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OXIDATIVE DEAROMATIC CYCLIZATION OF *N*-SUBSTITUTED BENZANILIDE DERIVATIVES: CONFORMATIONAL EFFECT OF AMIDE GROUPS ON THE REACTION

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Abstract – The synthesis of spirooxindoles with a hypervalent iodine reagent depended on *N*-substituted benzanilide derivatives as starting materials. Reaction yields of benzanilides containing various *N*-substituents were discovered to relate to the *cis* and *trans* conformations of the amide bond by *ab initio* molecular orbital calculations at the B3LYP/6-31G(d,p) and MP2/6-31G(d,p) levels, including full geometry optimizations. The relationship between the reaction and conformation of the starting material by quantum chemical calculations was applied to the formal synthesis of SR121463.

In recent years, many new biologically active spirooxindoles have been discovered.[1] The unique core structure and bioactive nature of these compounds have long been a focus of pharmaceutical development. One of these, named SR121463 **1**,[2] is manufactured by Sanofi and is a V_2 receptor antagonist (**Figure 1**).

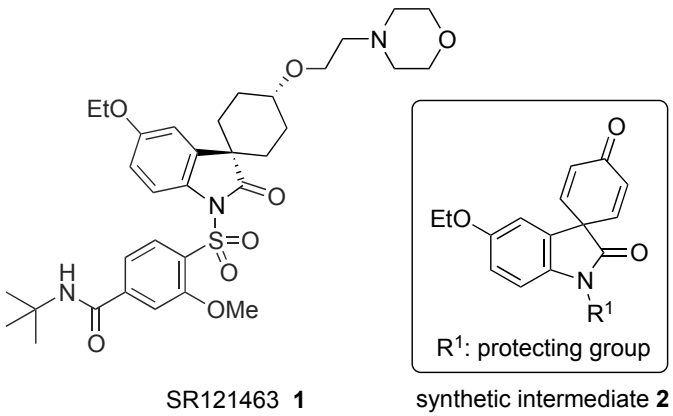


Figure 1. Structures of SR121463 and synthetic intermediate

The synthesis of a SR121463 intermediate **2** with *N*-methyl and benzyl protecting groups, has also been published using oxidative dearomatic reaction with hypervalent iodine reagent by Yu and co-workers in 2011.[3] This intermediate is useful in the synthesis of bioactive natural products such as phenanthridinone derivatives[4] using the dienone-phenol rearrangement,[5] and synthesis of a hydrocarbazole skeleton[6] by ring opening reaction of a lactam followed by aza-Michael addition (**Figure 2**). However, commercial applications utilizing intermediate **2** are inherently difficult due to issues with scaling up of the synthesis. For example, deprotection of the nitrogen when R is benzyl requires severe conditions such as in the Birch reduction.[7] Removal of protecting groups in total syntheses of bioactive natural products should proceed under mild conditions, otherwise the constructed structures will decompose. Therefore, the initial focus of this paper was to explore better protecting groups for intermediate **2**. Also, in the course of the screening, we employed computational methods to optimize our synthesis.

