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Synthesis of degradants and impurities of rabeprazole

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Abstract---Rabeprazole is an antiulcer drug comes under the Pharmacological class (antisecretory compounds) which is Proton-pump inhibitor, and It's used for heartburn, acid reflux and GORD (gastro-oesophageal reflux disease). Rabeprazole is also used to prevent and treat stomach ulcers. We have observed some of the metabolite and impurities during the process of synthesis of Rabeprazole. The main aim of the present work is to synthesis and characterisation of impurities and metabolites.

Keywords---metabolite, impurities, rabeprazole, anti-ulcerative drug.

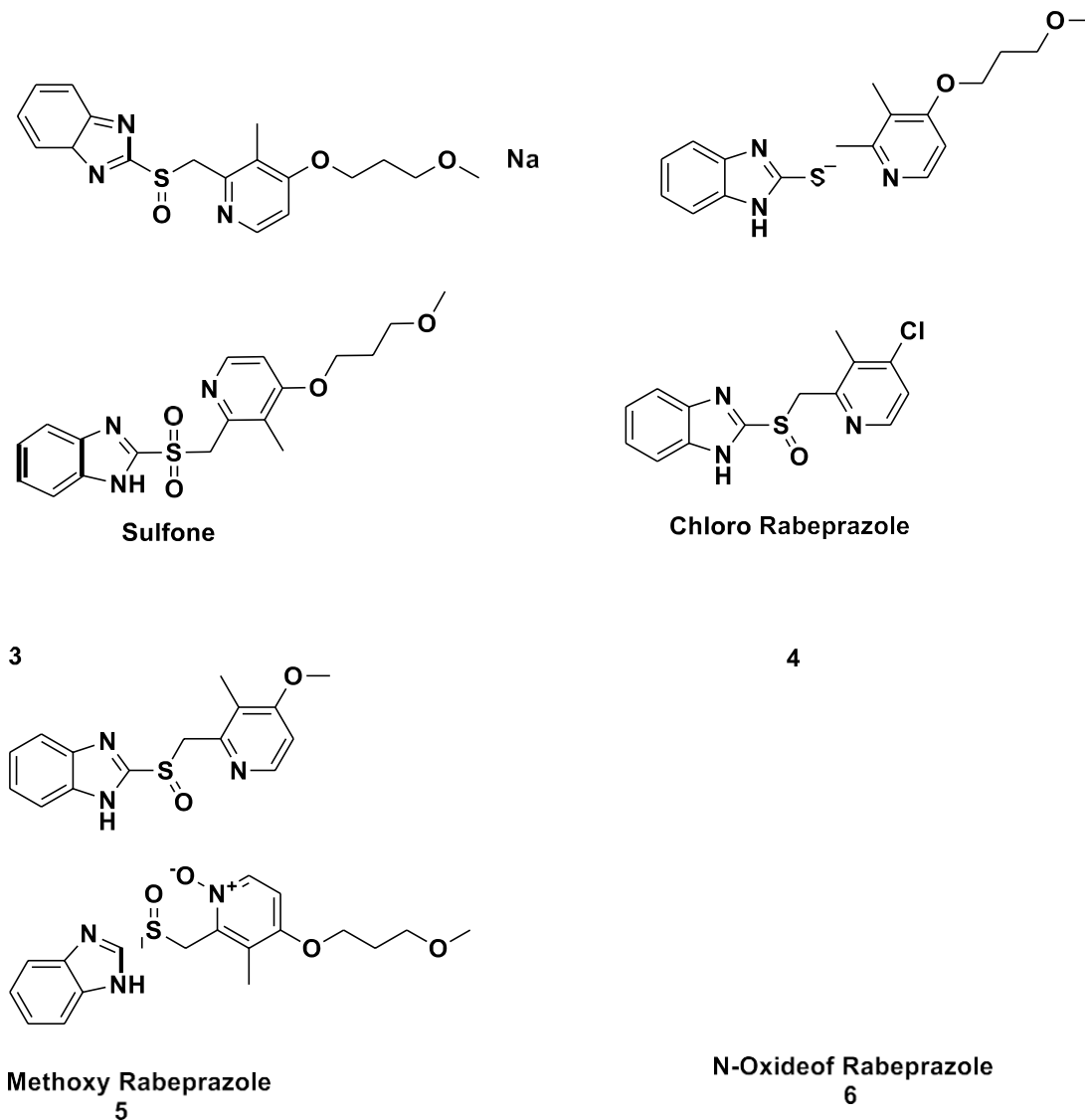
Introduction

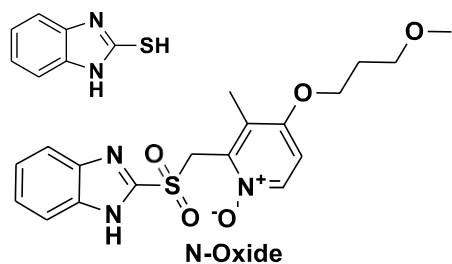
Rabeprazole belongs to class of antisecretory compounds which do not exhibit anticholinergic or histamine H₂-receptor antagonist properties, but suppress gastric acid secretion by inhibiting the gastric H⁺/K⁺ATPase (ATP- Adenosine Triphosphatase) at the secretory surface of the