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SYNTHESIS AND BIOLOGICAL EVALUATION OF FLAVONOIDS AND RELATED COMPOUNDS AS GASTROPROTECTIVE AGENTS

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Abstract: Several analogs of the gastroprotective molecule flavone have been synthesized and evaluated for gastroprotective activity. A C2-C3 double bond and an intact C ring appear necessary for optimum activity. Activity can be retained by replacing the 2-phenyl substituent with other groups but is eliminated when this ring is moved from the 2- to the 3-position.

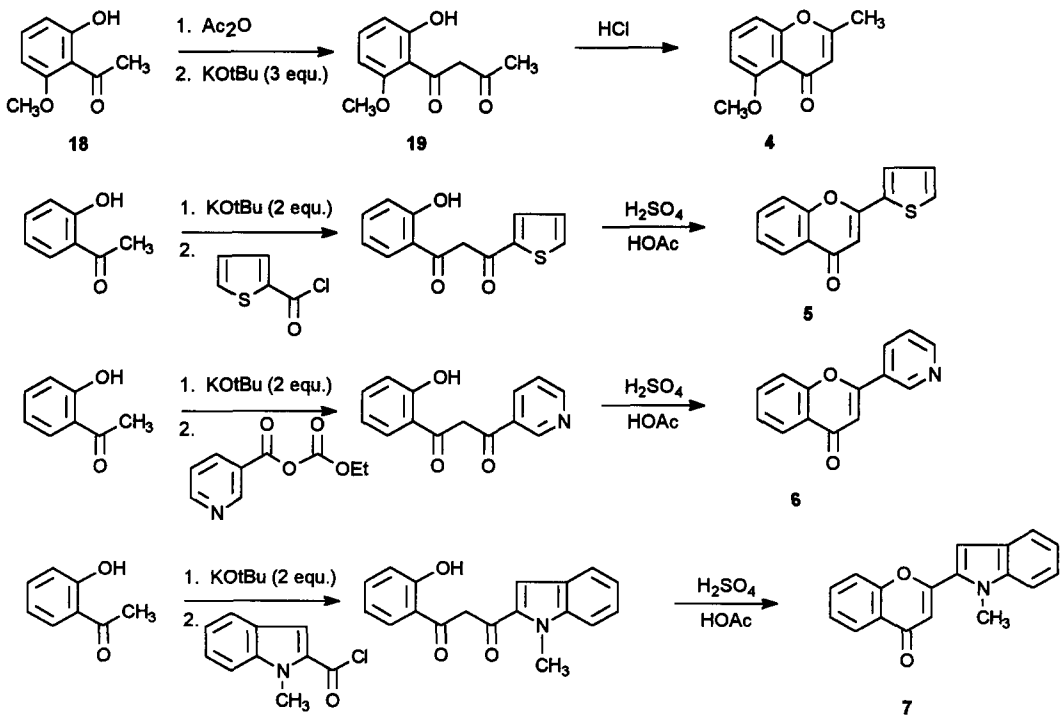
Gastric damage can affect as many as 25% of all patients taking non-steroidal anti-inflammatory drugs (NSAID's) on a chronic basis, and it probably represents the most frequent drug side effect in the United States.[1,2] Standard anti-ulcer medications are largely ineffective in preventing this damage.[3] The prostaglandin E_1 analog misoprostol has been found to be effective, but it has side effects which limit its general utility.[4] For these reasons, the development of a safe and effective gastroprotective drug, which can be coadministered to patients taking NSAID's, represents an important medical need.

Recently, we discovered that the simple unsubstituted molecule flavone (**1**) was gastroprotective in the rat ethanol damage model.[5] Several substituted flavones were also found to show good gastroprotective activity.[5] Flavones comprise a major subclass of a more broadly defined family of plant products known as flavonoids. We raised the question as to whether other types of flavonoids might possess gastroprotective properties, or, in a more general sense, what types of structural changes can be tolerated on the core flavone structure without loss of gastroprotective activity. Herein, we describe the effect of the following five types of changes on activity: modification of the aromatic B ring, shifting of the B ring from the 2- to the 3-position (i.e., isoflavones), saturation of the 2-3 double bond (i.e., flavanones), fragmentation of the C ring (i.e., chalcones), and heteroatomic replacements.

