBiodeg	\
1384	CCc1ccccc1C=C	NRB	0	
93	Nc1sccn1	NRB	0	
116	Clc1ccc(cc1)[S](=O)(=O)c2ccc(Cl)cc2	NRB	0	
1617	CCCCCCCCC=CCCCCCCCCO	RB	1	
1774	CCOC(=O)C(=O)OCC	RB	1	

```
                          core  MaxEStateIndex  MinEStateIndex  \
1384                  c1ccccc1        3.739537        1.085509
93                     c1cscn1        5.185185        0.634259
116   O=S(=O)(c1ccccc1)c1ccccc1       12.170229       -3.489784
1617                                   8.660967        0.362284
1774                                  10.436204       -0.926528

      MaxAbsEStateIndex  MinAbsEStateIndex       qed    MolWt  ...  \
1384           3.739537           1.085509  0.580073  132.206  ...
93             5.185185           0.634259  0.521525  100.146  ...
116           12.170229           0.212243  0.840921  287.167  ...
1617           8.660967           0.362284  0.284425  268.485  ...
1774          10.436204           0.192111  0.409630  146.142  ...

      fr_sulfide  fr_sulfonamd  fr_sulfone  fr_term_acetylene  fr_tetrazole  \
1384         0.0           0.0         0.0                0.0           0.0
93           0.0           0.0         0.0                0.0           0.0
116          0.0           0.0         1.0                0.0           0.0
1617         0.0           0.0         0.0                0.0           0.0
1774         0.0           0.0         0.0                0.0           0.0

      fr_thiazole  fr_thiocyan  fr_thiophene  fr_unbrch_alkane  fr_urea
1384          0.0          0.0           0.0               0.0      0.0
93            1.0          0.0           0.0               0.0      0.0
116           0.0          0.0           0.0               0.0      0.0
1617          0.0          0.0           0.0              11.0      0.0
1774          0.0          0.0           0.0               0.0      0.0

[5 rows x 204 columns]
```

Build training set and test set.

[5]:
```
train, test = train_test_split(df, test_size = 0.2, random_state = 42,
                               stratify=df[['ReadyBiodeg']])
train = train.reset_index(drop=True)
test = test.reset_index(drop=True)
```

[247]:
```
train['ReadyBiodeg'].value_counts()
```

[247]:
```
0    1043
1     545
Name: ReadyBiodeg, dtype: int64
```

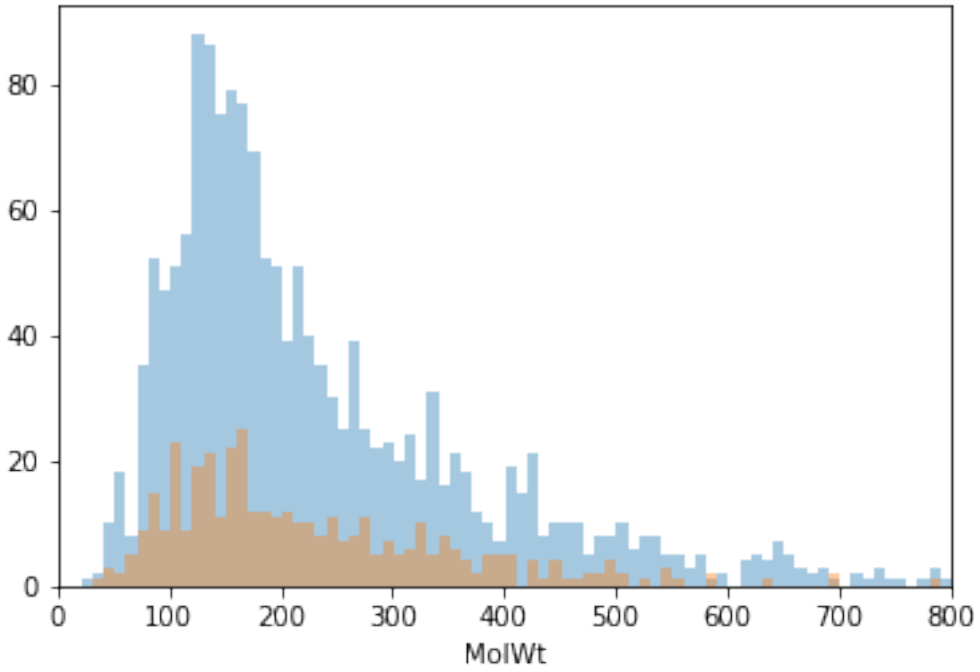
[248]:
```
test['ReadyBiodeg'].value_counts()
```

