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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Transition metals in organic synthesis - Part 83[#]: Synthesis and pharmacological potential of carbazoles

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Abstract A series of carbazole derivatives with promising pharmacological properties has been prepared using either an iron-mediated or a palladium-catalyzed synthetic approach. The carbazole alkaloids carbazoquinocin C, carbazomadurin A and B, epocarbazolin A and B, neocarazostatin B, and carquinostatin A are antioxidants acting as free-radical scavengers. Thus, they represent potential lead compounds for the development of novel drugs against diseases initiated by oxygen-derived free radicals. Initiated by the first naturally occurring carbazole alkaloids with antituberculosis (anti-TB) activity, clausine K and micromeline, a study on the structure–activity relationships for anti-TB-active carbazole derivatives has been carried out. The 6-oxygenated carbazoles glycozoline and glycozolinine show antibiotic activity towards several microorganisms. The 7-oxygenated carbazole siamenol exhibits anti-HIV activity.

Introduction

[#] Part 82: (Forke *et al*., 2007)

A broad structural range of carbazole alkaloids with useful biological activities has been isolated from nature (Chakraborty and Roy, 1991; Chakraborty 1993; Knölker and Reddy, 2002; Knölker 2005). Because of the pharmacological potential of these natural products, several research groups have developed diverse synthetic strategies (Chakraborty and Roy, 1991; Chakraborty 1993; Knölker and Reddy,

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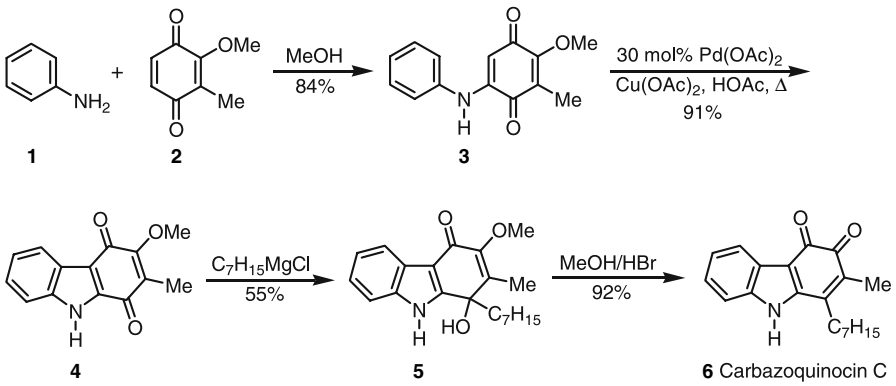
2002; Knölker 2005; Kawasaki and Sakamoto, 1994; Moody 1994; Hibino and Sugino, 1995; Kirsch 2001; Lemster and Pindur, 2002; Agarwal *et al*., 2005; Agarwal *et al*., 2006). We have described two highly efficient approaches using either an iron-mediated or a palladium-catalyzed construction of the carbazole framework (Knölker and Reddy, 2002; Knölker 2005; Agarwal *et al*., 2005; Agarwal *et al*., 2006). Both routes offer the advantage of functionalized building blocks, which can be combined by exploitation of transition-metal-mediated or catalyzed coupling reactions. Therefore, our synthetic strategy leads to highly convergent and short-step total syntheses of natural products and has been applied to structure–activity studies. In the present paper, we emphasize some recent achievements along these lines.

Results and Discussion

The carbazoquinocins, e.g., carbazoquinocin C, have been isolated from *Streptomyces violaceus* 2448-SVT2 (Tanaka *et al*., 1995). Our approach, using a palladium (II)-catalyzed oxidative cyclization as a key step, provides a simple four-step route to carbazoquinocin C (Scheme 1) (Knölker *et al*., 2002).

Regioselective addition of aniline (**1**) to 2-methoxy-3-methyl-1,4-benzoquinone (**2**) afforded the anilinobenzoquinone **3**. Treatment with catalytic amounts of palladium (II) acetate in the presence of cupric acetate as reoxidant led to 3-methoxy-2-methylcarbazole-1,4-quinone (**4**). Addition of heptylmagnesium chloride gave the carbazolequinol **5**, which on treatment with acid provided carbazoquinocin C (**6**) in four steps and 39% overall yield. Carbazoquinocin C shows a strong inhibition of lipid peroxidation induced by free radicals (Tanaka *et al*., 1995).

