Bioorganic & Medicinal Chemistry Letters 22 (2012) 1375–1379

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

An efficient synthesis of highly functionalized novel chromeno[4,3-*b*]pyrroles and indolizino[6,7-*b*]indoles as potent antimicrobial and antioxidant agents

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ARTICLE INFO

Article history:
Received 13 October 2011
Revised 26 November 2011
Accepted 12 December 2011
Available online 20 December 2011

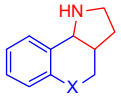
Keywords:
Azomethine ylide
1,3-DC reaction
Pictet–Spengler cyclization
Chromenopyrroles
Indolizinoindoles
Antimicrobial activity

ABSTRACT

A facile and efficient synthesis of novel chromeno[4,3-*b*]pyrroles has been accomplished by intramolecular 1,3-dipolar cycloaddition which on subsequent Pictet–Spengler cyclisation in presence of *p*-toluenesulfonic acid yielded indolizino[6,7-*b*]indoles. The synthesized chromenopyrroles and indolizinoindoles were evaluated for their antimicrobial and antioxidant activities. Compounds **7b**, **7e**, **7a** and **7d** exhibited respectively, good antibacterial and antifungal activities against tested pathogens when compared to reference control.

In the last few decades, the increasing incidence of infection caused by the rapid development of bacterial resistance to most of the known antibiotics is a serious health problem.[1] While many factors may be responsible for mutations in microbial genomes, it has been widely demonstrated that the improper use of antibiotics can greatly increase the development of resistant genotypes.[2] Further, the usage of most antimicrobial agents is limited due to the rapidly developing drug resistance in conjunction with the unsatisfactory status of present treatments of bacterial and fungal infections and drug side effects.[3–7] Therefore, the development of novel antimicrobial drugs possessing new mechanisms of action emerges as an important objective and much of the research efforts are directed towards the design of new agents comprising chromenopyrrole moiety.[8]

Chromeno[4,3-*b*]pyrrole plays a unique role in medicinal chemistry, as its similar structural motif (Fig. 1 X = NH) are found in naturally occurring martinelline or martinellic acid alkaloids and possess antibacterial activity and act as a bradykinin receptor antagonist.[9] On the other hand, naturally occurring chromene or chromane derivatives exhibit remarkable physiological properties and some pyrrolidine annulated benzopyran compounds are known as selective dopamine D_3 receptor antagonist.[10] Chromeno[4,3-*b*]pyrrole find utility in other areas of medicinal chemistry, in the treatment of impulsive disorders,[11] parkinson's disease,[12] psychoses, memory disorders[13] and anxiety.[14] Confalone and co-workers reported[15] the synthesis of chromeno[4,3-*b*]pyrrole through 1,3-dipolar cycloaddition via deprotonation route. Grigg et al.[16] also extensively studied the intramolecular azomethine ylide cycloaddition reaction for the synthesis of same type of compounds. Likewise, indolizinoindole ring systems are of interest to the pharmaceutical industry and have been used as intermediates in the preparation of diuretic compounds[17] which are also known to exhibit analgesic and anti-inflammatory activity.[18] Its derivatives act as β-turn mimics and display high binding affinity and selectivity of CCK_1 receptors.[19]



X = NH, Martinelline or Martinellic acid building blocks

X= O, Chromeneor Chromane derivatives

Figure 1. Representation of the fused pyrrole scaffold.

In this context, we have reported the synthesis of fused pyrrolidine and indolizinoindole heterocycles through 1,3-dipolar cycloaddition.[20] In addition, recently, we have embarked on a program on the synthesis of structurally diverse novel heterocycles employing intermolecular 1,3-dipolar cycloadition followed by their biological screening, which has brought to light various antimicrobial leads.[21] Our research group reported chromenopyrrole and

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doi:10.1016/j.bmcl.2011.12.061

indolizinoindole derivatives derived from electron deficient 4-(2-formylphenoxy)/4-(1-formylnaphthalen-2-yloxy)but-2-enoate with tryptophan ester hydrochloride by sequential intramolecular 1,3-dipolar cycloaddition reaction via *N*-Metalation route followed by Pictet–Spengler cyclization.[22]