gastric parietal cell. Rabeprazole blocks the final step of the gastric acid secretion. The presence of the impurities and metabolites which will have a significant impact on the quality and safety of the final drug. As per the ICH and EP and USP Monograph all the impurities and related substances must be in the limits of < 0.10%, by identifying and minimizing these impurities to can get high purity desired compound or product, as these impurities are not available in the market and which are highly useful to companies producing Rabeprazole. This is the main objective in the synthesis of these impurities.

Results and Discussions

Synthesis and information regarding these impurities and some of the precursors which are important for the synthesis of these impurities which are not available are also synthesised which are highly useful for the bulk manufacturers of Proton-pump inhibitor drug Rabeprazole and useful for the analytical development of the drug and regulatory agencies.

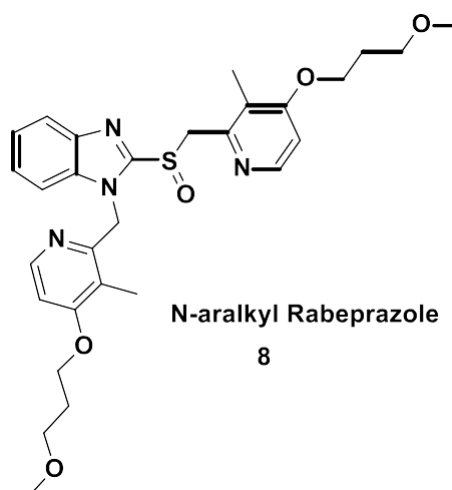
Fig 1. Impurities and metabolites of Rabeprazole
Sulfone