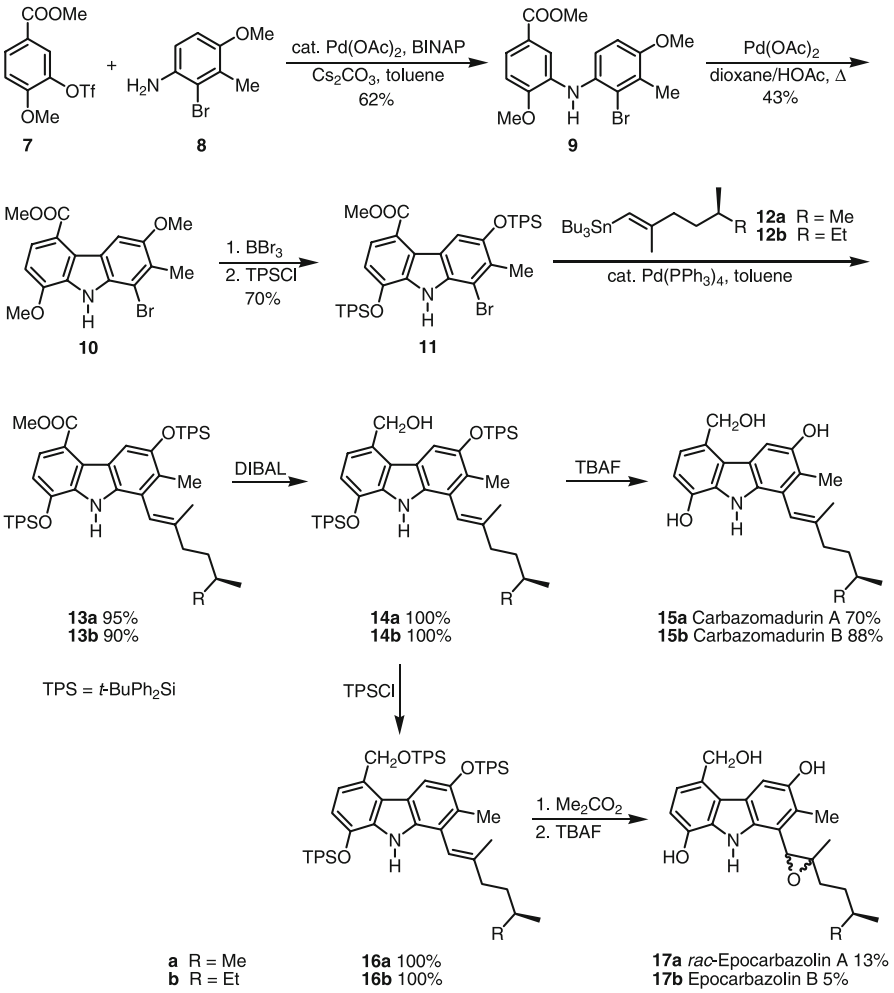
The carbazomadurins A and B have been isolated from the microorganism *Actinomadura madurae* 2808-SV1 (Kotoda *et al*., 1997). On screening for 5-lipoxygenase inhibitors, the structurally related epocarbazolins A and B were found in the actinomycete strain *Streptomyces anulatus* T688-8 (Nihei *et al*., 1993). A common approach to these natural products has been developed by sequential



Scheme 1 Palladium-catalyzed synthesis of carbazoquinocin C

application of three different palladium-catalyzed cross-coupling reactions (Scheme 2) (Knölker and Knöll, 2003; Knöll and Knölker, 2006).