In continuation of our research in the area of 1,3-dipolar cycloaddition reaction and Pictet–Spengler cylisation,[20c] herein we wish to report an expeditious and facile protocol for the synthesis of chromeno[4,3-*b*]pyrrole and indolizino[6,7-*b*]indole derivatives through intramolecular 1,3-dipolar cycloaddition reaction of azomethine ylide generated from electron rich 2-(allyloxy)benzaldehyde/-1-naphthaldehyde with tryptophan methyl ester hydrochloride followed by Pictet–Spengler cyclization. Interestingly, these chromeno[4,3-*b*]pyrroles and indolizino[6,7-*b*]indoles displayed significantly enhanced in vitro antibacterial, antifungal and antioxidant activities.

The prerequisite 2-(allyloxy)benzaldehyde/-1-naphthaldehyde were prepared according to literature procedure[23] and were subjected to intramolecular azomethine ylide cycloaddition reaction with tryptophan methyl ester hydrochloride. Thus, tryptophan methyl ester hydrochloride **3** and 2-(allyloxy)benzaldehyde **2a**/2-(allyloxy)-1-naphthaldehyde **2b** in CH_2Cl_2 with Et_3N stirred overnight at room temperature to afford imine **4a**–**b** and these were used for next step without further purification.

The crude imine was refluxed in toluene under Dean–Stark conditions for 12 h yielded chromeno[4,3-*b*]pyrrole-2-carboxylate derivatives **5a** and **6a** in 50–55% as a single diastereoisomer (Scheme 1). In the infrared (IR) spectrum of cycloadduct **5a**, the ester carbonyl group exhibited a strong absorption band at 1730 cm^{-1} and the indole NH appeared at 3292 cm^{-1}. The fusion at the ring junction was found to be *cis* from the spectroscopic data of the cycloadduct **5a**, the H_a proton appeared as a doublet at δ 4.36 ppm (J = 4.3 Hz) and H_b proton resonated as a multiplet in the region δ 2.39–2.42 ppm. The H_1 proton exhibited a doublet of doublet in the region δ 4.01–4.05 ppm (J = 10.6, 4.2 Hz) and H_2 proton appeared as multiplet at δ 3.60–3.67 ppm. The indole adjacent methylene protons resonated as two doublets at δ 3.21 and 3.38 ppm with geminal coupling constant (J = 14.2 Hz). The ^{13}C NMR spectrum of compounds **5a** showed a singal at δ 176.84 ppm due to ester carbonyl carbon. The presence of molecular ion peak at m/z 362.52 (M+) in the mass spectrum of **5a** confirms the formation of cycloadduct.

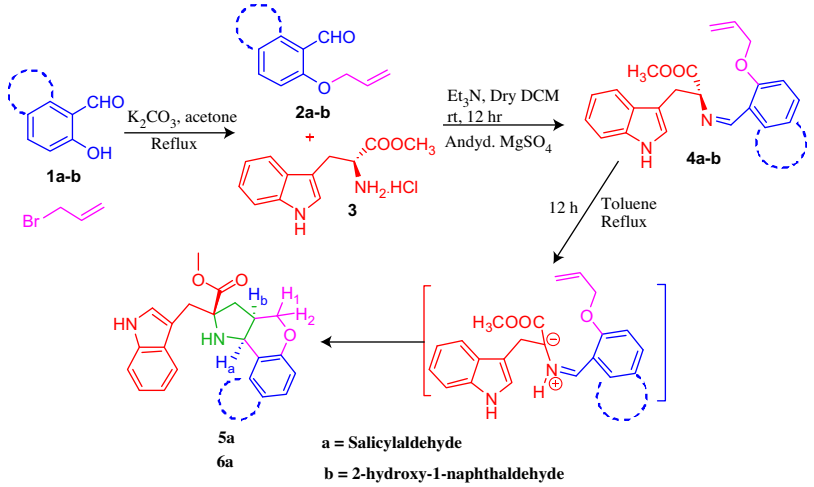
Finally, the structure of cycloadduct was unambiguously ascertained by single crystal X-ray diffraction analysis[24] of the cycloadduct **6a** (Fig. 2). In the molecular structure of **6a**, the pyrrolidine ring adopts a twist conformation and pyran ring adopts a twist boat conformation, whilst the molecular structure is stabilized by intermolecular N–H···O and C–H···O hydrogen bonds and also by week intermolecular π–π interactions.

