Corporate Research & Development ASTA Medica Group, Arzneimittelwerk Dresden GmbH, Germany

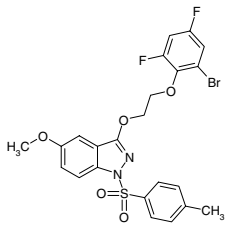
Indazole-3-oles and indazole-2-ones with anti-inflammatory activity

R. SCHINDLER, N. HOEFGEN, K. HEINECKE, H. POPPE and I. SZELENYI

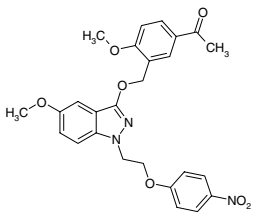
Looking for novel anti-allergic agents of low molecular weight, we synthesized a number of new indazole derivatives which showed a noticeable anti-inflammatory activity. 5-Methoxy-3-hydroxy-1*H*-indazole was sulphonylated in pyridine to obtain aryl-sulphonyl-indazole-3-yl esters [1]. Under alkaline conditions the arylsulphonyl group migrates from the 3-O position to the N-1 position in a movement similar to the known acyl migration [2]. 1-Benzyl- or other 1-alkylaryl-substituted indazoles were prepared by selective alkylation of the indazole skeleton in sodium hydroxide [3]. The subsequent alkylation of the 1-substituted 5-methoxy-1*H*-indazoles with halogenalkylaryls or halogenalkoxyaryls resulted in a mixture of two indazole derivatives. The ratio between the 1,3- and the 1,2-substituted 5-methoxy-indazoles depended on the reaction conditions, the steric hindrance and the electronic influence of the two starting materials.

Separation and purification is possible by repeated recrystallization. With preparative HPLC (SiO_2 60, 12 μm) both compounds were isolated in higher yields. Isocratic elution was performed, using a mobile phase of dichloromethane and ethyl acetate (95 : 5 v/v). Methanol was sometimes used instead of ethyl acetate.

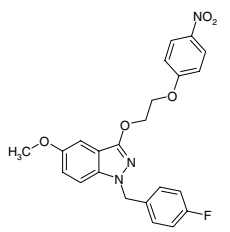
We synthesized a series of 100 new trisubstituted indazole derivatives. All compounds were characterized by CHN analysis, IR and $^1H/^{13}C$ NMR-spectroscopy. To establish the correct position of the substituents in **4** (aryl-SO_2 may be on N-1 or N-2, the benzyl residue on N-2 or N-1), we examined the NOE effects and the 2-D-COLOC experiments. The two-dimensional HC correlation showed a correlation between C=O and CH_2. The benzyl group should therefore be on N-2 position.



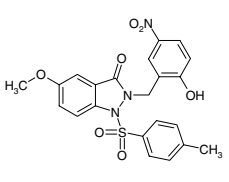
1



2



3



4

The anti-inflammatory activity of the indazoles was investigated, using the late phase eosinophilia model [4]. Actively sensitized and boosted guinea pigs were exposed to an ovalbumin aerosol (OA). After 24 h the bronchoalveolar lavage was performed and the eosinophils in the lavage fluid were counted. The percentage inhibition of the infiltration of eosinophils was determined by the number of eosinophils compared with a normal control group saline and an OA-challenged control group. The substances were administered i.p. as suspensions or orally 2 h before the antigen challenge.

Table: Inhibition of late phase eosinophilia

Compd.	Administration	Dose mg/kg	% Inhibition
1	i.p. −2h	10	61
	i.p. −2h/+4h	2 × 30	107
	p.o. −2h	30	65
2	i.p. −2h	10	68
3	i.p. −2h/+4h	2 × 30	98
4	i.p. −2h/+4h	2 × 30	97

In actively sensitized guinea pigs the administration of **1**, both i.p. and orally, significantly reduced the infiltration of eosinophils into the lungs. Indazoles **2**, **3** and **4** exhibit a high anti-inflammatory activity after i.p. administration. Further investigations are required. Compound **1** exhibits a dose-dependent anti-inflammatory activity and is expected to be useful in the treatment of a variety of eosinophilia-mediated disorders, including bronchial asthma. It was therefore selected for clearing up the *in vitro* mechanism and for investigating other animal species.

References

1 Anderson, R. M.; Leverett, B. R.: J. Chem. Soc. (C) 3313 (1971)
2 Auwers, K. v.; Demuth, W.: Liebigs Ann. **451**, 282 (1927)
3 Schindler, R.; Fleischhauer, I.; Hoefgen, N.; Sauer, W.; Egerland, U.; Poppe, H.; Heer, S.; Szelenyi, I.; Kutscher, B.; Engel, J.: Arch. Pharm. Pharm. Med. Chem. **331**, 13 (1998)
4 Chand, N.; Harrison, J. E.; Rooney, S. M.; Nolan, K. W.; DeVine, C. L.; Jakubicki, R. G.; Pillar, J.; Diamantis, W.; Sofia, R. D.: Allergy **48**, 624 (1993)

Received March 28, 2000
Accepted April 24, 2000

Dr. Rudolf Schindler
Arzneimittelwerk Dresden
Postfach 010131
D-01435 Radebeul