Palladium (0)-catalyzed Buchwald–Hartwig coupling of the aryl triflate **7** with the arylamine **8** afforded the *N*,*N*-diarylamine **9**. The subsequent palladium (II)-mediated oxidative cyclization provided the pentasubstituted carbazole skeleton **10**. Change of the protecting groups led to the disilyl ether **11**. Introduction of the appropriate side chain at C-1 by a palladium (0)-catalyzed Stille coupling with the alkenylstannanes **12a** and **12b** afforded the 1-alkenylcarbazoles **13**. Reduction of the methyl esters gave the benzylic alcohols **14** as crucial intermediates for both classes of compounds. Removal of the silyl protecting groups provided carbazomadurin A (**15a**) and carbazomadurin B (**15b**) (Knölker and Knöll, 2003; Knöll and Knölker, 2006). Conversion of the disilyl ethers **14** to the trisilyl-protected intermediates **16**



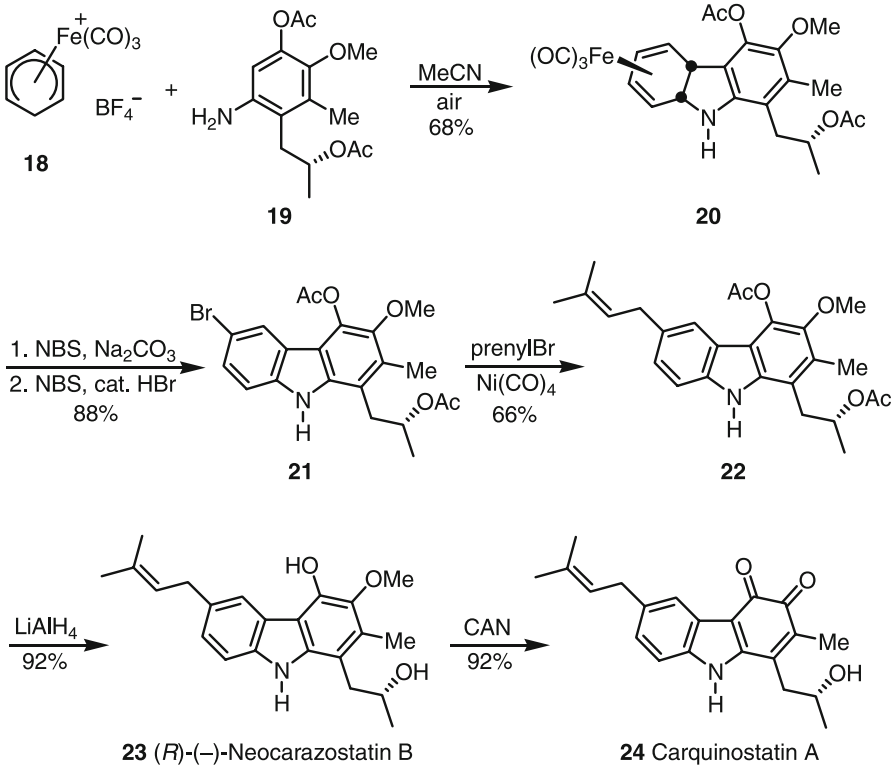
Scheme 2 Palladium-catalyzed synthesis of the carbazomadurins and epocarbazolins

followed by epoxidation with dimethyldioxirane and desilylation afforded racemic epocarbazolin A (**17a**) and epocarbazolin B (**17b**) (Knöll and Knölker, 2006).

The carbazomadurins A and B exhibit a strong neuronal cell protecting activity against L-glutamate-induced cell death. The epocarbazolins A and B are potent inhibitors of rat 5-lipoxygenase (epocarbazolin A: $IC_{50} = 2.4$ μM; epocarbazolin B: $IC_{50} = 2.6$ μM) (Nihei *et al*., 1993).

Neocarazostatin B has been isolated from the culture of *Streptomyces* sp. strain GP 38 (Kato *et al*., 1991). The structurally related carquinostatin A, obtained from *Streptomyces exfoliatus* 2419-SVT2, represents the corresponding *ortho*-quinone derivative (Shin-ya *et al*., 1993; Grammel *et al*., 1998). Using the iron-mediated carbazole construction, a straightforward synthesis of both alkaloids has been developed; moreover, the absolute configuration of neocarazostatin B could be assigned (Scheme 3) (Czerwonka *et al*., 2006).