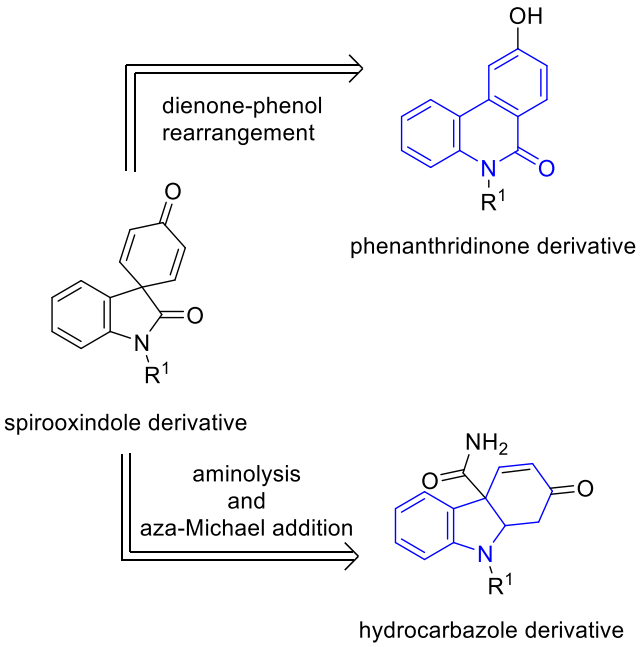
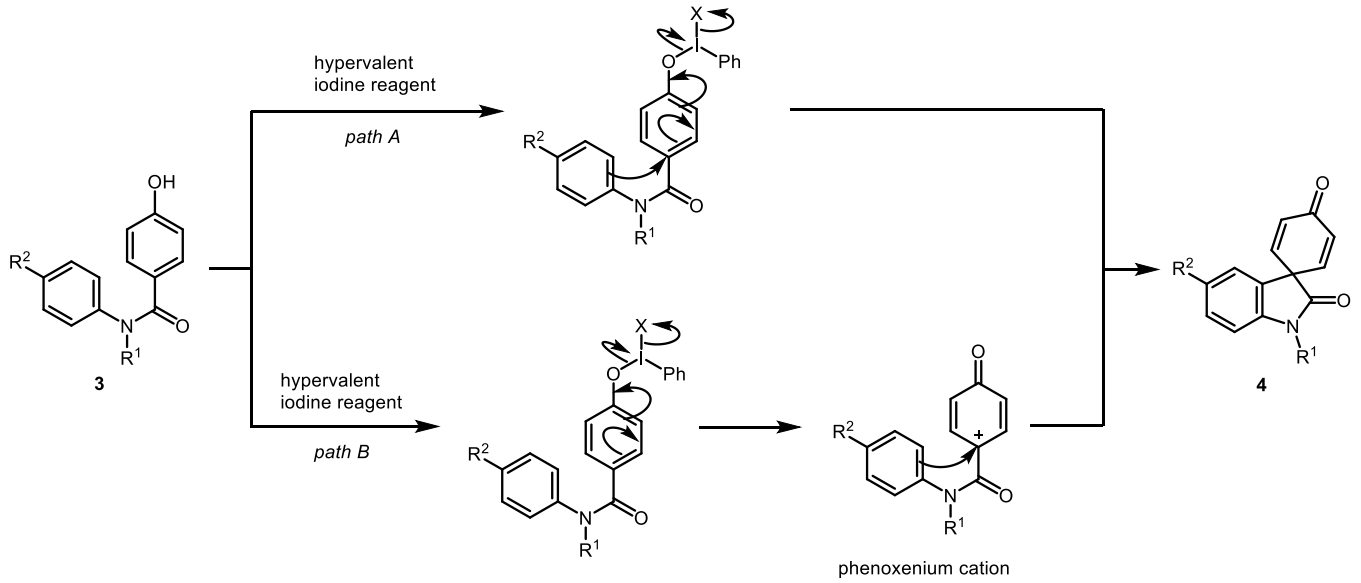


Figure 2. Syntheses of phenanthridinone and hydrocarbazole derivatives from spirooxindole derivative

Scheme 1 shows the synthesis of spirooxindole derivatives **4** from benzanilide derivatives **3** with hypervalent iodine reagent. Cyclization reaction by phenol oxidation with hypervalent iodine reagent has been proposed via two synthetic pathways, path A and path B.[8] However, neither route has been confirmed despite numerous studies.[9] In path A, cyclization, dearomatization and elimination reactions take place in order. In path B, on the other hand, phenoxenium cation is generated prior to the electrophilic aromatic substitution reaction. Compound **3** is generated from 4-hydroxybenzoic acid and aniline derivatives. The synthesis is designed and performed as described below.

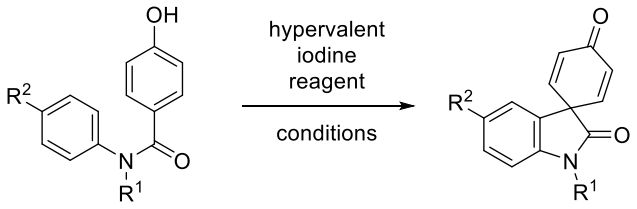


Scheme 1. Synthetic pathways of cyclization reaction by phenol oxidation with hypervalent iodine reagent

First, possible candidates for the starting material, **3a-3f** (**Table 1**), with various *N*-substituents were selected. *N*-Methyl and benzyl compounds, **3a-3d**, were prepared following published procedures.[3] Reported compounds **3a-3d** were synthesized to identify correlations between yield of cyclization reaction and amide conformation. The remaining two starting materials, *N*-methoxybenzanilide derivative **3e**[10] and *N*-phthaloylbenzanilide derivative **3f**,[10] were generated from 4-acetoxybenzoic acid[11] in 3 steps including arylation via nitrenium ion[12] with hypervalent iodine reagent. We also included two *N*-protecting groups reported in the literature: *N*-methoxy and *N*-phthaloyl groups. It was reported that *N*-methoxy group was easily deprotected under mild conditions such as hydrogenation,[13] and *N*-phthaloyl group was removed in two steps, hydrolysis with hydrazine followed by reduction.[14]

Second, the oxidative dearomatization reaction of the benzanilides was screened using **3a-3c**, **3e** and **3f** in 4 different solvents, $(CF_3)_2CHOH$, CF_3CH_2OH, MeOH, and CH_2Cl_2. Compound **3d** was also investigated in MeCN as a solvent. The yield of products **4a-4d** in **Table 1** shows that phenol oxidation with **3a-3d** afforded the desired spiro compounds **4a-4d** with excellent yields (entries 1-16), whereas the yield of the cyclization reaction with *N*-methoxy compound **3e** was much lower (entries 17-20). The amide **3f** produced spirooxindole **4f**[10] in moderate yield (entries 21-24). $PhI(OAc)_2$ (PIDA) was evaluated but it was found to be less effective than $PhI(OCOCF_3)_2$ (PIFA) (entry 15, 16). The result of the cyclization reactions showed that the differences between the yields of spirooxindole **4a-4f** depended on the various *N*-substituents in the starting materials. *N*-Methyl and benzyl compounds (**3a-3d**) afforded the best yields. However, it was not possible to predict which *N*-substituent would work better for the cyclization reactions.

