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Prediction of Activity Spectra and Synthesis of Some Substituted Coumarins

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Coumarin nucleus containing drugs have its own importance in drug chemistry. Coumarins and its substituted compounds possess various pharmacological activities and can be used in the treatment of cancer. Compounds of coumarins and substituted coumarins are prepared from phenol and malonic acid by cyclization with $POCl_3$ and fused $ZnCl_2$ and their activity were examined by computer based programmed called PASS (prediction of activity spectra for substances). The result of PASS studies shows that the substituted coumarins and unsubstituted coumarins show many important biological activities. Among that the unsubstituted coumarins shows properties such as phosphatase inhibitors, CYP2A3 substrate, antianemic, nitrate reductase inhibitor, histamine release inhibitor, *etc*. Predicted result shows that unsubstituted coumarins show strong activities than substituted coumarins.

Key Words: Heterocycles, Coumarins, Pechman condensation, Phenol, Biological activity, PASS.

INTRODUCTION

Heterocyclic compounds containing oxygen and heteroatom in ring enhance their biocidal application mainly in medicinal chemistry. The literature survey also revels that coumarin containing nucleus has numerous biological activity. Research scientists are trying to synthesize coumarin nucleus containing drugs and investigating their medicinal properties. Rehman *et al.*[1] had successfully studied *in vitro* antibacterial, antifungal and cytotoxic activities of coumarin. Shyamala *et al.*[2] examined several 3-aminocoumarins derivatives for their antifeeding and insect-growth-regulating activity. Okamoto *et al.*[3] studied chemical aspect of coumarin compound for prevention of hepatocellular carcinoma. Recently, most important investigation in view of medicinal properties of coumarins is carried out by Kostova *et al.*[4]. They studied structure-activity relationship of synthetic coumarins as HIV-1 inhibitors.

Keeping these importance of coumarin nucleus in medicinal field, the active biological properties of these compounds were tried to predict using computer based programmed which is developing as a methods for rapidly evaluating molecules for suspected biological activity and relative potency and designing molecules for desired biological activity called as PASS (prediction of activity spectra for substances)[5-11].

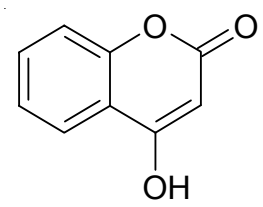
The applications of the programmed PASS to about 2,50,000 compounds are described. A total 565 different types of activity are included encompassing general pharmacological effects, specific mechanism of action, known toxicities and others. Application of this web-based computer service for prediction of activities of the kinds angiogenesis inhibitor, antiviral(HIV) and a set of activities that can be associated with antineoplastic action are reported[12].

EXPERIMENTAL

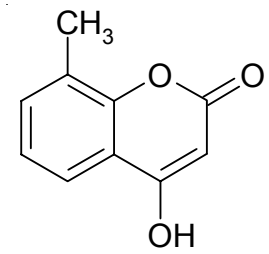
PASS internet predicts 900 pharmacological effects, mechanism of action, metagenicity, carcinogenicity, teratogenicity and embryo toxicity. The result of prediction is displayed in the computer automatically.

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

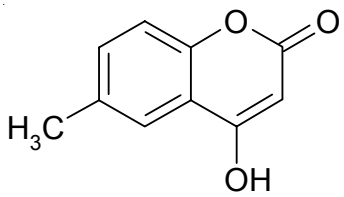
Synthesis of compounds: One pot synthesis of coumarins catalyzed by the solid base, calcined Mg-Al hydrotalcite was carried out by Ramani *et al.*[17]. Many scientist reported synthesis of coumarins by well known synthetic routes including Perkin, Rasching, Pechmann, Knoevenagel and Wittg reaction[18-20]. In present studies, 4-hydroxy coumarins (**I-IV**) were synthesized by reported methods[21-25].