Next we turned our attention to the synthesis of indolizino[6,7-*b*]indole derivatives **7a**–**e** and **8a**–**e** by annulations of chromeno/benzochromenopyrroles **5a** and **6a**. The indolizinoindoles are typically prepared via Pictet–Spengler cyclization reaction of chromeno/benzochromenopyrroles **5a**/**6a** with corresponding aromatic aldehyde in the presence of *p*-toluenesulfonic acid under thermal conditions in moderate yield (Scheme 2). The intramolecular cycloaddition and Pictet–Spengler cyclization were initially performed by conventional method under reflux in toluene and were subsequently investigated also under microwave irradiation in a focused microwave synthesizer, as this technique has evolved as a valuable alternative to conventional heating for the introduction of energy into reactions and has clear benefits in many chemical transformations,[25] including cycloaddition[25b] in terms of rate accelerations and yield enhancements. The reactions under microwave irradiation for 5–10 min afforded better yield of **5**, **6**, **7** and **8** than conventional heating. The results obtained for both methods are summarized in Table 1.

The Pictet–Spengler cyclized product was confirmed by spectral and elemental analysis. The cyclized product **7a** gave a singlet for H_c proton at δ 5.24 ppm and the *trans*-stereochemistry was confirmed by NOE studies. Irradiation of the benzylic proton (H_c) of **7a** at δ 5.24 did not cause any enhancement of the signal for the H_a proton, which appeared as a doublet at δ 3.97 (J = 4.4 Hz) (Fig. 3). A peak at m/z 450.84 (M^+) in the mass spectrum of the compound **7a** confirmed the formation of Pictet–Spengler cyclized product.

The synthesized compounds **5**, **6**, **7** and **8** were evaluated for their in vitro antibacterial activity against four bacterial strains *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeroginosa* and *Klebsiella pneumonia* and in vitro antifungal activity against *Fusarium oxysporum* and *Macrophomenaphaseolina* by agar diffusion method in dublicate, using tetracycline and carbendazim as reference control for antibacterial and antifungal activities, respectively. Further, these compounds were also studied for their antioxidant property.

Antibacterial activity of chromeno[4,3-b]pyrroles and indolizino[6,7-b]indoles (agar diffusion assay): The antibacterial activity of the synthesized twelve compounds against human bacterial pathogens as determined by agar diffusion method with tetracycline as reference control was investigated. Analysis of antimicrobial



Scheme 1. Synthesis of chromeno[4,3-*b*]pyrroles.

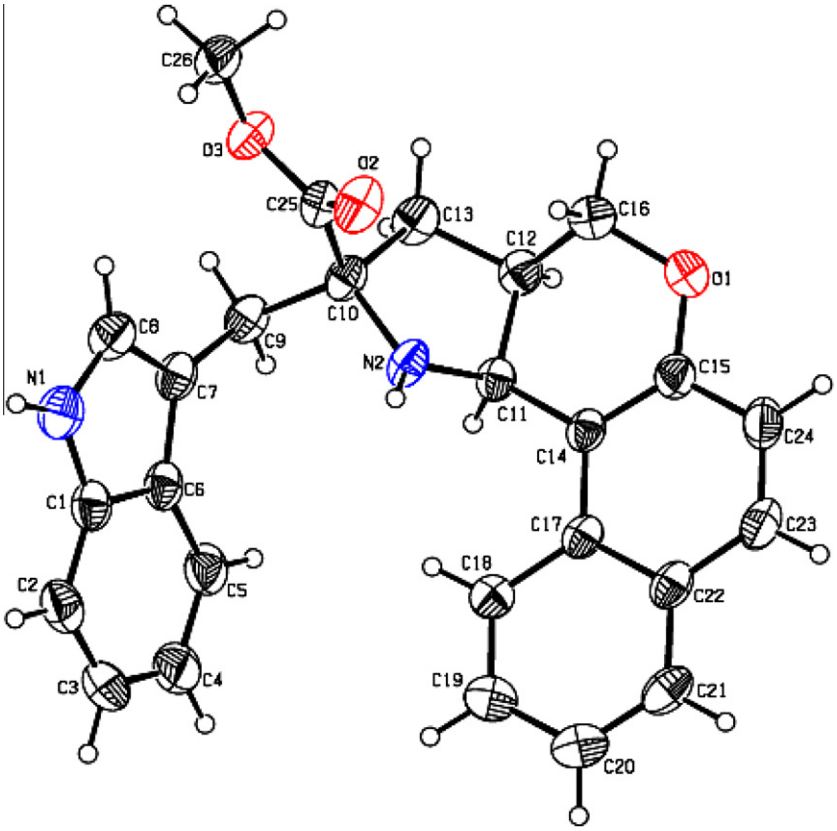
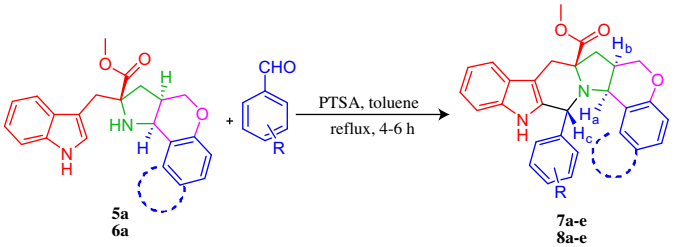