Reaction of the iron complex salt **18** with the arylamine **19** in air resulted in electrophilic substitution in situ followed by oxidative cyclization to the tricarbonyliron-coordinated dihydrocarbazole **20**. Aromatization with demetalation and subsequent electrophilic bromination afforded the 6-bromocarbazole **21**. Nickel-mediated prenylation and removal of the acetyl protecting groups from compound **22** provided (*R*)-(–)-neocarazostatin B (**23**). Oxidation with cerium (IV) ammonium

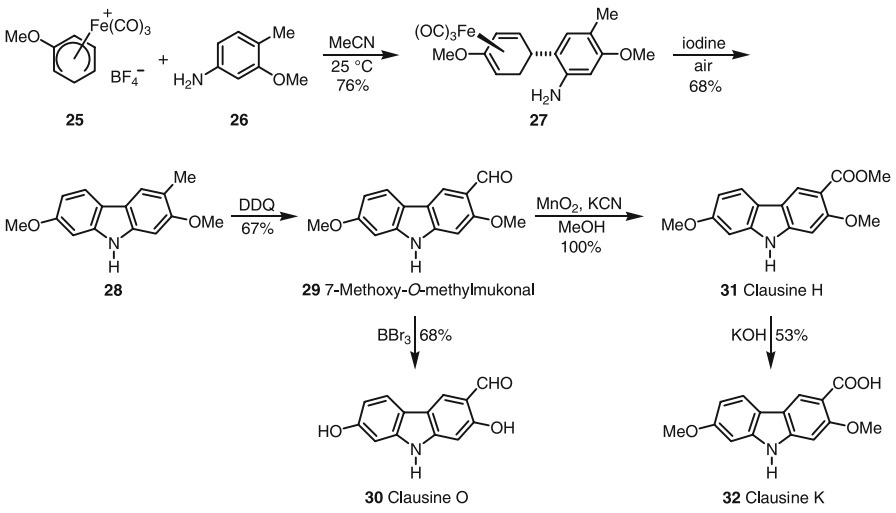


Scheme 3 Iron-mediated synthesis of (*R*)-(–)-neocarazostatin B and carquinostatin A

nitrate converted (*R*)-(–)-neocarazostatin B (**23**) into carquinostatin A (**24**). Neocarazostatin B is a potent inhibitor of the free-radical-induced lipid peroxidation in rat brain homogenate ($IC_{50} = 0.39$ μM) and was much more efficient than other well-known antioxidants (Kato *et al*., 1991). Carquinostatin A is also an efficient antioxidant and shows neuronal cell protecting activity against L-glutamate-induced cell death (Shin-ya *et al*., 1993).

7-Methoxy-*O*-methylmukonal has been isolated from the roots of *Murraya siamensis* (Ruangrungsi *et al*., 1990). Clausine O has been found in the root bark of the Chinese medicinal plant *Clausena excavata* (Wu *et al*., 1999). Clausine H (clauszoline-C) and clausine K (clauszoline-J) have been obtained from the stem bark of the same plant (Wu *et al*., 1996; Ito *et al*., 1996; 1997). Moreover, clausine K has also been obtained from the roots of *Clausena harmandiana* (Yenjai *et al*., 2000). The pharmacological potential initiated us to develop a simple iron-mediated approach to the 2,7-dioxygenated carbazole alkaloids (Scheme 4) (Kataeva *et al*., 2005).

Electrophilic substitution of 3-methoxy-4-methylaniline (**26**) by reaction with the 2-methoxy-substituted iron complex salt **25** afforded the iron complex **27**. Iron-mediated arylamine cyclization followed by aromatization provided 2,7-dimethoxy-3-methylcarbazole (**28**), which served as relay to the subsequent carbazole alkaloids having the same substitution pattern. Oxidation with 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) led to 7-methoxy-*O*-methylmukonal (**29**) and subsequent ether cleavage gave clausine O (**30**). Further oxidation of the aldehyde **29** to the methyl ester afforded clausine H (**31**), which on ester cleavage provided clausine K (**32**). Clausine H (clauszoline-C) exhibits antiplasmodial activity against *Plasmodium falciparum* ($IC_{50} = 5.5$–10.7 μg mL^{-1}) (Yenjai *et al*., 2000). Clausine K (clauszoline-J) shows weak antimycobacterial activity against *Mycobacterium*