Rabeprazole sulfone-N-oxide

7

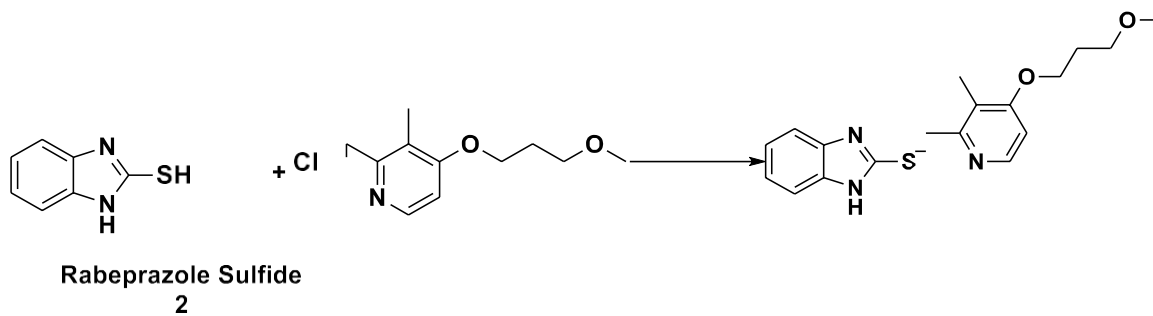


N-alkyl Rabeprazole

8

Synthesis Schemes

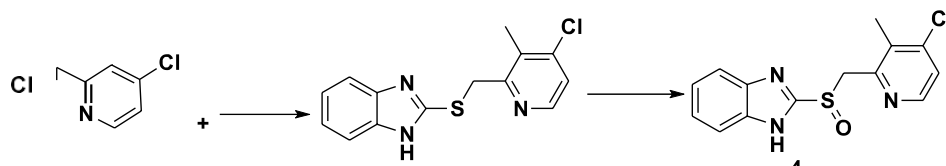
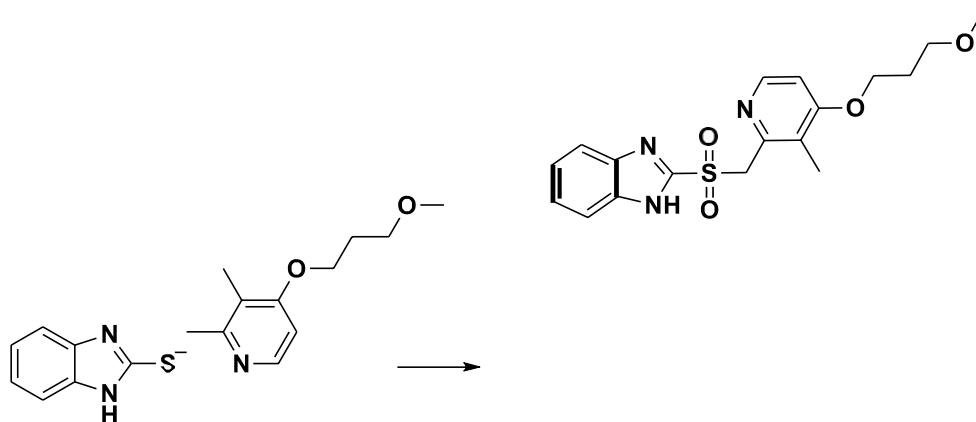
Scheme-1 Synthesis of Rabeprazole Sulfide (**2**)



Rabeprazole Sulfide

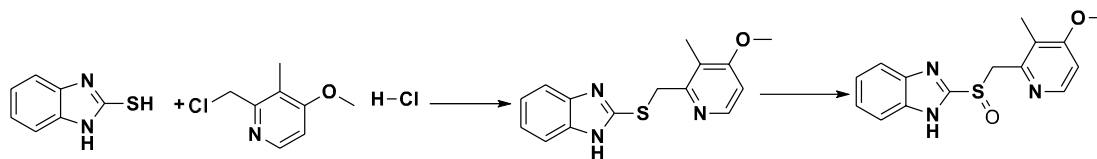
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Scheme-2 Synthesis of Rabeprazole Sulfone (**3**) from Rabeprazole Sulfide (**2**)

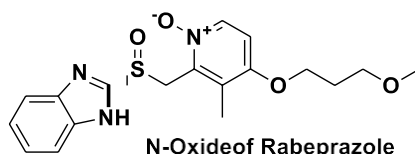
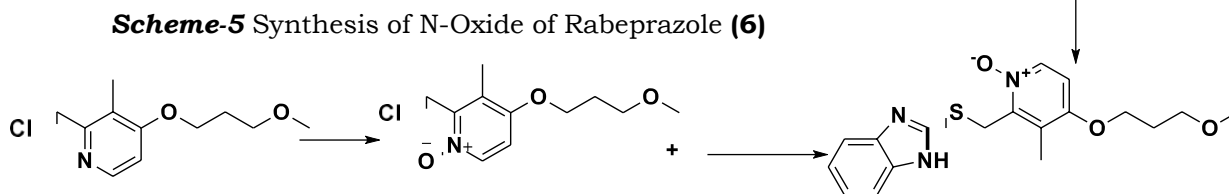