[248]:
```
0    261
1    136
Name: ReadyBiodeg, dtype: int64
```

Calculated molecular weight distributions.

[230]:
```
fig, ax = plt.subplots()
for a in [train['MolWt'], test['MolWt']]:
    sns.distplot(a, bins=range(1, 810, 10), ax=ax, kde=False)
ax.set_xlim([0, 800])
```

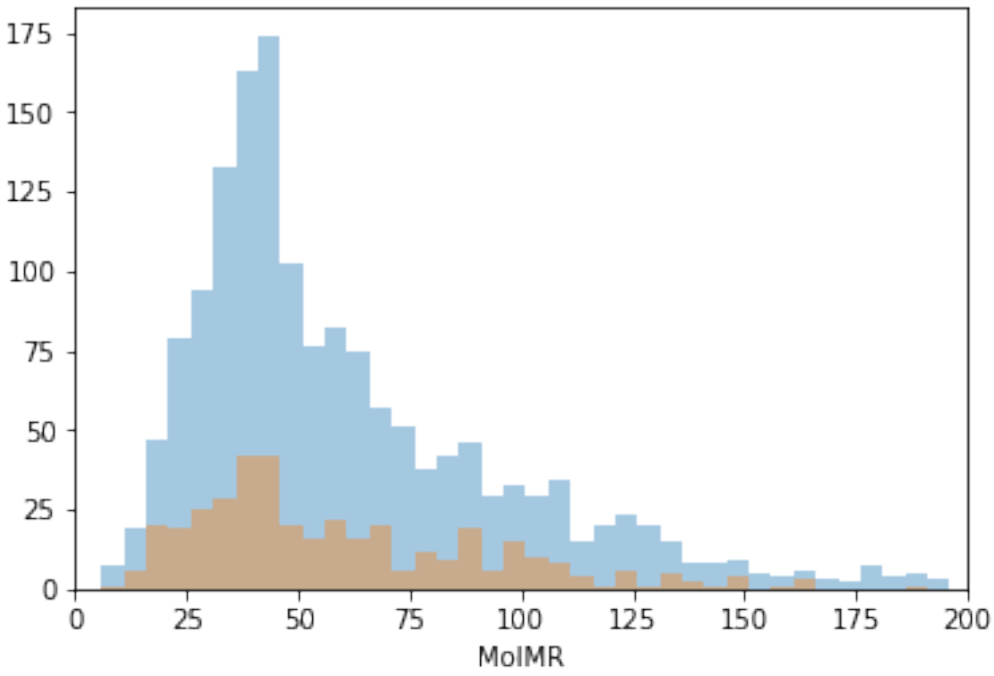
[230]:
```
(0, 800)
```



Calculated molar refractivity distributions.

[236]:
```
fig, ax = plt.subplots()
for a in [train['MolMR'], test['MolMR']]:
    sns.distplot(a, bins=range(1, 201, 5), ax=ax, kde=False)
ax.set_xlim([0, 200])
```