The structures of the compounds utilized in this study are indicated in Table 1. Compounds **10**, **11**, **14**, and **15** were purchased from commercial sources.[6] Compounds **2**, **3**, **8**, **9**, **12**, and **17** were prepared as previously described.[7] The synthesis of 2-substituted chromones **4-7** is indicated in Scheme 1. Hydroxyacetophenone **18**[8] was acetylated with acetic anhydride, and the resulting ester was treated with three equivalents of potassium t-butoxide (KOtBu) to form the diketone **19**. Cyclization with hydrochloric acid afforded chromone **4**.[9] Thienylchromone **5**[10] and indolylchromone **7**[9] were synthesized from hydroxyacetophenone and the appropriate heterocyclic acid chloride using a KOtBu-mediated diketone synthesis as the key step,[11] followed by treatment of the intermediate diketone with acid. Pyridine **6**[10] was

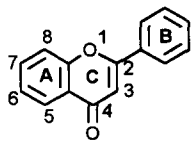
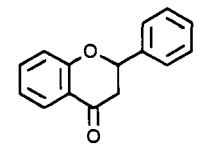
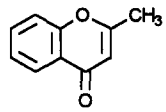
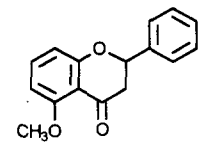
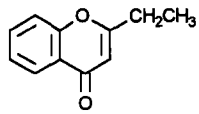
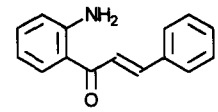
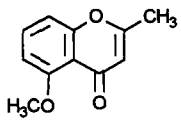
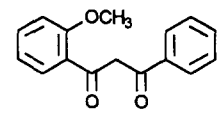
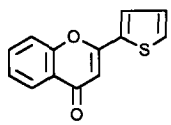
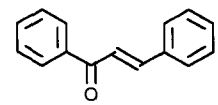
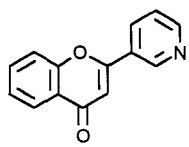
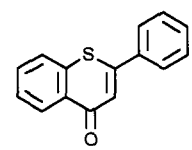
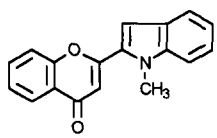
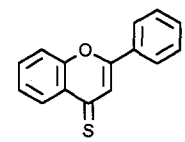
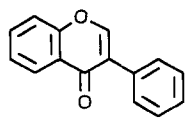
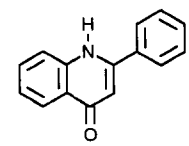
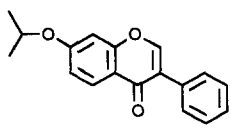
prepared in a similar way except a mixed anhydride, rather than an acid chloride, was used as the heterocyclic electrophile. Diketone **13**[12] was prepared by heating a mixture of acetophenone, methyl o-anisate and sodium hydride in tetrahydrofuran. Finally, flavothione **16**[13] was synthesized from flavone using Lawesson's Reagent.

SCHEME 1



All compounds were evaluated for their gastroprotective properties in the rat ethanol-induced damage model[5,14] following intraperitoneal administration. Groups consisting of 7-10 rats were pretreated with drug prior to ethanol administration, and treatment mean damage was compared to control mean damage (group received ethanol but no drug) to determine percent protection ("% PROTECT.", Table 1, with standard error, SE, in parentheses) of the corpus region of the stomach. Data for cimetidine and PGE_2 are also shown for comparison. Potency data in the form of ED_{50} values (with 95% confidence limits shown in parentheses) are included for compounds **1-3**. In most cases, a structure-activity pattern has emerged for the parameters under investigation. For example, the data suggest that with regard to the aromatic B ring, a wide range of changes can be tolerated without loss of gastroprotective activity. One can replace the aromatic ring with a small alkyl group, as in alkylchromones **2-4**, and still retain gastroprotective properties. One can also replace the phenyl ring with heterocyclic rings of similar size (i.e., thiophene **5** and pyridine **6**) or even of much larger size (i.e., indole **7**) and retain the activities of the parent flavone molecule. On the other hand, we have found that a number of changes on the flavone molecule are not tolerated. For instance, moving the flavone B ring from the 2-position to the 3-position, as in the case of isoflavones **8** and **9**, leads to loss of

TABLE 1: GASTROPROTECTION DATA FOR COMPOUNDS **1-17** (20 mg/kg) FOLLOWING INTRAPERITONEAL ADMINISTRATION IN THE RAT ETHANOL DAMAGE MODEL