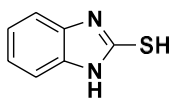
Chloro Rabeprazole

Methoxy Rabeprazole

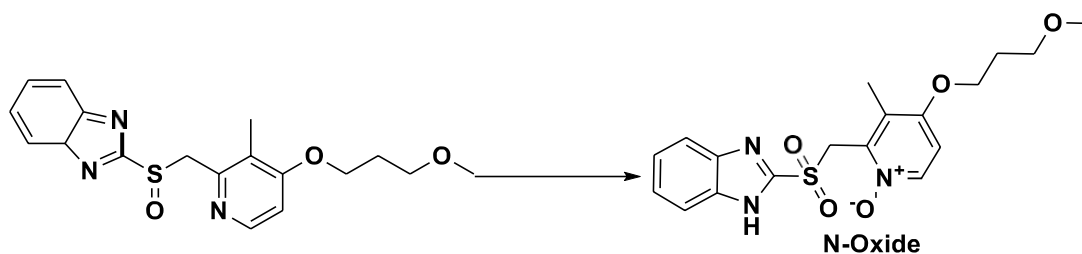


N-Oxide of Rabeprazole





Scheme-6 Synthesis of Rabeprazole sulfone-N-oxide (**7**)



Rabeprazole free base

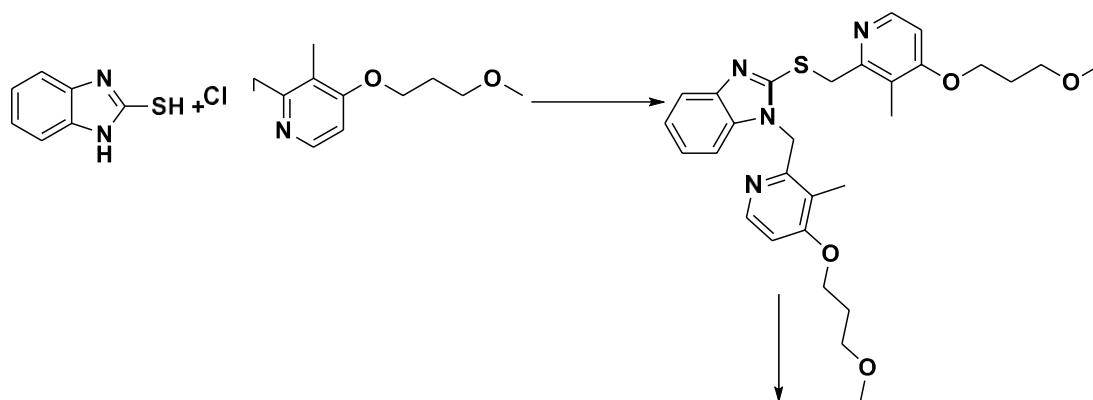
Rabeprazole sulfone-N-oxide

1

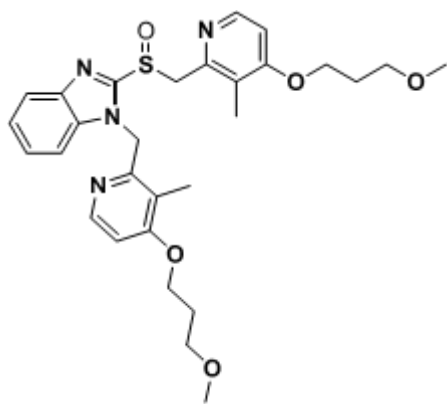
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Scheme-7 ROS-1 Synthesis of N-aralkyl Rabeprazole (**8**)