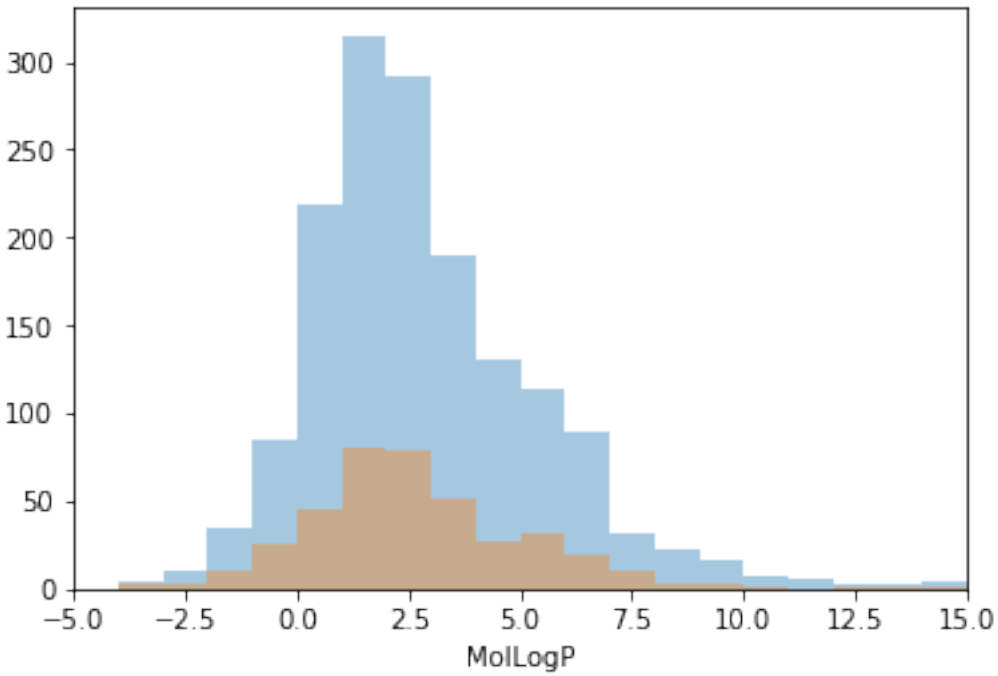
[236]:
```
(0, 200)
```



Calculated logP distributions.

[239]:
```
fig, ax = plt.subplots()
for a in [train['MolLogP'], test['MolLogP']]:
    sns.distplot(a, bins=range(-5, 16, 1), ax=ax, kde=False)
ax.set_xlim([-5, 15])
```

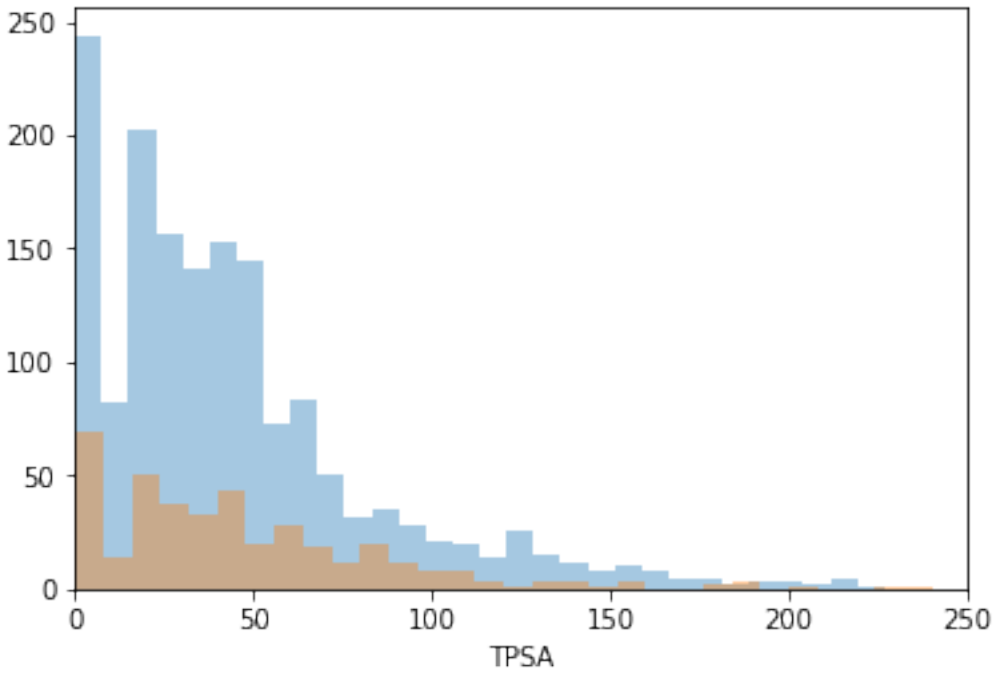
[239]:
```
(-5, 15)
```



Calculated topological polar surface area distribution.