Figure 2. ORTEP diagram of **6a**.



R = a) *p*-H, b) *p*-Cl, c) *p*-CH_3, d) *p*-OCH_3, e) *m*-NO_2

Scheme 2. Synthesis of indolizino[6,7-*b*]indoles.

results indicated that the presence of electron withdrawing groups attached to the phenyl ring were generally more active than the other derivatives and the importance of electron withdrawing groups in enhancing the antimicrobial activity is supported by P. Sharma et al.[26] Antimicrobial results revealed that the maximum antibacterial activity was observed for compounds **7b** and **7e** against all the tested pathogens at low concentration. Compounds **5a**, **6a**, **8b** and **8e** showed good antibacterial activity compared to reference control tetracycline. Compounds **7c**, **7d**, **8c** and **8d** exhibited moderate activity against all the tested antibacterial pathogens. Compounds **7a** and **8a** showed good activity at higher concentration level. The above antimicrobial results demonstrate that all the synthesized compounds showed good antibacterial activity, which are comparable to the reference control. It was observed that all the antibacterial activities of the present studied compounds are dose dependant. Further clinical studies are required to validate the effective compounds of the present study as an antimicrobial agent. The results are summarized in Table 2. The structure activity relationship demonstrates that indolizinoindoles **7b**, **7e**, **8a** and **8e** showed excellent to good activity at low

Table 1
Comparison of the reaction times and yields for the conventional and microwave-assisted 1,3-dipolar cycloaddition and Pictet–Spengler cyclization

Entry	Compounds	R	Conventional method toluene, reflux		Microwave assisted (100 °C, 100 W)	
			Yield	Time (hr)	Yield	Time (min)
1	**5a**	Chromenopyrrole	50	12	78	10
2	**6a**	Benzochromenopyrrole	55	12	81	9
3	**7a**	H	65	6	85	6
4	**7b**	Cl	68	4	88	5
5	**7c**	CH_3	70	5	92	7
6	**7d**	OCH_3	65	5	83	9
7	**7e**	3-NO_2	72	4	86	5
8	**8a**	H	66	5	79	7
9	**8b**	Cl	78	4	84	6
10	**8c**	CH_3	76	5	83	8
11	**8d**	OCH_3	74	5	86	10
12	**8e**	3-NO_2	75	4	90	6

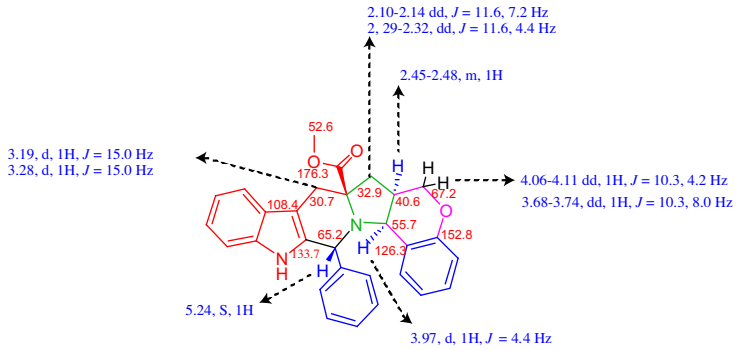


Figure 3. Selected ^{1}H and ^{13}C NMR chemical shifts of **7a**.