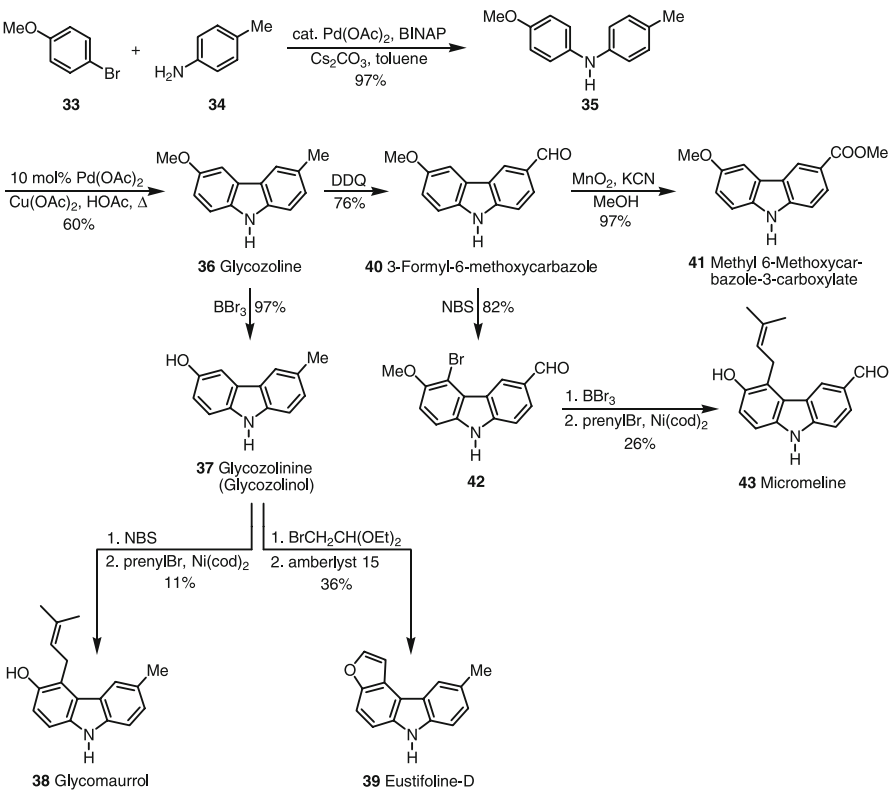


Scheme 4 Iron-mediated synthesis of 2,7-dioxygenated carbazole alkaloids

tuberculosis $H_{37}Ra$ (MIC_{90} = 100 μg mL^{-1} = 369 μM) (Sunthitikawinsakul *et al.*, 2003).

Glycozoline and glycozolinine (glycozolinol) were isolated first from *Glycosmis pentaphylla* (Chakraborty 1966; Mukherjee *et al.*, 1983; Bhattacharyya *et al.*, 1984). Glycomaurrol has been found in the stem bark of *Glycosmis mauritiana* (Kumar *et al.*, 1989). Eustofoline-D, isolated from the root bark of *Murraya euchrestofolia* (Ito and Furukawa, 1990), has an unprecedented furo[2,3-*c*]carbazole framework and is one of only four natural furocarbazoles currently known (Fröhner *et al.*, 2004; Knölker and Reddy, 2005). 3-Formyl-6-methoxycarbazole and methyl 6-methoxycarbazole-3-carboxylate have been isolated from the roots of *Clausena lansium* (Li *et al.*, 1991). An antituberculosis bioassay-directed fractionation of the stem bark extract of *Micromelum hirsutum* led to the isolation of micromeline along with 3-formyl-6-methoxycarbazole (Ma *et al.*, 2005). Using the palladium-catalyzed synthesis we gained access to a whole series of 6-oxygenated carbazole alkaloids (Scheme 5) (Forke *et al.*, 2007).