[246]:
```
fig, ax = plt.subplots()
for a in [train['TPSA'], test['TPSA']]:
    sns.distplot(a, bins=50, ax=ax, kde=False)
ax.set_xlim([0, 250])
```

[246]:
```
(0, 250)
```



[7]:
```
X_train = train.drop(columns=['SMILES', 'SMILESbeta', 'EndPt', 'ReadyBiodeg'])
X_test = test.drop(columns=['SMILES', 'SMILESbeta', 'EndPt', 'ReadyBiodeg'])
y_train = np.ravel(train[['ReadyBiodeg']])
y_test = np.ravel(test[['ReadyBiodeg']])
```

[8]:
```
print(X_train.shape)
print(X_test.shape)
print(len(y_train))
print(len(y_test))
```

```
(1588, 200)
(397, 200)
1588
397
```

Identify near zero variance descriptors.

[9]:
```
def variance_threshold_selector(data, threshold = 0.5):
    selector = VarianceThreshold(threshold)
    selector.fit(data)
    return data[data.columns[selector.get_support(indices = True)]]

nzv = variance_threshold_selector(X_train, 0.0)

X_train = X_train[nzv.columns]
X_test = X_test[nzv.columns]
```

[10]:
```
print(X_train.shape)
print(X_test.shape)
```

```
(1588, 184)
(397, 184)
```

Identify highly correlated descriptors.

[11]:
```
corr_matrix = X_train.corr().abs()
upper = corr_matrix.where(np.triu(np.ones(corr_matrix.shape),
                                  k = 1).astype(np.bool))
to_drop = [column for column in upper.columns
           if any(upper[column] > 0.85)]

X_train = X_train[X_train.columns.drop(to_drop)]
X_test = X_test[X_test.columns.drop(to_drop)]
```

[12]:
```
print(X_train.shape)
print(X_test.shape)
```

```
(1588, 134)
(397, 134)
```

Center and scale descriptors.

[13]:
```
scaler = StandardScaler()
scaler.fit(X_train)

X_train_std = scaler.transform(X_train)
X_test_std = scaler.transform(X_test)
```

Machine Learning: random forest.

[14]:
```
rf = RandomForestClassifier(random_state = 42)
```

[15]:
```
print('Parameters currently in use:\n')
pprint(rf.get_params())
```

```
Parameters currently in use:

{'bootstrap': True,
 'class_weight': None,
 'criterion': 'gini',
 'max_depth': None,
 'max_features': 'auto',
 'max_leaf_nodes': None,
 'min_impurity_decrease': 0.0,
 'min_impurity_split': None,
 'min_samples_leaf': 1,
 'min_samples_split': 2,
 'min_weight_fraction_leaf': 0.0,
```

```
 'n_estimators': 'warn',
 'n_jobs': None,
 'oob_score': False,
 'random_state': 42,
 'verbose': 0,
 'warm_start': False}
```

Build a search grid.