Table 1. Syntheses of spirooxindoles with various *N*-substituents



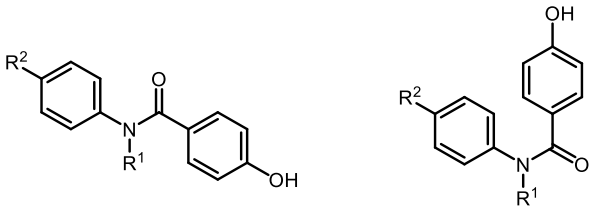
3 **4**

entry	starting material	R^1	R^2	hypervalent iodine reagent (eq.)	solvent	time (min.)	temp. (°C)	yield of **4** (%)
1	**3a**	-Me	-H	PIFA (1.1)	$(CF_3)_2CHOH$	1	0	81
2					CF_3CH_2OH	3	rt	99
3					MeOH	10	rt	80
4					CH_2Cl_2	15	rt	83
5	**3b**	-CH_2Ph	-H	PIFA (1.1)	$(CF_3)_2CHOH$	1	rt	83
6					CF_3CH_2OH	1		90
7					MeOH	5		82
8					CH_2Cl_2	20		85
9	**3c**	-Me	-OEt	PIFA (1.1)	$(CF_3)_2CHOH$	1	rt	91
10					CF_3CH_2OH	5		91
11					MeOH	5		85
12					CH_2Cl_2	10		89
13	**3d**	-CH_2Ph	-OEt	PIFA (1.1)	$(CF_3)_2CHOH$	1	rt	83
14					CF_3CH_2OH	5		85
15				PIDA (2.0)	MeOH	>120		31
16					MeOH	15		91
17				PIFA (1.1)	CH_2Cl_2	15		75
18					MeCN	15		52
19	**3e**	-OMe	-OEt	PIFA (1.1)	$(CF_3)_2CHOH$	30	0	25
20				PIFA (1.5)	CF_3CH_2OH	60	rt	25
21				PIFA (1.1)	MeOH	60	rt	31
22				PIFA (1.5)	CH_2Cl_2	30	0	14
23	**3f**	-NPhth	-OEt	PIFA (1.1)	$(CF_3)_2CHOH$	5	rt	55
24					CF_3CH_2OH	5		43
25					MeOH	5		14
26					CH_2Cl_2	5		40

In order to build a better predictive model, the impact of amide conformations (**Figure 3**) in the cyclization reactions was investigated. It was reported that *cis N*-methylbenzanilide is the predominant conformer according to NMR analysis.[15]

The *cis-trans* conformations of each candidate material (**3a-3f**) were determined by employing computational methods, specifically quantum chemical calculations. Both *ab initio* DFT molecular orbital calculations at the B3LYP/6-31G(d,p) level and *ab initi*o molecular orbital calculations at the MP2/6-31G(d,p) level using the Gaussian09 program package[16] can estimate the energetics of each conformation to determine the most stable form, and both tools were used to identify the *cis-trans*

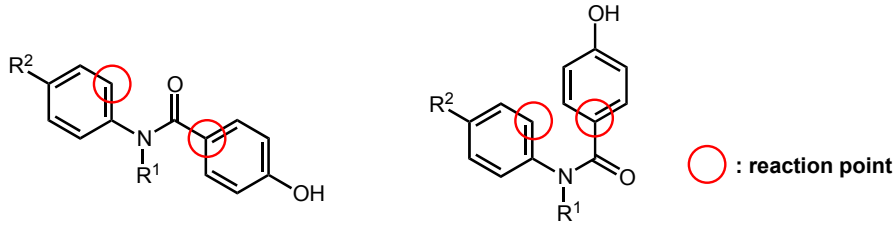
conformations of all starting materials (**3a-3f**). Note that the complete analysis for all conformations, including methoxy groups, were not performed at this time. One of the optimized structures of *cis* and *trans* conformers for each compound were calculated. The energetics would vary a little if complete calculations were performed on the most stable *cis* and *trans* conformers. Such calculations using Hamiltonian algorithm[17] is in progress and will be published elsewhere. The *trans-cis* ratio was estimated by the Boltzmann distribution law at 300 K (*k*T product is 0.596 kcal/mol at 300 K). The calculated results were compared to the yields of synthetic products **4a-4f** (**Table 2**).