Palladium (0)-catalyzed coupling of *p*-bromoanisole (**33**) with *p*-toluidine (**34**) and subsequent palladium (II)-catalyzed oxidative cyclization of the resulting *N*,*N*-diarylamine **35** provided glycozoline (**36**). Glycozoline (**36**) was then used as relay

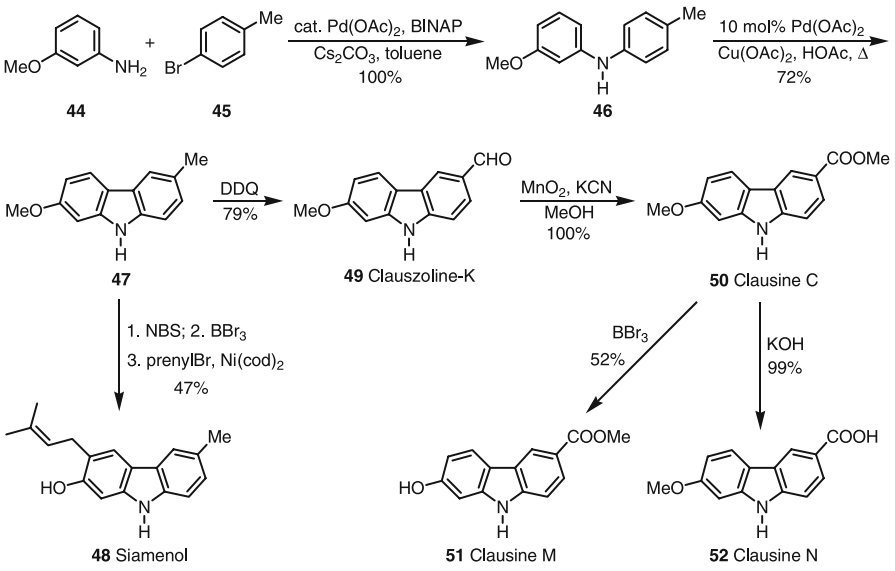


Scheme 5 Palladium-catalyzed synthesis of 6-oxygenated carbazole alkaloids

to all the other 6-oxygenated carbazole alkaloids. Ether cleavage gave glycozolinine (glycozolinol) (**37**). Regioselective bromination of **37** at C-5 followed by nickel-mediated prenylation provided glycomaurrol (**38**). Annulation of the furan ring at glycozolinine (**37**) led to eustifoline-D (**39**). Oxidation of glycozoline (**36**) using DDQ afforded 3-formyl-6-methoxycarbazole (**40**). Further selective oxidation (aldehyde to ester) provided methyl 6-methoxycarbazole-3-carboxylate (**41**). Bromination of **40** to 5-bromo-3-formyl-6-methoxycarbazole (**42**) followed by ether cleavage and nickel-mediated prenylation gave micromeline (**43**). Glycozoline and glycozolinine (glycozolinol) are antibiotics, with glycozolinine showing much stronger antibiotic activity (Chakraborty *et al*, 1975). Antimycobacterial activity against the *Mycobacterium tuberculosis* strain $H_{37}Rv$ was reported for 3-formyl-6-methoxycarbazole ($MIC_{90} = 15.6\ \mu g\ mL^{-1} = 69\ \mu M$) and micromeline ($MIC_{90} = 31.5\ \mu g\ mL^{-1} = 113\ \mu M$) (Ma *et al*., 2005).

The organic extract of the plant *Murraya siamensis*, collected in Thailand, has been reported to exhibit anti-HIV activity. Siamenol has been isolated in a bioassay-guided fractionation of this extract (Meragelman *et al*., 2000). More recent investigations of the Chinese medicinal plant *Clausena excavata* led to the isolation of clauszoline-K, clausine C (clauszoline-L), clausine M, and clausine N (Wu *et al*., 1999; Wu *et al*., 1996; Ito *et al*., 1997). A straightforward synthetic route to the 7-oxygenated carbazole alkaloids has been realized by using the palladium-catalyzed approach (Scheme 6) (Krahl *et al*., 2006).