[16]:
```
# Number of trees in random forest
n_estimators = [int(x) for x in np.linspace(start = 100, stop = 1000, num = 10)]
# Number of features to consider at every split
max_features = ['auto', 'sqrt']
# Maximum number of levels in tree
max_depth = [int(x) for x in np.linspace(10, 110, num = 11)]
max_depth.append(None)
# Minimum number of samples required to split a node
min_samples_split = [2, 5, 10]
# Minimum number of samples required at each leaf node
min_samples_leaf = [1, 2, 4]
# Method of selecting samples for training each tree
bootstrap = [True, False]
```

[17]:
```
random_grid = {'n_estimators': n_estimators,
               'max_features': max_features,
               'max_depth': max_depth,
               'min_samples_split': min_samples_split,
               'min_samples_leaf': min_samples_leaf,
               'bootstrap': bootstrap}

pprint(random_grid)
```

```
{'bootstrap': [True, False],
 'max_depth': [10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, None],
 'max_features': ['auto', 'sqrt'],
 'min_samples_leaf': [1, 2, 4],
 'min_samples_split': [2, 5, 10],
 'n_estimators': [100, 200, 300, 400, 500, 600, 700, 800, 900, 1000]}
```

[18]:
```
# First create the base model to tune
rf = RandomForestClassifier(random_state = 42)
# Random search of parameters, using 3 fold cross validation,
# search across 100 different combinations, and use all available cores
rf_random = RandomizedSearchCV(estimator = rf, param_distributions = random_grid,
                               n_iter = 100, scoring = 'neg_mean_absolute_error',
                               cv = 3, verbose = 2, random_state = 42,
                               n_jobs = -1, return_train_score = True)
```

[19]:
```
rf_random.fit(X_train_std, y_train)
```

```
Fitting 3 folds for each of 100 candidates, totalling 300 fits

[Parallel(n_jobs=-1)]: Using backend LokyBackend with 4 concurrent workers.
[Parallel(n_jobs=-1)]: Done  33 tasks      | elapsed:   34.6s
[Parallel(n_jobs=-1)]: Done 154 tasks      | elapsed:  2.5min
[Parallel(n_jobs=-1)]: Done 300 out of 300 | elapsed:  4.6min finished
```

[19]:
```
RandomizedSearchCV(cv=3, error_score='raise-deprecating',
          estimator=RandomForestClassifier(bootstrap=True, class_weight=None,
criterion='gini',
            max_depth=None, max_features='auto', max_leaf_nodes=None,
            min_impurity_decrease=0.0, min_impurity_split=None,
            min_samples_leaf=1, min_samples_split=2,
            min_weight_fraction_leaf=0.0, n_estimators='warn', n_jobs=None,
            oob_score=False, random_state=42, verbose=0, warm_start=False),
          fit_params=None, iid='warn', n_iter=100, n_jobs=-1,
          param_distributions={'n_estimators': [100, 200, 300, 400, 500, 600,
700, 800, 900, 1000], 'max_features': ['auto', 'sqrt'], 'max_depth': [10, 20,
30, 40, 50, 60, 70, 80, 90, 100, 110, None], 'min_samples_split': [2, 5, 10],
'min_samples_leaf': [1, 2, 4], 'bootstrap': [True, False]},
          pre_dispatch='2*n_jobs', random_state=42, refit=True,
          return_train_score=True, scoring='neg_mean_absolute_error',
          verbose=2)
```

Report the best parameters.

[20]:
```
rf_random.best_params_
```

[20]:
```
{'bootstrap': False,
 'max_depth': 20,
 'max_features': 'sqrt',
 'min_samples_leaf': 4,
 'min_samples_split': 10,
 'n_estimators': 600}
```

Save the model.

[21]:
```
import pickle
f = open('RandomForest.pkl', 'wb')
pickle.dump(rf_random, f)
f.close()
```

Predict endpoint (ready biodegradability) for compounds in the test set.