trans-benzanilide **3** *cis*-benzanilide **3**

Figure 3. *cis-trans* Conformations of amide bond of benzanilide **3**

Table 2. Comparison of reaction yield and B3LYP/6-31G(d,p) and MP2/6-31G(d,p) total energies of *cis* and *trans* conformations of amide bonds of benzanilides **3**



trans-benzanilide **3** *cis*-benzanilide **3**

entry	starting material	energy [a.u.]		Δ*E* (*trans-cis*) [kcal/mol]	ratio at 300 K (*cis* : *trans*)	yield of **4** (%)*
		cis	*trans*			
B3LYP/6-31G(d,p)						
1	**3a**	-746.544453	-746.539481	3.12	1 : 0.00533	81
2	**3b**	-977.602999	-977.595583	4.65	1 : 0.000410	83
3	**3c**	-900.389066	-900.384022	3.17	1 : 0.00490	91
4	**3d**	-1131.447946	-1131.438950	5.65	1 : 0.0000765	83
5	**3e**	-975.544321	-975.547944	-2.27	0.0222 : 1	25
6	**3f**	-1372.939529	-1372.937754	1.11	1 : 0.155	55
MP2/6-31G(d,p)						
1	**3a**	-744.305375	-744.298414	4.36	1 : 0.000665	81
2	**3b**	-974.645940	-974.637055	5.57	1 : 0.0000873	83
3	**3c**	-897.695408	-897.688375	4.41	1 : 0.000612	91
4	**3d**	-1128.036452	-1128.027030	5.91	1 : 0.0000494	83
5	**3e**	-972.661310	-972.661707	-0.24	0.669 : 1	25
6	**3f**	-1368.695258	-1368.694586	0.42	1 : 0.494	55

*: 1,1,1,3,3,3-hexafluoroisopropanol as a solvent

The result of the calculations correlates very closely with the yields of the cyclization reaction. According to the data, amides **3a-d**, which are predominantly *cis* compounds, gave high yields of the products **4a-d**. On the other hand, benzamide **3e** with the *N*-methoxy group provided a low yield of **4e**. The dipole moments of the carbonyl and methoxy groups are one of the possible factors contributing to the *trans*-conformation of *N*-methoxyamide **3e** (**Figure 4**). In addition, steric hindrance of the methoxy group is smaller than the methyl group allowing easier *cis* to *trans* conformational change. The calculated results for *N*-phthaloylamide **3f** show that the *trans*-conformation is predominant, probably due to both dipole moments and steric hindrance.

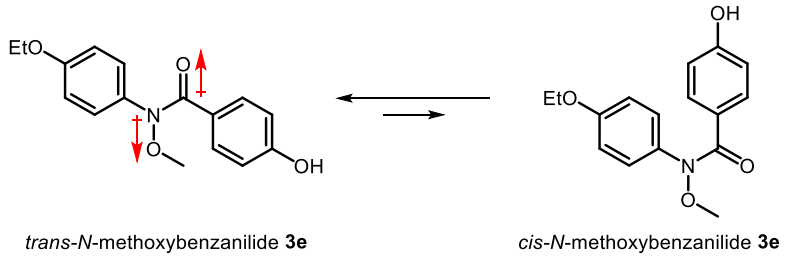
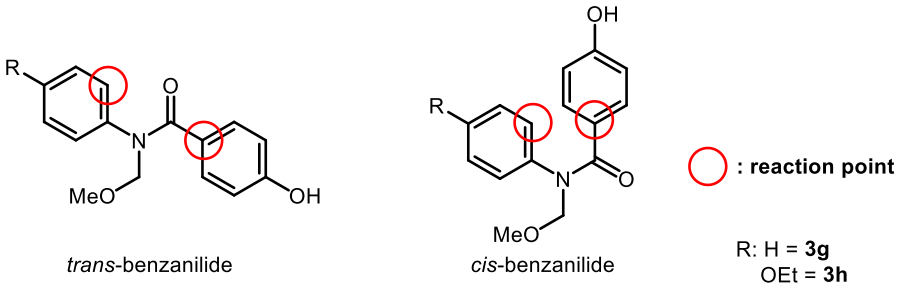


Figure 4. Dipole moments of carbonyl and methoxy groups

These calculations provide a practical way to identify *cis-trans* conformations of compounds to find better starting materials to generate products with high yields, however no one has yet reported utilizing quantum chemical calculations for *cis-trans* conformations of amide bonds. Such calculations are useful, since the reaction points in the *cis* form of benzanilide derivatives are closer than those in the *trans* form, hence the higher yields.