Table 2
Effect of chromno[4,3-*b*]pyrroles **5a**, **6a** and indolizino[6,7-*b*]indoles **7**(**a**–**e**) and **8**(**a**–**e**) on the growth of human pathogens *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas areoginosa* and *Klebsiella pneumonia*

S. No	Compounds	Concentration of compounds(μg/ml) Zone of inhibition (nm)															
		Bacillus subtilis				*Staphylococcus aureus*				*Pseudomonas aeroginosa*				*Klebsiella pneumonia*			
		25	50	75	100	25	50	75	100	25	50	75	100	25	50	75	100
1	**5a**	11	15	20	26	10	15	20	23	10	15	21	23	11	15	21	23
2	**6a**	10	15	19	24	9	13	18	24	9	14	20	21	10	14	20	23
3	**7a**	9	11	20	25	9	11	18	25	9	12	20	24	9	11	19	26
4	**7b**	13.5	21	26	36	20	21	24	29	16	22	25	36	16	20	25	30
5	**7c**	9	12	15	20	9	13	17	18	8	12	16	19	8	13	18	19
6	**7d**	8	11	18	19	-	12	16	18	7	11	15	20	8	11	19	20
7	**7e**	14	21	28	40	20	22	24	36	17	24	26	40	15	20	25	36
8	**8a**	9	12	20	24	9	13	18	26	9	13	18	25	10	12	17	24
9	**8b**	12	18	21	26	14	17	20	28	12	16	20	26	11	15	22	25
10	**8c**	9	14	16	20	9	12	17	19	8	14	17	20	9	12	17	21
11	**8d**	9	12	17	20	9	11	18	20	10	12	16	19	9	11	18	20
12	**8e**	12	19	24	29	19	20	24	28	14	20	24	30	13	18	22	27
	Tetracycline	15	24	29	40>	22	24	29	40>	20	26	28	40>	18	22	28	40>

concentration presumably ascribable to the presence of both indolizinoindole nucleus and electron withdrawing group (–Cl, –NO_2) substituted in the phenyl ring and in compounds **5a** and **6a**, the presence of chromeno[4,3-*b*]pyrrole unit may be responsible for their activity. From overall antibacterial activity results (Table 2), it was observed that indolizinoindoles **7b** and **7e** were the effective inhibitors against all the bacterial pathogens at lower concentration comparable to standard drug tetracycline.

Antifungal activity of chromeno[4,3-b]pyrroles and indolizino[6,7-b]indoles (*Minimum Inhibitory Concentration*): The minimum inhibitory concentration (MIC) of the tested compounds against plant fungal pathogens ranged from 20 to 110 μg/ml. Compound **7a** and **7d** were effective in controlling both fungal pathogens namely *F. oxysporum* and *M. phaseolina* with MIC values of (30 and 40 μg/ml) and (35 and 50 μg/ml), respectively. Compounds **8a** and **8e** effectively inhibited fungal pathogen *F. oxysporum* with MIC (30 and 85 μg/ml) and (35 and 90 μg/ml), respectively. Similarly, compounds **7b**, **7e** and **8c** effectively inhibited fungal pathogens *M. phaseolina* with MIC (70 and 20 μg/ml), (90 and 25 μg/ml) and (85 and 30 μg/ml), respectively, and other compounds **5a**, **6a**, **7c**, **8b** and **8d** inhibited mycelial growth at higher concentration between 60 and 110 μg/ml, compared to the reference control carbendazim ranged 15 and 20 μg/ml. In general most of the synthesized compounds inhibited mycelial growth at higher concentration (50–125 μg/ml). The results are summarized in Table 3.