[22]:
```
pred = rf_random.predict(X_test_std)
```

[249]:
```
pred
```

[249]:
```
array([1, 1, 0, 1, 1, 0, 1, 0, 0, 1, 1, 0, 1, 0, 0, 0, 1, 0, 1, 0, 1, 1,
       1, 0, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 0, 1, 0, 0, 1, 1, 0,
       0, 1, 1, 1, 0, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 0, 0, 0, 1,
       0, 0, 0, 1, 0, 0, 0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,
       0, 0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 1, 0, 0, 0, 1, 1, 0, 0, 0, 1, 1,
```

```
1, 0, 0, 0, 0, 0, 0, 1, 0, 0, 1, 0, 0, 1, 0, 0, 0, 0, 1, 1, 0, 0,
0, 1, 1, 0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 1, 1, 0, 0, 0, 0, 1, 0, 0,
1, 1, 0, 0, 1, 1, 0, 0, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0, 1, 0, 0, 0,
0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 0, 0, 0, 0,
0, 0, 1, 1, 1, 0, 1, 0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 1, 0, 0, 1, 0,
0, 0, 0, 0, 0, 0, 1, 0, 1, 0, 0, 0, 0, 0, 0, 1, 0, 1, 1, 1, 0, 0,
0, 0, 0, 1, 0, 0, 0, 0, 0, 0, 0, 1, 0, 1, 0, 0, 0, 0, 1, 0, 0, 1,
1, 0, 0, 0, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 0, 0, 0, 1,
1, 0, 0, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 0, 1, 0, 0, 0, 1, 0,
0, 0, 1, 0, 0, 1, 1, 0, 0, 0, 0, 0, 0, 1, 1, 1, 0, 0, 1, 1, 0, 0,
0, 1, 0, 0, 1, 1, 1, 1, 0, 0, 0, 0, 1, 1, 1, 0, 1, 0, 1, 0, 0, 0,
0, 1, 0, 0, 0, 0, 0, 1, 0, 0, 1, 0, 0, 0, 1, 0, 0, 0, 0, 0, 1, 1,
1, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0,
1], dtype=int64)
```

Evaluate model performance, using kappa statistic.

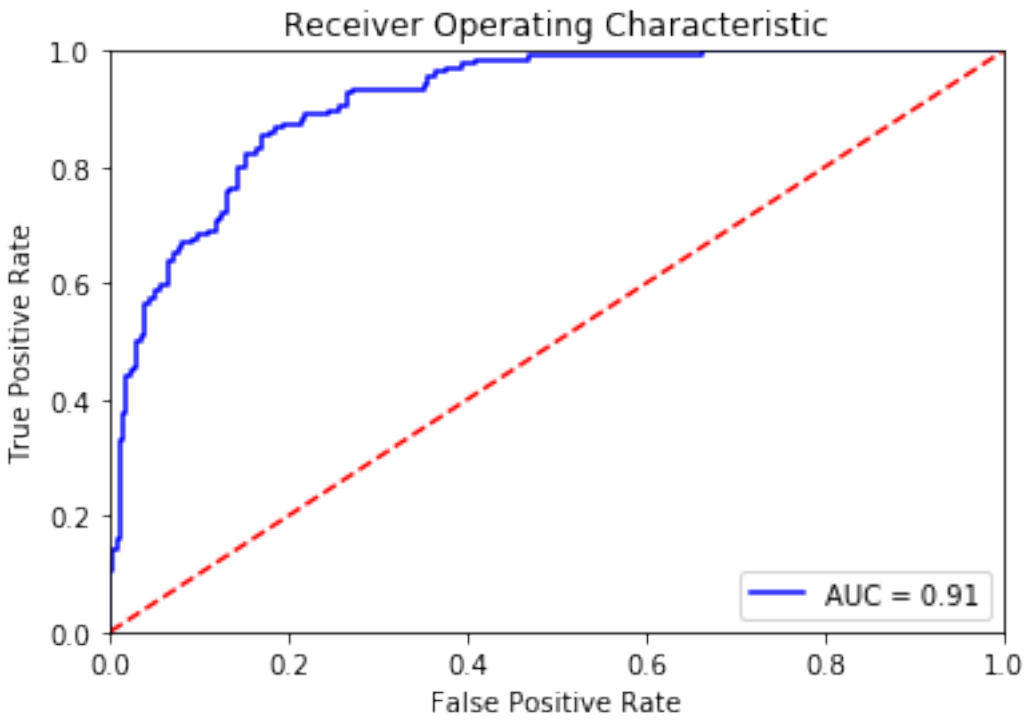
[23]:
```
kappa = metrics.cohen_kappa_score(y_test, pred)
print('Kappa: {:.2f}'.format(kappa))
```

```
Kappa: 0.61
```

Plot ROC curve; calculate the area under the curve (AUC).