Table 3. Calculations of *cis* and *trans* conformations of *N*-methoxymethylbenzanilide derivatives **3g**, **h** with B3LYP/6-31G(d,p) and MP2/6-31G(d,p)

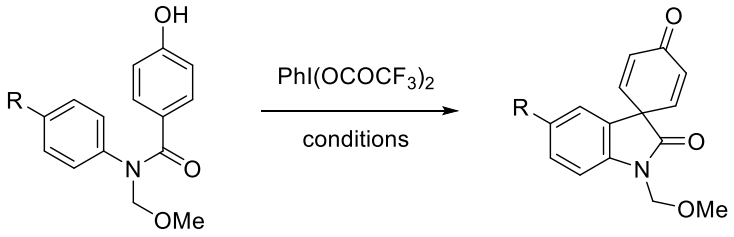


entry	starting material	energy [a.u.]		ΔE (*trans-cis*) [kcal/mol]	ratio at 300 K (*cis* : *trans*)
		cis	*trans*		
B3LYP/6-31G(d,p)					
1	**3g**	-861.068100	-861.064440	2.29	1 : 0.02135
2	**3h**	-1014.914950	-1014.911500	2.18	1 : 0.02553
MP2/6-31G(d,p)					
1	**3g**	-858.512474	-858.506150	3.96	1 : 0.00130
2	**3h**	-1011.904137	-1011.897700	4.05	1 : 0.00112

Although the starting materials that showed high yields of the products so far were **3a-3d**, they are not actually ideal compounds since it is known that the *N*-methyl group cannot be removed and deprotecting the *N*-benzyl group requires severe conditions. Therefore, more effective *N*-protecting groups were investigated as the next step. Synthesis of a spirooxindole with the *N*-methoxymethyl (MOM) group, which can be deprotected using acid hydrolysis, was evaluated. Initial screening was performed using *ab initio* DFT molecular orbital calculations on *N*-methoxymethylbenzanilide derivatives to find possible compounds with the *cis* form, and two candidates, **3g** and **3h,** were selected (**Table 3**).

N-Methoxymethyl compounds (**3g**, **3h**) were obtained from 4-benzyloxybenzanilide derivatives in 2 steps following literature procedures.[18] After the oxidative dearomatization reaction of compounds **3g**, **3h**, spirooxindole derivatives **4g**, **4h** were obtained in excellent yields (**Table 4**).

Table 4. Syntheses of spirooxindoles with *N*-methoxymethyl substituent

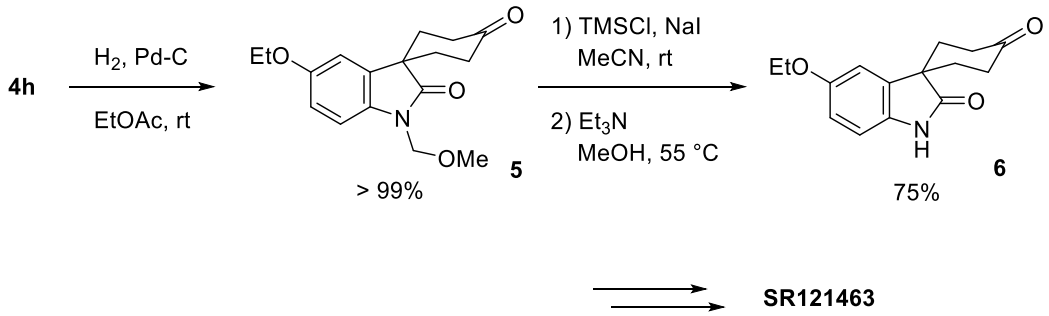


3g: R = H
3h: R = OEt

4g: R = H
4h: R = OEt

entry	starting material	R	PIFA (eq.)	solvent	time (min.)	temp. (°C)	yield of **4** (%)
1	**3g**	-H	1.1	$(CF_3)_2CHOH$	10	0	46
2			1.2	CF_3CH_2OH	20		64
3				MeOH	60		85
4				CH_2Cl_2	22		61
5	**3h**	-OEt	1.2	$(CF_3)_2CHOH$	3	0	97
6				CF_3CH_2OH	5	0	94
7				MeOH	30	rt	93
8				CH_2Cl_2	60	rt	69

The oxidative dearomatization reaction of *N*-methoxymethylbenzanilide **3h** was applied to the synthesis of SR121463 intermediate **6** (**Scheme 2**). Catalytic hydrogenation of spirodienone **4h** in ethyl acetate at room temperature produced spirocyclohexanone **5** in >99% yield. The deprotection of the methoxymethyl group was carried out by treating **5** with trimethylsilyl iodide in acetonitrile at ambient temperature and triethylamine in methanol at 55 °C to give intermediate **6**.[19] The structure of **6**[20] was confirmed by spectroscopic data, which was identical to reported data by Curran and co-workers.[21] Therefore, the synthesis afforded **6** under mild conditions.



Scheme 2. Concise synthesis of SR121463 intermediate **6**

In summary, we presented a concise synthesis of a SR121463 intermediate under mild conditions by oxidative dearomatization cyclization with hypervalent iodine reagent as a key step. It is proposed that *N*-MOM will be a better protecting group, not only for synthesis of the intermediate **2**, but perhaps also for other bioactive compounds since the deprotection can be performed under mild conditions. Hypervalent iodine reagent could also react with the nitrogen of the amide, however, we believe *N*-Me, Bn and MOM substituted amides were sufficiently protected, allowing the reaction to occur on the hydroxy group in the spirooxindole synthesis. In addition, we established a practical way to identify *cis-trans* conformations of amides to screen for better reactive compounds to give higher yields. We identified a correlation between experimental data and *ab initio* DFT molecular orbital calculations, and successfully identified better benzamide derivatives for the target compound. This correlation suggests more applicability of these calculations to screen compounds for improved reactivity. This is also the first report to demonstrate that the *cis-trans* conformations of amide bonds can have an effect on the yield of oxidative dearomatization cyclizations.