Antioxidant activity of chromeno[4,3-b]pyrroles and indolizino[6,7-b]indoles: In the present antioxidant study, DPPH radical scavenging method was chosen to evaluate antioxidant potential of chromenopyrroles and indolizinoindoles. DPPH radical scavenging activity evaluations are standard assays in antioxidant activity studies and facilitate rapid screening for radical scavenging activity. DPPH (1,1-diphenyl-2-picryl-hydrazyl) radical scavenging activity[27] of chromenopyrroles and indolizinoindoles were determined by spectrophotometrically[28] according to Blois's method.[29]

Table 3
Effect of chromno[4,3-*b*]pyrroles **5a**, **6a** and indolizino[6,7-*b*]indoles **7**(**a**–**e**) and **8**(**a**–**e**) on mycelia growth of plant fungal pathogens *Fusarium oxysporum* and *Macrophomenaphaseolina*

S. No	Compounds	Minimum Inhibitory Concentration (μg/ml)	
		F. oxysporum	*M. phaseolina*
1	**5a**	75	60
2	**6a**	85	60
3	**7a**	30	40
4	**7b**	70	20
5	**7c**	110	80
6	**7d**	35	50
7	**7e**	90	25
8	**8a**	30	85
9	**8b**	90	105
10	**8c**	85	30
11	**8d**	100	95
12	**8e**	35	90
	Carbendazim	20	15

All the 12 compounds were tested for their interaction with the stable free radical DPPH and this interaction, in turn, indicates their radical scavenging activity. The percentage of inhibition was compared with respective standard drug L-ascorbic acid. The results in percentage are expressed as the ratio of absorbance decrease at 517 nm and the absorbance of DPPH solution in the absence of chromenopyrrole and indolizinoindoles. The analysis of Table 4

Table 4
DPPH radical scavenging activity of chromno[4,3-*b*]pyrroles **5a**, **6a** and indolizino[6,7-*b*]indoles **7**(**a**–**e**) and **8**(**a**–**e**)

S. No	Compounds	Concentration (μg/mL)					
		Absorbance (50 μg)	%	Absorbance (500 μg)	%	Absorbance (1000 μg)	%
	L-Ascorbic acid[a]	0.037	95	0.025	97	0.007	99
1	**5a**	0.626	29	0.430	51	0.350	64
2	**6a**	0.596	33	0.427	52	0.302	66
3	**7a**	0.635	28	0.410	53	0.262	70
4	**7b**	0.702	21	0.505	43	0.282	68
5	**7c**	0.668	24	0.446	49	0.236	73
6	**7d**	0.638	28	0.444	50	0.282	68
7	**7e**	0.722	18	0.513	42	0.264	70
8	**8a**	0.731	17	0.596	33	0.268	69
9	**8b**	0.650	26	0.498	44	0.222	75
10	**8c**	0.658	26	0.410	53	0.110	87
11	**8d**	0.721	18	0.462	48	0.168	81
12	**8e**	0.621	30	0.415	53	0.285	67
	Control	0.8897					

[a] Reference drug used for antioxidant evaluation

discloses that the radical scavenging activity of chromenopyrroles and indolizinoindoles on DPPH radicals increases with the increasing concentration. It was observed that all the compounds showed good antioxidant activity at 1000 μg/mL. Compounds **8c** and **8d** showed maximum activity at a concentration of 1000 μg/mL.

In conclusion, we have synthesized a series of novel chromeno[4,3-*b*]pyrroles and indolizino[6,7-*b*]indoles by sequential intramolecular 1,3-dipolar cycloaddition and subsequent Pictet-Spengler cyclization. Four leads compounds **7b**, **7e**, **8b** and **8e**, displayed the potent activity against four selected bacterial pathogens and two compounds **7a** and **7d** exhibited good activity against two fungal organisms. Compounds **8c** and **8d** showed good antioxidant potential. The quantitative structure–activity relationship (QSAR) demonstrates that indolizino[6,7-*b*]indole with electron withdrawing groups (–NO_2, –Cl) attached directly to the phenyl ring were essential for activity. Further studies on the activity of these compounds in an expanded panel of organisms and in vivo efficacy models will be reported in due course.

Acknowledgements

NA, AIM and UK gratefully acknowledge Deanship of Scientific Research at King Saud University and this work funded through the research grant RGP-VPP-128. Also, the authors thank King Saud University for providing lab facilities.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.12.061.

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