N-aralkyl Rabeprazole ROS-1

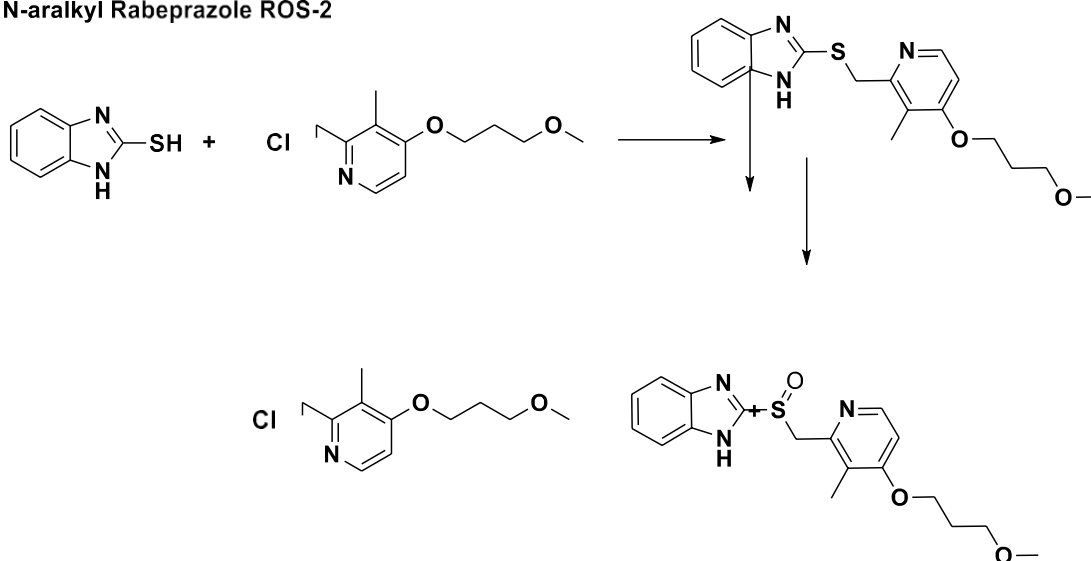


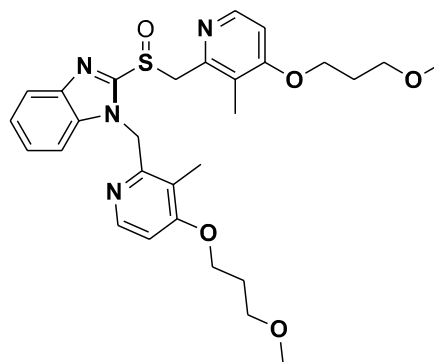
N-aralkyl Rabeprazole



Scheme-8 ROS-2 Synthesis of N-aralkyl Rabeprazole (**8**)

N-aralkyl Rabeprazole ROS-2





N-aralkyl Rabeprazole

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Experimental

All compound synthesised were well analysed and charactered, ^1H NMR were recorded at 400 MHz. The mass analysis was performed on Waters LC-MS mass spectrometer. Melting points were determined on capillary melting-point apparatus without correction. The solvents and reagents were used without any further purification.

Rabeprazole Sulfide 2

2-(((4-(3-methoxypropoxy)-3-methylpyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole

To a stirred solution of 1H-benzo[d]imidazole-2-thiol (3.85g), NaOH (1.875g) in acetone 25mL, and water 25mL, a solution of 2-(chloromethyl)-4-(3-methoxypropoxy)-3-methylpyridine (5.0 g,) in water (25.0 mL) was added dropwise over a period of 45 min at 15–25°C. after the addition completed, the precipitated solid was filtered, washed with 50:50 mixture of acetone and water (10.0 mL),dried in vaccum oven at 45° C to provide compound Rabeprazole Sulfide 6.0 g, 85% yield.

Mp: 116–118° C; $m/z+1\text{H}$ ES-MS : 344;

Rabeprazole Sulfone 3

2-(((4-(3-methoxypropoxy)-3-methylpyridin-2-yl)methyl)sulfonyl)-1H-benzo[d]imidazole

Prepare a solution of mCPBA (5.0 g, 20.2 mmol) in chloroform (17.0 mL) was added to a solution of 2 (10.0 g, 20.2 mmol) in chloroform (17.0 mL) and MeOH(9.0 mL) dropwise for about 30mins at room temperature condition. Stir for 30 mins after additions, TLC indicates completions of starting material. Reaction mass was added to the 5% NaOH solution), and the pH was adjusted to 7–7.5 with acetic acid, organic layer was separated, and extracted with 3% NaOH aqueous solution, washed with chloroform, Acetone (25.0 mL) was added to theaqueous phase and cooled to 5–10 C. pH was adjusted to 8–8.5 with AcOH; the isolated solid was

filtered, washed with 1:1 mixture of water and acetone (20.0 mL), and dried, to get compound Rabeprazole Sulfone 2.5 g, 76% yield.
Mp: 138–142 C; m/z+1H ES-MS 376.0

Rabeprazole Chloro Impurity 4

2-(((4-chloro-3-methylpyridin-2-yl)methyl)sulfinyl)-1H-benzimidazole

To a round bottom flask, 1H-benzo[d]imidazole-2-thiol (3.9 g, 12.95mmol), NaOH (4.6 g, 115.0 mmol), and water (30 mL), was added a solution of 4- chloro-2-(chloromethyl)-3-methylpyridine (4.6g, 12.25mmol) in water (10 mL) at Room Temperature for 30 min. Stirring was continued for additional 1h at the same temperature, a solid was separated which was filtered,dried under vacuum to get 2-(((4-chloro-3-methylpyridin-2-yl)methyl)thio)-1H- benzo[d]imidazole 6g, 95%.