Palladium (0)-catalyzed amination of *p*-bromotoluene (**45**) with *m*-anisidine (**44**) to the *N*,*N*-diarylamine **46** followed by palladium(II)-catalyzed oxidative cyclization led to 7-methoxy-3-methylcarbazole (**47**) (Fig. 1) (Krahl *et al*., 2006), which served as a relay to 7-oxygenated carbazole alkaloids. Regioselective bromination at



Scheme 6 Palladium-catalyzed synthesis of 7-oxygenated carbazole alkaloids

C-6, cleavage of the methyl ether and nickel-mediated prenylation afforded siamenol (**48**). Oxidation of **47** with DDQ led to clauszoline-K (**49**) (Fig. 2) [crystal data for clauszoline-K (**49**): $C_{14}H_{11}NO_2$, $M = 225.24$, orthorhombic, space group: *P*bca, $a = 7.163(1)$, $b = 13.245(1)$, $c = 22.516(2)$ Å, $V = 2136.2(4)$ Å^3, $Z = 8$, $\rho_{calc} = 1.401$ g cm^{-3}, $\mu = 0.095$ mm^{-1}, $T = 198(2)$ K, $\lambda = 0.71073$ Å, θ range = 3.08–35.00°; reflections collected: 69965, independent: 4709 (R_{int} = 0.0282). The structure was solved by direct methods and refined by full-matrix least-squares on F^2; $R_1 = 0.0457$, $wR_2 = 0.1193$ [$I > 2\sigma(I)$]. CCDC-633273 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Further oxidation led to clausine C (clauszoline-L) (**50**) (Fig. 3) (Krahl *et al*., 2006). Ether cleavage of clausine C (**50**) afforded clausine M (**51**), while ester cleavage gave clausine N (**52**). Siamenol showed HIV inhibition in the XTT-tetrazolium assay ($EC_{50} = 2.6$ μg mL^{-1}) (Meragelman *et al*., 2000).

Based on the reports of naturally occurring carbazole alkaloids with inhibiting activity against *M. tuberculosis* (Sunthitikawinsakul *et al*., 2003; Ma *et al*., 2005), we started a project to investigate the structure–activity relationships for this class of compounds (Choi *et al*., 2006). The present study provides further data on the