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REFERENCES AND NOTES

1. (a) C. Marti and E. M. Carreira, *Eur. J. Org. Chem.*, 2003, 2209; (b) C. V. Galliford and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2007, **46**, 8748; (c) L. Hong and R. Wang, *Adv. Synth. Catal.*, 2013, **355**, 1023.
2. C. Serradeil-Le Gal, C. Lacour, G. Valette, G. Garcia, L. Foulon, G. Galindo, L. Bankir, B. Pouzet, G. Guillon, C. Barberis, D. Chicot, S. Jard, P. Vilain, C. Garcia, E. Marty, D. Raufaste, G. Brossard, D. Nisato, J. P. Maffrand, and G. LeFur, *J. Clin. Invest.*, 1996, **98**, 2729.
3. Z. Yu, X. Ju, J. Wang, and W. Yu, *Synthesis*, 2011, 860.
4. (a) D. Weltin, V. Picard, K. Aupeix, M. Varin, D. Oth, J. Marchal, P. Dufour, and P. Bischoff, *Int. J.*

Immunopharmacol., 1995, **17**, 265; (b) T. Harayama, H. Akamatsu, K. Okamura, T. Miyagoe, T. Akiyama, H. Abe, and Y. Takeuchi, *J. Chem. Soc.*, *Perkin Trans. 1*, 2001, 523; (c) J. Karthikeyan and C.-H. Cheng, *Angew. Chem. Int. Ed.*, 2011, **50**, 9880; (d) S. Mishra, S. De, B. N. Kakde, D. Dey, and A. Bisai, *Indian J. Chem.*, 2013, **52A,** 1093; (e) K. Tanimoto, N. Nakagawa, K. Takeda, M. Kirihata, and S. Tanimori, *Tetrahedron Lett.*, 2013, **54**, 3712; (f) Z. Liang, J. Zhang, Z. Liu, K. Wang, and Y. Zhang, *Tetrahedron*, 2013, **69**, 6519; (g) M. Yuan, L. Chen, J. Wang, S. Chen, K. Wang, Y. Xue, G. Yao, Z. Luo, and Y. Zhang, *Org. Lett.*, 2015, **17**, 346; (h) M. Feng, B. Tang, N. Wang, H.-X. Xu, and X. Jiang, *Angew. Chem. Int. Ed.*, 2015, **54**, 14960.

5. (a) S. Bo, M. Deng, and Q. Wang, *Org. Lett.*, 2013, **15**, 1606; (b) M. Yoshida, T. Nozaki, T. Nemoto, and Y. Hamada, *Tetrahedron*, 2013, **69**, 9609.
6. J.-Y. Du, C. Zeng, X.-J. Han, H. Qu, X.-H. Zhao, X.-T. An, and C.-A. Fan, *J. Am. Chem. Soc.*, 2015, **137**, 4267.
7. (a) H. Venkatesan, M. C. Davis, Y. Altas, J. P. Snyder, and D. C. Liotta, *J. Org. Chem.*, 2001, **66**, 3653; (b) T. Ohgi and S. M. Hecht, *J. Org. Chem.*, 1981, **46**, 1232; (c) M. Y. Kim, J. E. Starrett, Jr., and S. M. Weinreb, *J. Org. Chem.*, 1981, **46**, 5383; (d) S. Sugasawa and T. Fujii, *Chem. Pharm. Bull.*, 1958, **6**, 587; (e) P. A. Jacobi, H. L. Brielmann, and S. I. Hauck, *Tetrahedron Lett.*, 1995, **36**, 1193; (f) R. M. Williams and E. Kwast, *Tetrahedron Lett.*, 1989, **30**, 451; (g) M. Barbier, *Heterocycles*, 1985, **23**, 345; (h) J. E. Semple, P. C. Wang, Z. Lysenko, and M. M. Joullié, *J. Am. Chem. Soc.*, 1980, **102**, 7505; (i) E. G. Baggiolini, H. L. Lee, G. Pizzolato, and M. R. Uskokovic, *J. Am. Chem. Soc.*, 1982, **104**, 6460; (j) G. F. Field, W. J. Zally, L. H. Sternbach, and J. F. Blount, *J. Org. Chem.*, 1976, **41**, 3853.
8. (a) J. S. Swenton, A. Callinan, Y. Chen, J. J. Rohde, M. L. Kerns, and G. W. Morrow, *J. Org. Chem.*, 1996, **61**, 1267; (b) Y. Kita, M. Arisawa, M. Gyoten, M. Nakajima, R. Hamada, H. Tohma, and T. Takada, *J. Org. Chem.*, 1998, **63**, 6625; (c) Y. Kita, *YAKUGAKU ZASSHI*, 2002, **122**, 1011; (d) A. M. Harned, *Tetrahedron Lett.*, 2014, **55**, 4681.
9. (a) L. Kürti, P. Herczegh, J. Visy, M. Simonyi, S. Antus, and A. Pelter, *J. Chem. Soc., Perkin Trans. 1*, 1999, 379; (b) Y.-T. Wang, K. J. Jin, S. H. Leopold, J. Wang, H.-L. Peng, M. S. Platz, J. Xue, D. L. Phillips, S. A. Glover, and M. Novak, *J. Am. Chem. Soc.*, 2008, **130**, 16021; (c) P. J. Hanway and A. H. Winter, *J. Am. Chem. Soc.*, 2011, **133**, 5086; (d) P. J. Hanway, J. Xue, U. Bhattacharjee, M. J. Milot, Z. Ruixue, D. L. Phillips, and A. H. Winter, *J. Am. Chem. Soc.*, 2013, **135**, 9078.
10. **3e**: mp 166-168 ºC; ^{1}H NMR (400 MHz, CD_3OD) δ 7.40 (d, 2H, J = 8.8 Hz), 7.22 (d, 2H, J = 8.8 Hz), 6.90 (d, 2H, J = 8.8 Hz), 6.68 (d, 2H, J = 8.8 Hz), 4.02 (q, 2H, J = 7.0 Hz), 3.70 (s, 3H), 1.37 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 170.0, 161.5, 160.2, 133.7, 132.1, 129.5, 125.9, 115.9, 115.7, 64.8, 61.4, 15.0; IR (KBr) 3224, 2939, 1635, 1597, 1512, 1442, 1350, 1257, 1226,

1165 cm^{-1}; HRMS (EI) Calcd for $C_{16}H_{17}NO_4$ 287.1158, Found 287.1157; Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.87; H, 5.94; N, 4.85. **3f**: mp 139-142 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, 2H, J = 3.2 Hz), 7.77-7.74 (m, 2H), 7.44-7.40 (m, 2H), 7.36 (d, 2H, J = 8.6 Hz), 6.89-6.77 (m, 3H), 6.59 (d, 2H, J = 8.6 Hz), 3.97 (q, 2H, J = 7.0 Hz), 1.37 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 158.9, 158.6, 134.8, 131.7, 129.9, 129.7, 129.2, 124.0, 123.8, 120.6, 115.0, 113.0, 63.7, 14.6; IR (KBr) 3317, 2985, 1735, 1651, 1604, 1512, 1327, 1280, 1242, 1172, 1111 cm^{-1}; HRMS (EI) Calcd for $C_{23}H_{18}N_2O_5$ 402.1216, Found 402.1199; Anal. Calcd for $C_{23}H_{18}N_2O_5$: C, 68.65; H, 4.51; N, 6.96. Found: C, 68.36; H, 4.79; N, 6.68. **4e**: mp 99-102 ºC; ^1H NMR (400 MHz, CD_3OD) δ 7.11 (d, 1H, J = 8.4 Hz), 7.00 (dd, 1H, J = 8.8 Hz and 2.4 Hz), 6.79 (d, 2H, J = 9.8 Hz), 6.69 (d, 1H, J = 2.4 Hz), 6.53 (d, 2H, J = 9.8 Hz), 4.04 (s, 3H), 3.97 (q, 2H, J = 7.0 Hz), 1.34 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 187.1, 167.8, 158.2, 145.4, 134.3, 132.3, 125.4, 116.7, 113.3, 110.5, 65.3, 64.4, 56.2, 15.1; IR (KBr) 3070, 2985, 2939, 2877, 1743, 1666, 1604, 1473, 1404, 1280, 1211, 1072 cm^{-1}; HRMS (EI) Calcd for $C_{16}H_{15}NO_4$ 285.1001, Found 285.1029; Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.23; H, 5.31; N, 4.86. **4f**: mp 219-220 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02-7.99 (m, 2H), 7.90-7.88 (m, 2H), 6.87 (dd, 1H, J = 8.4 Hz and 2.4 Hz), 6.84 (d, 2H, J = 10.0 Hz), 6.77 (d, 1H, J = 8.4 Hz), 6.69 (d, 1H, J = 2.4 Hz), 6.61 (d, 2H, J = 10.0 Hz), 3.97 (q, 2H, J = 7.0 Hz), 1.39 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.7, 168.9, 163.2, 156.9, 142.5, 135.3, 133.8, 131.6, 129.6, 124.7, 124.4, 115.6, 112.0, 109.6, 64.1, 54.3, 14.6; IR (KBr) 2978, 1797, 1743, 1666, 1496, 1458, 1273, 1165 cm^{-1}; HRMS (EI) Calcd for $C_{23}H_{16}N_2O_5$ 400.1059, Found 400.1039; Anal. Calcd for $C_{23}H_{16}N_2O_5$ C, 69.00; H, 4.03; N, 7.00. Found: C, 68.72; H, 4.19; N, 6.83.

11. C. H. R. M. Wilsens, B. A. J. Noordover, and S. Rastogi, *Polymer*, 2014, **55**, 2432.
12. (a) Y. Kikugawa and M. Kawase, *Chem. Lett.*, 1990, 581; (b) R. Samanta, J. O. Bauer, C. Strohmann, and A. P. Antonchick, *Org. Lett.*, 2012, **14**, 5518; (c) M. Kawase, T. Kitamura, and Y. Kikugawa, *J. Org. Chem.*, 1989, **54**, 3394; (d) K. Murata, M. Tsukamoto, T. Sakamoto, S. Saito, and Y. Kikugawa, *Synthesis*, 2008, 32.
13. X. Zhou, T. Xiao, Y. Iwama, and Y. Qin, *Angew. Chem. Int. Ed.*, 2012, **51**, 4909.
14. Y. Kikugawa, A. Nagashima, T. Sakamoto, E. Miyazawa, and M. Shiiya, *J. Org. Chem.*, 2003, **68**, 6739.
15. (a) I. Azumaya, K. Yamaguchi, H. Kagechika, S. Saito, A. Itai, and K. Shudo, *YAKUGAKU ZASSHI*, 1994, **114**, 414; (b) I. Azumaya, *YAKUGAKU ZASSHI*, 2001, **121**, 117; (c) R. Yamasaki, A. Tanatani, I. Azumaya, H. Masu, K. Yamaguchi, and H. Kagechika, *Cryst. Growth Des.*, 2006, **6**, 2007.
16. Gaussian 09, Revision **C.01**, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb,

J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, M. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

17. K. Ohtawara and H. Teramae, *Chem. Phys. Lett.*, 2004, **390**, 84.
18. A. Bodzioch, M. Zheng, P. Kaszynski, and G. Utecht, *J. Org. Chem.*, 2014, **79**, 7294.
19. S. Yokoshima, H. Tokuyama, and T. Fukuyama, *Angew. Chem. Int. Ed.*, 2000, **39**, 4073.
20. **4h**: mp 110-112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, 1H, J = 8.8 Hz), 6.89 (dd, 1H, J = 8.8 Hz and 2.8 Hz), 6.62 (d, 1H, J = 2.8 Hz), 6.62 (d, 2H, J = 10.2 Hz), 6.53 (d, 2H, J = 10.2 Hz), 5.15 (s, 2H), 3.96 (q, 2H, J = 6.9 Hz), 3.35 (s, 3H), 1.37 (t, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.1, 171.6, 156.3, 143.3, 135.1, 131.4, 126.8, 115.6, 111.8, 111.2, 72.2, 64.2, 56.5, 56.4, 14.7; IR (KBr) 2939, 1728, 1666, 1496, 1327, 1273, 1188, 1087 cm^{-1}; HRMS (EI) Calcd for $C_{17}H_{17}NO_4$ 299.1158, Found 299.1176; Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.28; H, 5.62; N, 4.73. **5**: mp 115-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, 1H, J = 8.6 Hz), 6.85 (d, 1H, J = 2.4 Hz), 6.82 (dd, 1H, J = 8.6 Hz and 2.4 Hz), 5.13 (s, 2H), 4.00 (q, 2H, J = 7.2 Hz), 3.34 (s, 3H), 3.19-3.11 (m, 2H), 2.49 (dt, 2H, J = 15.2 Hz and 5.4 Hz), 2.19-2.14 (m, 4H), 1.41 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4, 179.6, 155.7, 134.2, 133.9, 113.0, 111.0, 110.1, 71.2, 64.1, 56.2, 46.1, 36.8, 33.8, 14.9; IR (KBr) 2939, 1705, 1597, 1489, 1450, 1342, 1327, 1188, 1095 cm^{-1}; HRMS (EI) Calcd for $C_{17}H_{21}NO_4$ 303.1471, Found 303.1474; Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.19; H, 6.97; N, 4.65. **6**: mp 192-194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 6.86 (d, 1H, J = 8.4 Hz), 6.83 (d, 1H, J = 2.4 Hz), 6.77 (dd, 1H, J = 8.4 Hz and 2.4 Hz), 4.00 (q, 2H, J = 7.0 Hz), 3.20-3.12 (m, 2H), 2.50 (dt, 2H, J = 15.2 Hz and 5.5 Hz), 2.25-2.11 (m, 4H), 1.41 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7, 181.8, 155.2, 135.0, 133.2, 112.9, 111.1, 110.3, 64.1, 46.3, 36.8, 33.5, 14.8; IR (KBr) 3163, 3047, 2901, 1712, 1697, 1604, 1489, 1465, 1303, 1203, 1049; HRMS (EI) Calcd for $C_{15}H_{17}NO_3$ 259.1208, Found 259.1212; Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.32; H, 6.46; N, 5.38.
21. F. González-López de Turiso and D. P. Curran, *Org. Lett.*, 2005, **7**, 151.