To a solution of 2-(((4-chloro-3-methylpyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole (3.2g, 11.04mmol), 35ml of dichloromethane was added m-CPBA (2.29gm, 13.25mmol) in 20ml of dichloromethane temperature 10°C to 15°C for 20 mins. After stirring for 20 mins, 10ml of 50% NaOH solution was added to the reaction mass. The reaction mass pH was adjusted to 8.0 – 8.5with acetic acid, extracted with dichloromethane (3X10 mL). The solvent was evaporated. The obtained crude was treated with ether at 10°C to get a solid precipitated . Filtered,dried to get Rabeprazole Chloro Impurity : 2g, 50%.

Methoxy Rabeprazole 5

2-(((4-methoxy-3-methylpyridin-2-yl)methyl)sulfinyl)-1H-benzo[d]imidazole

To a solution of 2-chloromethyl-4(methoxy)-3-methylpyridine (3gm 10 g, 14.42mmol) in 10ml of water was added a solution of 3.5gm 23.3mmol of 1H-benzo[d]imidazole-2-thiol, in 3% NaOH Solution 30ml is added dropwise at room temperature for 30min. Solid precipitated was filtered and washed with cold water to get 2-(((4-methoxy-3-methylpyridin-2-yl)methyl)thio)-1H- benzo[d]imidazole 3.2g, 82%.

2-(((4-methoxy-3-methylpyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole 3g, 10.51mmol) in 30 ml of dichloromethane was added a solution of m-CPBA (2.58gm, 14.93mmol) in 25ml of dichloromethane at 10°C for 30mins. 10ml of 50% NaOH solution was added to the reaction mass. pH was adjusted to 8.0 with acetic acid, extracted with dichloromethane, organic layer was evaporated, crude was treated with ether at 5°C to get solid precipitate.to get **Methoxy Rabeprazole 5** 1.3g, 50%.

N-Oxideof Rabeprazole

2-(((1H-benzo[d]imidazol-2-yl)sulfinyl)methyl)-4-(3-methoxypropoxy)-3-methylpyridine 1-oxide

To a solution of 2-(chloromethyl)-4-(3-methoxypropoxy)-3-methylpyridine (3.0gm, 13.06mmol) in 27ml of chloroform, was added m-CPBA (2.48gm, 14.37mmol) was

added in portion wise at 5°C for about 1hr and maintained for 1 h. Then, the reaction mixture was washed with saturated sodium bicarbonate solution, water, dried, and concentrated in vacuo. The obtained residue was triturated with ethyl acetate; the separated solid was filtered and dried at 40°C overnight to get 2.57gm, 80%. This compound stability and were immediately used for the next step.

References

- Ray, Purna C.; Mittapelli, Vasantha; Rohatgi, Amit; Tyagi, Om Dutt [Synthetic Communications, 2007, vol. 37, # 17, p. 2861 - 2868]
- Radl, Stanislav; Klecan, Ondrej; Havlicek, Jaroslav [Journal of Heterocyclic Chemistry, 2006, vol. 43, #6, p. 1447 - 1453]
- Reddy, Ganta Madhusudhan; Mukkanti, Kaga; Bhaskar, Boluggodu Vijaya; Reddy, PadiPratap [Synthetic Communications, 2009, vol. 39, # 2, p. 278 - 290]
- DIPHARMA FRANCIS S.R.L. - EP1921075, 2008, A2
- Pingili, R. Reddy; Jambula, M. Reddy; Ganta, M. Reddy; Ghanta, M. Reddy; Sajja; Sundaram; Boluggodu, V. Bhaskar [Pharmazie, 2005, vol. 60, # 11, p. 814 - 818]