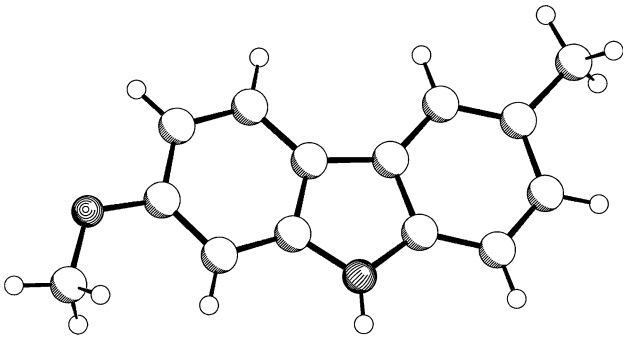


Fig. 1 Crystal structure of 7-methoxy-3-methylcarbazole (**47**), CCDC-609679

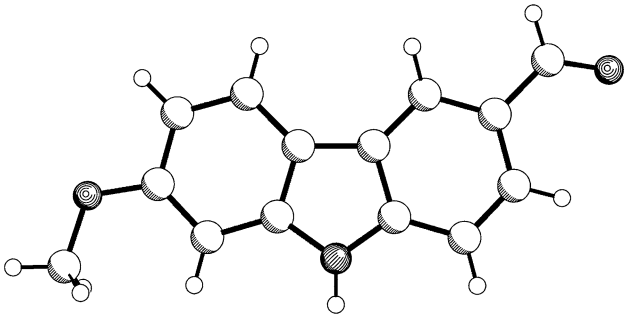


Fig. 2 Crystal structure of clauszoline-K (**49**), CCDC-633273

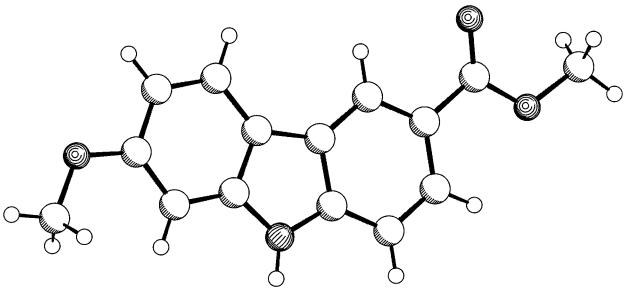


Fig. 3 Crystal structure of clausine C (clauszoline-L) (**50**), CCDC- 609678

anti-TB activity of carbazole derivatives (Table 1). Minimum inhibitory concentration (MIC_{90}) values for inhibition of *M. tuberculosis* $H_{37}Rv$ were determined using the microplate alamar blue assay (MABA) (Collins and Franzblau, 1997; Pauli *et al*., 2005). Rifampin (rifampicin) and isoniazid were used as positive

Table 1 Antituberculosis activity, cytotoxicity, and selectivity indices of carbazole derivatives

Compound	Name	MIC_{90} [a]	IC_{50} [b]	SI [c]
4	3-methoxy-2-methylcarbazole-1,4-quinone	8	>128	>16
21	6-bromocarbazole derivative	55	25	0.5
28	2,7-dimethoxy-3-methylcarbazole	>128	>128	–
29	7-methoxy-*O*-methylmukonal	>128	96	<0.8
30	clausine O	89	114	1.3
32	clausine K (clauszoline-J)	>128	25	<0.2
36	glycozoline	>128	–	–
37	glycozolinine (glycozolinol)	123	57	0.5
39	eustifoline-D	>128	>128	–
40	3-formyl-6-methoxycarbazole	99	>128	>1.3
41	methyl 6-methoxycarbazole-3-carboxylate	32	>128	>4.0
42	5-bromo-3-formyl-6-methoxycarbazole	>128	78	<0.6
43	micromeline	>128	–	–
47	7-methoxy-3-methylcarbazole	>128	–	–
48	siamenol	22	15	0.7
49	clauszoline-K	>128	–	–
50	clausine C (clauszoline-L)	>128	–	–
51	clausine M	19	35	1.8
52	clausine N	>128	–	–
RMP	rifampin (rifampicin)	0.09	105	1167
INH	isoniazid	0.4	>128	>320

[a] Minimum inhibitory concentration (μM) against *M. tuberculosis* $H_{37}Rv$ in the MABA assay.

[b] Cytotoxicity on Vero cells. Both values are means of three replicate experiments; >128 indicates values higher than the maximum concentration applied.

[c] Selectivity index: $SI = IC_{50}/MIC_{90}$

controls in the assay and solvent as negative control. All compounds were tested for in vitro cytotoxicity toward Vero cells (African green monkey kidney cells) (Pauli *et al*., 2005; Falzari *et al*., 2005). The MIC_{90} value found for natural clausine K (clauszoline-J) (**32**) (369 μM) (Sunthitikawinsakul *et al*., 2003) was much higher than the highest concentration applied in our assay (128 μM). Moreover, a different strain of *M. tuberculosis* ($H_{37}Ra$) was used in that assay. The MIC_{90} reported for natural micromeline (**43**) (113 μM) (Ma *et al*., 2005) was in the range of the highest concentration used herein. This may explain why no anti-TB activity was found for clausine K (**32**) and micromeline (**43**) in the present study. However, a weak anti-TB activity described for natural 3-formyl-6-methoxycarbazole (**40**) ($MIC_{90} = 69$ μM) (Ma *et al*., 2005) could be confirmed. The promising antituberculosis activity of 3-methoxy-2-methylcarbazole-1,4-quinone (**4**) (Choi *et al*., 2006) was confirmed as well. Also methyl 6-methoxycarbazole-3-carboxylate (**41**) exhibited anti-TB activity and was nontoxic for the mammalian cell line. Some other compounds screened in this study showed weak anti-TB activity but were found to be cytotoxic at the same time: the 6-bromocarbazole derivative **21**, clausine O (**30**), glycozolinine (glycozolinol) (**37**), siamenol (**48**), and clausine M (**51**).

In conclusion, carbazoles represent a novel class of potential anti-TB drug candidates. Further structural modifications of the identified hits for improvement of the efficacy are in progress.

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