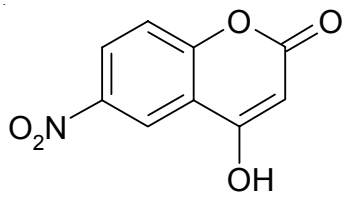
4-Hydroxy coumarin (**I**)



8-Methyl-4-hydroxy coumarin (**II**)



6-Methyl-4-hydroxy coumarin (**III**)



6-Nitro-4-hydroxy coumarin (IV)

Phenol (27 g), malonic acid (30 g), $POCl_3$ (50 mL) and fused $ZnCl_2$ (120 g) were mixed together and mixture was heated at 60-65 ºC for 4 h. It was then decomposed by adding crushed ice and the sticky solid was then treated with saturated

solution of $NaHCO_3$, filtered and the filtrate was acidified with conc. HCl just to neutral point when some oily material separated. It was removed and the solution was then acidifying with excess of conc. HCl, when 4-hydroxy coumarin separated. It was then crystallized from ethanol as yellow needles. Other substituted coumarins were also prepared by following same procedure.

Basic elements of PASS

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 pre-clinical testing now.

Chemical structure description: Multi-level neighbourhoods of atoms (MNA) structure descriptors of a molecule are generated on the basis of connection table and table of atoms types presented by the compounds.

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.

Biological activity spectrum: As described above, PASS predicts simultaneously 400 kinds of activity with mean accuracy of prediction about 85 % on the basis of the compounds structural formula. 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.

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

RESULTS AND DISCUSSION

Interpreting the results of prediction: PASS Internet predicts biological activity spectrum on the basis of structural formula of the compound. The compounds are considered equivalent in PASS if they have the same molecular formulae and the same set of MNA descriptors.

The result of prediction is presented (Table-1) as the list of activities with appropriate Pa and Pi sorted in descending order of difference (Pa-Pi) > 0.

Pa and Pi are the estimates of probability for the compound to be active and inactive, respectively for each type of activity from the biological activity spectrum. Their values vary from 0.000 to 1.000. It is reasonable that only those types of activities may be revealed by the compound, where Pa > Pi and so they are put into the biological activity spectrum.

If Pa > 0.7, the compound is 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.

TABLE-1
PREDICTED BIOLOGICAL ACTIVITY SPECTRUM OF
FOR 4-HYDROXY COUMARINS

No.	Pa	Pi	Activity
			4-Hydroxy coumarin (**I**)
1	0.883	0.020	Monodehydroascorbate reductase (NADH) inhibitor
2	0.865	0.017	Phosphatase inhibitor
3	0.754	0.026	Sickle-cell anemia treatment
4	0.717	0.010	NADPH:Quinone reductase inhibitor
5	0.692	0.010	Anticonvulsant
6	0.615	0.012	Carcinogenic, group 2B
7	0.579	0.015	Nitrilase inhibitor
8	0.534	0.034	Cholestanetriol 26-monooxygenase inhibitor
9	0.542	0.046	Antianemic
10	0.468	0.022	Carcinogenic
			8-Methyl-4-hydroxy coumarin (**II**)
1	0.938	0.005	Psychosexual dysfunction treatment
2	0.906	0.006	Antineurotic
3	0.895	0.010	Phosphatase inhibitor
4	0.745	0.007	CYP2A3 substrate
5	0.696	0.022	Uroporphyrinogen-III synthase inhibitor
6	0.686	0.059	Sickle-cell anemia treatment
7	0.622	0.040	Histidinol dehydrogenase inhibitor
8	0.575	0.032	Antianemic
9	0.555	0.012	Alcohol dehydrogenase (NADP+) inhibitor
10	0.523	0.028	Nitrate reductase inhibitor
			6-Methyl-4-hydroxy coumarin (**III**)
1	0.881	0.013	Phosphatase inhibitor
2	0.746	0.029	Sickle-cell anemia treatment
3	0.606	0.005	Aldehyde dehydrogenase (NAD+) inhibitor
4	0.588	0.007	Aldehyde dehydrogenase inhibitor
5	0.598	0.029	Leukotriene C4 antagonist
6	0.569	0.013	Carcinogenic, group 2B
7	0.570	0.034	Antianemic
8	0.488	0.020	Carcinogenic
9	0.437	0.027	Bone formation stimulant
10	0.390	0.024	Alcohol dehydrogenase (NADP+) inhibitor
11	0.425	0.063	Anticonvulsant
			6-Nitro-4-hydroxy coumarin (**IV**)
1	0.928	0.006	Phosphatase inhibitor
2	0.817	0.008	Sickle-cell anemia treatment
3	0.723	0.010	Kinase inhibitor
4	0.728	0.017	Histidinol dehydrogenase inhibitor
5	0.673	0.008	Vitamin-K-epoxide reductase inhibitor
6	0.651	0.014	Antianemic
7	0.624	0.031	Cathepsin G inhitor
8	0.518	0.015	Bone formation stimulant
9	0.481	0.026	Sleep disorders treatment
10	0.476	0.025	Chemopreventive

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).

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REFERENCES

1. S.U. Rehman, Z.H. Chohan, F. Gulnaz, C.T. Supran, *J. Enzyme Inhibit. Med. Chem.*, **20**, 333 (2005).
2. B.S. Shyamala, P.V. Ananthlakshmi, V.J. Raju, P.N. Rao and P.U. Reddy, *Spring J. Chem.*, **5**, 23 (1992).
3. T. Okamoto, T. Kobayashi and S. Yoshida, *Curr. Med. Chem.*, **5**, 47 (2005).
4. S.R. Kostova, P. Genova and R. Argirova, *Bioinorg. Chem. Appl.*, 68274 (2006).
5. M.H. Elnagdi and H. Wamhoff, *J. Heterocycl. Chem.*, **18**, 1287 (1981).
6. Y. Tominaga, S. Ohno, S. Kohra, H. Fujito and H. Mazume, *J. Heterocycl. Chem.*, **28**, 1039 (1991).
7. M. Sakamoto, K. Miyazawa and Y. Tomimatsu, *Chem. Pharm. Bull.*, **25**, 3360 (1977).
8. G.J. Doad, I. Dorcas, O.F. Scheinmann, P.A. Bates and M.B. Hurthouse, *J. Chem. Soc. Perkin Trans. I*, 2993 (1988).
9. U. Urleb, *J. Heterocycl. Chem.*, **32**, 69 (1995).
10. T. Okabe, E. Taniguchi and K. Maekawa, *J. Fac. Agric. Kyushu. Univ.*, **17**, 195 (1973); *Chem. Abstr.*, **79**, 32002 (1973).
11. T. La Noce, E. Bellasio, A. Vigevani and E. Testa, *Ann. Chim. (Rome)*, **62**, 647 (1972).
12. V.V. Poroikov, D.A. Filimonov, W.-D. Ihlenfeldt and M.C. Nicklaus, *J. Chem. Inf. Comput. Sci.*, **43**, 228 (2003).
13. N. Yoshida, K. Wachi and K. Tanaka, *Japan Kokai*, **82**, 171095 (1974); *Chem. Abstr.*, **82**, 171095 (1975).
14. M. Kidwai and N. Negi, *Monatsh. Fur. Chemie*, **128**, 85 (1997).
15. M.A. Salama and S.A. El-Essa, *Indian J. Chem.*, **40**, 678 (2001).
16. Nizamuddin, M. Mishra, M.K. Srivastava and M.H. Khan, *Indian J. Chem.*, **40B**, 49 (2001).
17. A. Ramani, B.M. Chandra, S. Velu and S. Sivasanker, *Green Chem.*, **1**, 163 (1999).
18. A.K. Chatterjee, F. Dean Toste, S.D. Goldberg and R.H. Grubbs, *Pure Appl. Chem.*, **75**, 421 (2003).
19. C.H. Schroder and K.P. Link, *J. Am. Chem. Soc.*, **79**, 3291 (1957); A.M.A. Drug Evaluations, Publishing Sciences Group Inc., Littleton, MA, edn. 3, p. 121 (1977).
20. Y.L. Chen, T.C. Wang, S.C. Liang, C.M. Teng and C.C. Tzeng, *Chem. Pharm. Bull.*, **44**, 1591 (1996); Y.L. Chen, T.C. Wang, K.H. Lee, C.C. Tzeng and C.M. Teng, *Helv. Chem. Acta*, **79**, 651 (1996).
21. S.K. De and R.A. Gibbs, *Synthesis*, 1231 (2005).
22. M.K. Potdar, S.S. Mohile and M.M. Salunkhe, *Tetrahedron Lett.*, **42**, 9285 (2005).
23. O'Kennedy, R.D.Thornes, Coumarins: Biology, Application and Mode of Action, Wiley & Sons, Chichester (1997).
24. M. Zahradnik, The Production and Application of Fluorescent Brightening Agents, Wiley & Sons (1992).
25. M. Maeda, Laser Dyes, Academic Press, New York (1994).

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