CMPD	STRUCTURE	% PROTECT. (SE)	CMPD	STRUCTURE	% PROTECT. (SE)
1		88 (5) [ED_{50}: 6.9 mg/kg (4.4-16.9)]	**10**		24 (17)
2		76 (8) [ED_{50}: 5.4 mg/kg (4.1-7.4)]	**11**		32 (15)
3		74 (12) [ED_{50}: 4.3 mg/kg (0.5-9.7)]	**12**		36 (14)
4		81 (5)	**13**		19 (24)
5		82 (7)	**14**		32 (35)
6		97 (1)	**15**		67 (11)
7		74 (8)	**16**		58 (13)
8		< 10	**17**		17 (24)
9		< 10	**CIMETIDINE**	(52 mg/kg, oral administration)	14 (39)
			PGE_2	(0.1 mg/kg, oral administration)	64 (19)

biological activity. Similarly, activity is greatly reduced when the carbon-carbon bond in the 2-3 position is changed from a double bond to a single bond, as is the case with flavanones **10** and **11**. We have also found that any effort to fragment the C ring leads to reduction in activity, as is the case with chalcone **14**, aminochalcone **12** or methoxydiketone **13**. Finally, we have found variable results when the oxygen atoms of flavone are replaced with other heteroatoms. Replacement of either oxygen atom with sulfur produces compounds (**15**, **16**) with intermediate levels of activity. Somewhat surprisingly, quinolone **17** shows reduced gastroprotective activity; however, this may be due to limited bioavailability, since the compound is poorly soluble in the suspension vehicle.[5]

In summary, we have found that in the rat ethanol-induced gastric damage model, flavone gastroprotection requires a C2-C3 double bond and an intact C ring. The phenyl ring at the 2-position cannot be moved to the 3-position but can be replaced by a variety of smaller and larger substituents.

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References and Notes

1. Geis, G. S.; Stead, H.; Wallemark, C.; Nicholson, P. A. *J. Rheumatol.* **1991**, *18 (suppl 28)*, 11.
2. Fries, J. F.; Miller, S. R.; Spitz, P. W.; Williams, C. A.; Hubert, H. B.; Bloch, D. A. *Gastroenterology* **1989**, *96*, 647.
3. a. McCarthy, D. M. *Gastroenterology* **1989**, *96*, 662. b. Lanza, F.; Robinson, M.; Bowers, J.; Griffin, J.; Kogut, D.; Kogan, F. Warner C. *Gastroenterology* **1988**, *94*, A250.
4. Monk, J. P.; Clissold, S. P. *Drugs* **1987**, *33*, 1.
5. Ares, J. J.; Outt, P. E.; Randall, J. L.; Murray, P. D.; Weisshaar, P. S.; O'Brien, L. M.; Ems, B. L.; Kakodkar, S. V.; Kelm, G. R.; Kershaw, W. C.; Werchowski, K. M.; Parkinson, A. *J. Med. Chem.* **1995**, *38*, 4937.
6. Compounds **10** and **11** were obtained from Indofine Chemicals. Compounds **14** and **15** were obtained from the Aldrich Chemical Company.
7. a. Hirao, I.; Yamaguchi, M.; Hamada, M. *Synthesis* **1984**, 1076. b. Prakash, O.; Pahuja, S.; Goyal, S., Sawhney, S.; Moriarty, R. M. *Synlett.* **1990**, 337. c. Feuer, L.; Nogradi, M.; Gettsegen, A.; Vermes, B.; Strelisky, J.; Wolfner, A.; Farkas, L.; Antus, S.; Toth, M. K.; U. S. Patent 4,166,862; 1979. d. Donnelly, J. A.; Farrell, D. F. *J. Org. Chem.* **1990**, 55, 1757. e. Staskun, B.; Israelstam, S. S. *J. Org. Chem.* **1961**, *26*, 3191.
8. Lau, C. K.; Belanger, P. C.; Defresne, C.; Scheigetz, J. *J. Org. Chem.* **1987**, *52*, 1670.
9. This compound has been fully characterized by NMR (^{1}H, ^{13}C), MS and elemental analysis.
10. Devitt, P. F.; Timoney, A.; Vickars, M. A. *J. Org. Chem.* **1961**, *26*, 4941.
11. Ares, J. J.; Outt, P. E.; Kakodkar, S. V.; Buss, R. C.; Geiger, J. C. *J. Org. Chem.* **1993**, *58*, 7903.
12. Kiuchi, F.; Chen, X.; Tsuda, Y. *Chem. Pharm. Bull.* **1990**, *38*, 1862.
13. Baker, W.; Harborne, J. B.; Ollis, W. D. *J. Chem. Soc.* **1952**, 1303.
14. Robert, A.; Nezamis, J. E.; Lancaster, C.; Hanchar, *J. Gastroenterology* **1979**, *77*, 433.

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