[24]:
```
probs = rf_random.predict_proba(X_test_std)
preds = probs[:,1]
fpr, tpr, threshold = metrics.roc_curve(y_test, preds)
roc_auc = metrics.auc(fpr, tpr)

plt.title('Receiver Operating Characteristic')
plt.plot(fpr, tpr, 'b', label = 'AUC = %0.2f' % roc_auc)
plt.legend(loc = 'lower right')
plt.plot([0, 1], [0, 1],'r--')
plt.xlim([0, 1])
plt.ylim([0, 1])
plt.ylabel('True Positive Rate')
plt.xlabel('False Positive Rate')
plt.show()
```



Print confusion matrix.

[25]:
```
print(confusion_matrix(y_test, pred))
```

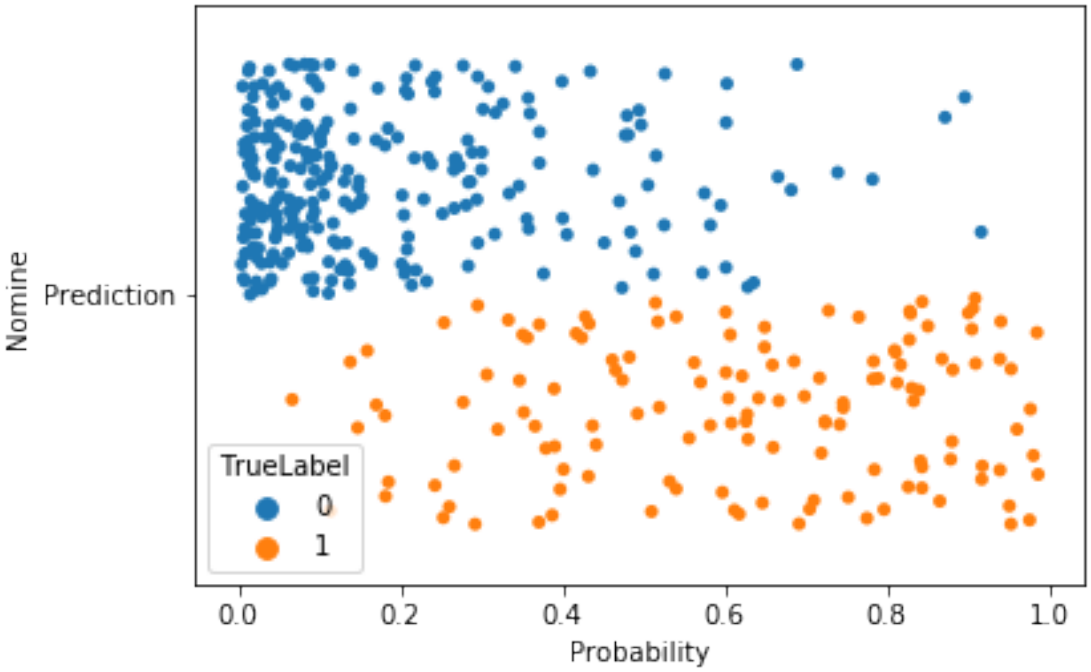
```
[[239  22]
 [ 45  91]]
```

'Plot' the confusion matrix.

[27]:
```
col_names =  ['TrueLabel', 'Nomine', 'Probability']
plotDF  = pd.DataFrame(columns = col_names)
```

[28]:
```
plotDF['TrueLabel'] = y_test
plotDF['Nomine'] = 'Prediction'
plotDF['Probability'] = preds
```

[29]:
```
confusionPlot = sns.stripplot(x = 'Probability', y = 'Nomine', hue =␣
↪'TrueLabel', jitter = 0.4, dodge = True, data = plotDF)
```


Nomine
Prediction
TrueLabel
0
1
0.0
0.2
0.4
0.6
0.8
1.0
Probability

[ ]: