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**Research Article**

# Pass biological activity spectrum predictions of chromones in the enhanced open NCI database browser

**Vishal W. Banewar***

*P G Department of Chemistry, Govt. Vidarbha Institute of Science & Humanities, Amravati – 444 604 (MS) India*

**QR Code**

***Correspondence Info:**
Vishal W. Banewar,
Assistant Professor,
P G Department of Chemistry,
Govt. Vidarbha Institute of Science & Humanities,
Amravati – 444 604 (MS) India

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## Abstract

Chromone nucleus containing drugs have its own importance in drug chemistry. Chromones and its substituted compounds possess various pharmacological activities and acts as HIV – 1 Protease inhibitors. The concept of Biological Activity Spectrum served as a basis for developing PASS (Prediction of Activity Spectra for Substances) software products. Evaluation of the general biological potential of molecule is possible using computer based program PASS that predicts more than 780 pharmacological effects on the basis of structural formula of compounds. The result of PASS studies shows that substituted and unsubstituted Chromone show many important biological activities. PASS also predicts some unwanted activities of Chromone, providing medicinal chemists with the means to increase the efficiency of projects.

**Keywords:** Heterocycles, Chromones, PASS, Computer Prediction, Biological Activity.

## 1. Introduction

Heterocyclic compounds containing oxygen and heteroatom in ring enhance their biocidal application mainly in medicinal chemistry. The literature survey also reveals that Chromone containing nucleus has numerous biological activity. Research scientists not only from India but also from all over world are trying to synthesize Chromone nucleus containing drug and investing their medicinal properties.

But the major reason for failure in drug R & D is

1) Low efficiency,
2) Non – safe pharmacological toxicity,
3) Non appropriate pharmacokinetic properties [1].

Due to the directed way of testing chemical compounds in drug research and development, many projects fails because serious adverse effect and toxicity are discovered too late and many existing prospective activities are remains unstudied. Sometimes, new action of old compounds is found during clinical trials or practical use of medicine, and that become a reason for new indication of drug.

Keeping these aspects in failure of drug research and development project and importance of Chromone nucleus in medicinal chemistry, in the present study we have investigated the possibilities of utilizing computer aided prediction to estimate the general biological potential of Chromone nucleus. This computer aided program is now a days developing as a method for rapidly evaluating molecules for suspected biological activity and relative potency and designing molecules for biological activity called PASS (Prediction of Activity Spectra for Substances)[2-8].

## 2. Material & Methods

### a) Brief Description of PASS

PASS predicts more than 780 pharmacological effects, mechanism of action, metagenicity, carcinogenicity, teratogenicity and embryotoxicity on the basis of structural formulae of compounds with average accuracy in leave-

one-out cross-validation (LOOCV) being 85%[9-11]. Applications of the program PASS to about more than half a million compounds are described. A total 565 different types of activity are included encompassing general pharmacological effects, specific mechanism of action, known toxicities and others. Application of this web-based computer service for prediction of activities of the kinds "Angiogenesis inhibitor", "Antiviral (HIV)" and a set of activities that can be associated with antineoplastic action are reported [12].

The result of PASS prediction displayed in computer automatically.

PASS gives information regarding

1) Finding most probable new leads with required activity spectra among the compounds from in-house and commercial databases.
2) Revealing new effects and mechanism of action for the old substances in corporate and private databases.
3) Determining the assays that are more relevant for a particular compound [13-16].

**b) Basic elements of PASS:**

**i) Training Set:**

PASS training set consists of about 46,000 of biologically active compounds. They include about 16,000 already launched drugs and 30,000 drug-candidates under clinical or advanced preclinical testing now.

**ii) Chemical Structure Description:**

For the description of chemical structure in PASS, we developed original descriptors called Multilevel Neighborhood of Atoms (MNA)[17]. MNA are generated on the basis of connection table and table of atoms types presented by the compounds.

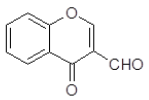
**iii) Biological Activity Description:**

Biological activity is the result of chemical compounds interaction with the biological entity. In clinical study, human organism represents biological entity. Any biologically active compound reveals wide spectrum of different effects. Some of them are useful in treatment of definite diseases but the others cause various side effects and toxic effects. Biological activity spectrum of a compound presents each of its activity despite of the difference in essential condition of its experimental determination.

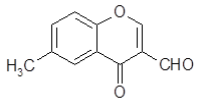
**c) Biological Activity Spectrum:**

Biological Activity Spectrum is a concept that is crucial to PASS and that provides the rational for predicting many biological activities types for different compounds. Within this concept, biological activity is considered to be an intrinsic property of the compound depending only on its structure [18-20]. Hence, we may use PASS for the prediction of the biological activity spectrum for existing compounds and compounds, which are only planned to be synthesized. By using qualitative representation of biological activity, it is possible to combine data collected from many different sources with the same training set.

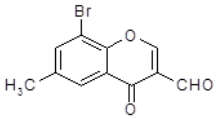
Revealing new effects and mechanism of action is considered below is the example of prediction the biological activity spectrum of compounds, which are only planned to be synthesized.



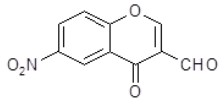

**3-Formylchromone (I)**




**6-methyl-3 formylchromone (II)**




**8-bromo-6-methyl-3-formylchromone (III)**




**6-nitro-3-formylchromone (IV)**

**Table 1: Predicted Biological Activity Spectrum for Compound I**

22 Substructure descriptors; 1 new. 197 Possible activities at Pa > 30%

| Activity | $P_a$ | $P_i$ |
|---|---|---|
| Ferredoxin-nitrite reductase inhibitor | 0.487 | 0.008 |
| Oxidoreductase inhibitor | 0.567 | 0.090 |
| Nitrate reductase (NADH) inhibitor | 0.489 | 0.017 |
| Neurotrophic factor | 0.499 | 0.028 |
| Quercetin 2,3-dioxygenase inhibitor | 0.477 | 0.007 |
| Leucine dehydrogenase inhibitor | 0.469 | 0.009 |
| Acylphosphatase inhibitor | 0.487 | 0.028 |
| Protein-tyrosine kinase (PTK, not ETK, WZC) inhibitor | 0.478 | 0.021 |
| Sleep disorders treatment | 0.481 | 0.026 |
| Chemopreventive | 0.476 | 0.025 |
| Nucleoside-diphosphatase inhibitor | 0.479 | 0.032 |
| Carcinogenic, female mice | 0.481 | 0.037 |
| (S)-3-amino-2-methylpropionate transaminase inhibitor | 0.461 | 0.017 |
| GABA aminotransferase inhibitor | 0.486 | 0.043 |
| (S)-2-hydroxy-acid oxidase inhibitor | 0.440 | 0.012 |
| Scytalone dehydratase inhibitor | 0.460 | 0.034 |
| Carcinogenic, male mice | 0.464 | 0.040 |
| Tyrosine-ester sulfotransferase inhibitor | 0.430 | 0.013 |
| Phosphatidylinositol kinase inhibitor | 0.466 | 0.041 |
| Hydroxymethylbilane synthase inhibitor | 0.437 | 0.024 |
| Insecticide | 0.426 | 0.014 |
| Succinate-semialdehyde dehydrogenase inhibitor | 0.414 | 0.002 |
| CYP2A10 substrate | 0.419 | 0.010 |
| CYP2A1 substrate | 0.496 | 0.088 |
| Glutamate-1-semialdehyde 2,1-aminomutase inhibitor | 0.430 | 0.022 |
| Benzaldehyde dehydrogenase (NAD+) inhibitor | 0.409 | 0.001 |
| Phenol 2-monooxygenase inhibitor | 0.433 | 0.027 |
| Orcinol 2-monooxygenase inhibitor | 0.410 | 0.006 |
| Dihydrobenzophenanthridine oxidase inhibitor | 0.418 | 0.014 |
| 2-Enoate reductase inhibitor | 0.419 | 0.020 |
| Antiamyloidogenic | 0.414 | 0.016 |
| Histamine release inhibitor | 0.453 | 0.057 |
| Porphobilinogen synthase inhibitor | 0.408 | 0.014 |
| N-(5-amino-5-carboxypentanoyl)-L-cysteinyl-D-valine synthase inhibitor | 0.411 | 0.025 |
| Hydroxynitrilase inhibitor | 0.392 | 0.007 |

**Table 2: Predicted Biological Activity Spectrum for Compound II**

26 Substructure descriptors, 0 new. 145 Possible activities at Pa > 30%

| Activity | $P_a$ | $P_i$ |
|---|---|---|
| O-Pyrocatechuate decarboxylase inhibitor | 0.456 | 0.006 |
| Phosphatidylinositol kinase inhibitor | 0.484 | 0.033 |
| Formate dehydrogenase inhibitor | 0.471 | 0.023 |
| Aryl-acylamidase inhibitor | 0.532 | 0.085 |
| Betaine-aldehyde dehydrogenase inhibitor | 0.460 | 0.014 |
| Neurotrophic factor enhancer | 0.539 | 0.101 |
| Leucine dehydrogenase inhibitor | 0.445 | 0.011 |
| Trans-1,2-dihydrobenzene-1,2-diol dehydrogenase inhibitor | 0.452 | 0.027 |
| Ferredoxin-nitrite reductase inhibitor | 0.438 | 0.013 |
| Valine-tRNA ligase inhibitor | 0.472 | 0.049 |
| (S)-3-amino-2-methylpropionate transaminase inhibitor | 0.442 | 0.022 |
| Toxic | 0.491 | 0.073 |
| CYP2C substrate | 0.466 | 0.050 |
| Trypanothione-disulfide reductase inhibitor | 0.446 | 0.034 |
| Malate dehydrogenase inhibitor | 0.438 | 0.027 |
| Acetylindoxyl oxidase inhibitor | 0.427 | 0.020 |
| Quinoprotein glucose dehydrogenase inhibitor | 0.515 | 0.109 |
| Antiamyloidogenic | 0.418 | 0.015 |
| Phenol 2-monooxygenase inhibitor | 0.430 | 0.028 |
| Eye irritation, weak | 0.430 | 0.033 |
| Tyrosine-ester sulfotransferase inhibitor | 0.408 | 0.015 |
| Hydroxymethylbilane synthase inhibitor | 0.422 | 0.030 |
| Insecticide | 0.407 | 0.016 |
| Contraceptive male | 0.410 | 0.022 |
| Nitrate reductase (NADH) inhibitor | 0.413 | 0.029 |
| Succinate-semialdehyde dehydrogenase inhibitor | 0.377 | 0.003 |
| Acylphosphatase inhibitor | 0.389 | 0.016 |
| L-lysine 6-transaminase inhibitor | 0.419 | 0.049 |
| (S)-canadine synthase inhibitor | 0.411 | 0.041 |
| Nucleoside-diphosphatase inhibitor | 0.381 | 0.013 |
| Benzaldehyde dehydrogenase (NAD+) inhibitor | 0.415 | 0.048 |
| Hemostatic | 0.413 | 0.053 |
| Glutamate-1-semialdehyde 2,1-aminomutase inhibitor | 0.385 | 0.028 |
| Hydroxynitrilase inhibitor | 0.344 | 0.010 |
| Pyridoxamine-phosphate oxidase inhibitor | 0.350 | 0.016 |

**Table 3: Predicted Biological Activity Spectrum for Compound III**

29 Substructure descriptors; 0 new. 98 Possible activities at Pa > 30%

| Activity | $P_a$ | $P_i$ |
|---|---|---|
| Pyridoxine 5-dehydrogenase inhibitor | 0.468 | 0.006 |
| Eye irritation, weak | 0.484 | 0.025 |
| Excitatory amino acid antagonist | 0.477 | 0.018 |
| Pyridoxamine-pyruvate transaminase inhibitor | 0.454 | 0.001 |
| Benzoate 4-monooxygenase inhibitor | 0.440 | 0.021 |
| NADPH:quinone reductase inhibitor | 0.434 | 0.026 |
| Phosphatidylinositol kinase inhibitor | 0.443 | 0.045 |
| Formate dehydrogenase inhibitor | 0.416 | 0.036 |
| Nitrate reductase (NADH) inhibitor | 0.409 | 0.030 |
| Leucine dehydrogenase inhibitor | 0.387 | 0.020 |
| (S)-3-amino-2-methylpropionate transaminase inhibitor | 0.401 | 0.037 |
| Benzaldehyde dehydrogenase (NAD+) inhibitor | 0.359 | 0.001 |
| Malate dehydrogenase inhibitor | 0.388 | 0.041 |
| O-Pyrocatechuate decarboxylase inhibitor | 0.352 | 0.007 |
| Urokinase-type plasminogen activator receptor antagonist | 0.358 | 0.014 |
| Betaine-aldehyde dehydrogenase inhibitor | 0.372 | 0.029 |
| **Table 3 continue.....** | | |
| Antiinfective | 0.393 | 0.053 |
| Mandelonitrile lyase inhibitor | 0.355 | 0.015 |
| Insecticide | 0.366 | 0.027 |
| Plasmin inhibitor | 0.368 | 0.030 |
| Dihydroxy-acid dehydratase inhibitor | 0.429 | 0.090 |
| Succinate-semialdehyde dehydrogenase inhibitor | 0.339 | 0.004 |
| Antiamyloidogenic | 0.371 | 0.039 |
| Plasminogen activator inhibitor | 0.353 | 0.023 |
| Toxic | 0.431 | 0.103 |
| Trypanothione-disulfide reductase inhibitor | 0.389 | 0.062 |
| Ferredoxin-nitrite reductase inhibitor | 0.359 | 0.036 |
| Alzheimer's disease treatment | 0.401 | 0.081 |
| Trans-1,2-dihydrobenzene-1,2-diol dehydrogenase inhibitor | 0.362 | 0.042 |
| Hydroxymethylbilane synthase inhibitor | 0.377 | 0.058 |
| Interferon agonist | 0.406 | 0.093 |
| Trans-cinnamate 4-monooxygenase inhibitor | 0.439 | 0.132 |
| Antiviral (Adenovirus) | 0.374 | 0.070 |
| Neurotransmitter uptake inhibitor | 0.411 | 0.117 |
| Alcohol dehydrogenase (NADP+) inhibitor | 0.332 | 0.037 |
| Pyridoxamine-phosphate oxidase inhibitor | 0.314 | 0.025 |

**Table 4: Predicted Biological Activity Spectrum for Compound IV**

28 Substructure descriptors; 1 new. 240 Possible activities at Pa > 30%

| Activity | $P_a$ | $P_i$ |
|---|---|---|
| Carcinogenic, group 2B | 0.494 | 0.018 |
| CYP2A6 substrate | 0.498 | 0.025 |
| CYP2A11 substrate | 0.495 | 0.028 |
| Vitamin-K-epoxide reductase (warfarin-insensitive) inhibitor | 0.496 | 0.031 |
| Hydroxymethylbilane synthase inhibitor | 0.474 | 0.014 |
| Plastoquinol-plastocyanin reductase inhibitor | 0.473 | 0.019 |
| 3-Oxoadipate enol-lactonase inhibitor | 0.484 | 0.032 |
| Vasodilator | 0.490 | 0.042 |
| Myosin ATPase inhibitor | 0.481 | 0.033 |
| Nitrate reductase inhibitor | 0.486 | 0.038 |
| Lactose synthase inhibitor | 0.473 | 0.028 |
| Cytochrome P450 inhibitor | 0.496 | 0.055 |
| Mutagenic | 0.452 | 0.014 |
| Insecticide | 0.443 | 0.012 |
| Nicotinamidase inhibitor | 0.444 | 0.017 |
| Lactate 2-monooxygenase inhibitor | 0.478 | 0.054 |
| 3-Hydroxyphenylacetate 6-hydroxylase inhibitor | 0.430 | 0.009 |
| Membrane permeability inhibitor | 0.523 | 0.103 |
| Carcinogenic, group 2A | 0.445 | 0.026 |
| Mutagenic, Salmonella | 0.431 | 0.014 |
| Carcinogenic, female rats | 0.449 | 0.033 |
| Alcohol O-acetyltransferase inhibitor | 0.491 | 0.080 |
| CYP3A3 substrate | 0.477 | 0.076 |
| DNA ligase (ATP) inhibitor | 0.429 | 0.030 |
| Trans-pentaprenyltranstransferase inhibitor | 0.490 | 0.093 |
| CYP2B substrate | 0.424 | 0.029 |
| Prostaglandin antagonist | 0.458 | 0.066 |
| Succinate-semialdehyde dehydrogenase inhibitor | 0.394 | 0.003 |
| Strictosidine beta-glucosidase inhibitor | 0.443 | 0.052 |
| Glutathione-disulfide reductase inhibitor | 0.405 | 0.015 |
| Antituberculosic | 0.410 | 0.021 |
| Beta-mannosidase inhibitor | 0.464 | 0.076 |
| (R)-Pantolactone dehydrogenase (flavin) inhibitor | 0.479 | 0.092 |
| Ferredoxin-NADP+ reductase inhibitor | 0.466 | 0.080 |
| Undecaprenyl-diphosphatase inhibitor | 0.450 | 0.067 |
| Excitatory amino acid antagonist | 0.416 | 0.033 |

## 3. Result and Discussion

The total no. of PASS prediction incorporated in the Enhanced NCI Data Brows is 64 188 21 as of now. PASS predicts biological activity spectrum on the basis of structural formula of compounds.

When the user of the web server selects query type, "PASS prediction range ……. "a separate sector pop up window appears in which the user can scroll through 565 possible predicted activities. A specific activity has to be selected, and the type of prediction (Probability of activity [$P_a$] or inactivity [$P_i$] respectively) has to be specified.

The Pa and Pi values vary from 0.000 to 1.000. To define the threshold for selecting type of activity to predicted, the cutoff value should be chosen. Only activities with $P_a$ value greater than the chosen threshold will be given in predicted activity spectra.

If Pa > 0.7, the compound is very likely to reveal its activity in experiments, but in this case, the chance of being the analogue of the known pharmaceutical agents for this compound is also high.

If 0.5 < Pa > 0.7, the compound is likely to reveal this activity in experiments, but this probability is less and the compound is not so similar to the known pharmaceutical agents.

If Pa < 0.5, the compound is unlikely to reveal this activity in experiments, but if the presence of this activity is confirmed in the experiment, the compound might be a New Chemical Entity (NCE).

However it is necessary to keep in mind: PASS cannot predict whether compound become a drug, it only provided the 'food for thought' for the medicinal chemists.

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