A Convenient Synthesis of Aryl-Substituted *N*-Carbamoyl/*N*-Thiocarbamoyl Narcotine and Related Compounds

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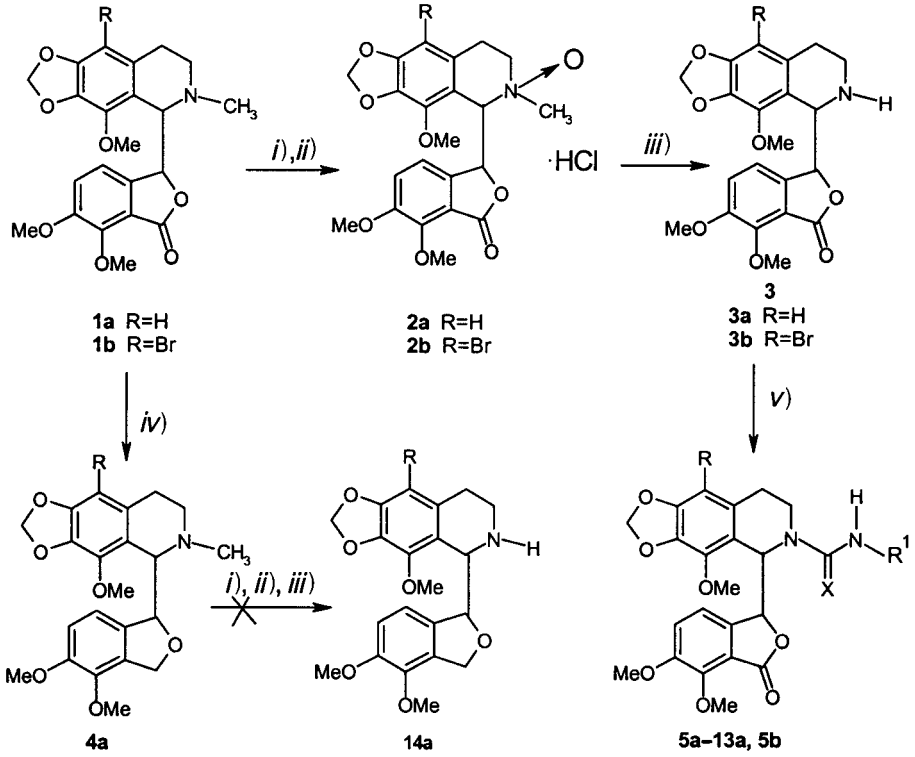
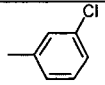
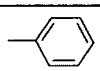
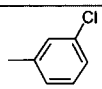
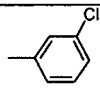
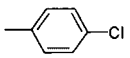
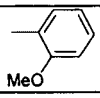
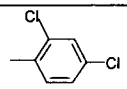
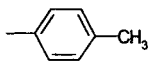
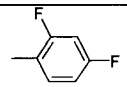
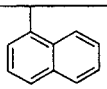
The reaction of nornarcotine and 5-bromonornarcotine, synthesized from noscapine, with suitable aromatic isocyanates or isothiocyanates provides a general method for the synthesis of aryl-substituted *N*-carbamoyl or *N*-thiocarbamoylnarcotine and related compounds. Similarly, **15a** has been prepared *via* the reduction of the lactone ring moiety of noscapine. Also, an improved procedure, which utilizes narcotine *N*-oxide · HCl for generation of nornarcotine, is described.

Introduction. – Alkaloids and their analogs are important targets in chemical synthesis mainly because a large number of these compounds possess pronounced biological and pharmacological activities [1]. The basic isoquinoline-skeletal structure of various aporphine alkaloids, namely, (±)-thaliporphine, (±)-*N*-methylaurotetanine, and (±)-isoboldine have been found to be of significant biological and biogenetic interest [2]. Noscapine, for example, a phthalide-isoquinoline alkaloid derived from opium, known for its antitussive action [3][4] has recently been described as a prospective antineoplastic agent [5]. *Ye et al.* reported that noscapine has potent antitumor activity against solid lymphoid tumors induced in mice and, hence, exhibits outstanding therapeutic potential. In our earlier communication, we focussed on structural modulations of papaverine, a naturally occurring isoquinoline-based alkaloid isolated from *Papaver somniferum* [6], and reported the synthesis of urea/thiourea derivatives of papaverine, which were found to be more efficacious in terms of specificity and action in their antispasmodic effect. On similar lines of thought, we have also synthesized *N*-carbamoyl/*N*-thiocarbamoyl analogs of noscapine and other related compounds, which might prove as well to be more efficacious and less cytotoxic. Hence, new synthetic methodologies leading to novel antitumor agents are highly desired. In a recent publication from our laboratory [7], we have discussed the structure and the fragmentation patterns of narcotine and *N*-carbamoyl/*N*-thiocarbamoyl analogs of narcotine-related compounds. In the present paper, our interest circumscribes the synthetic procedures of *N*-demethylation and preparation of *N*-carbamoyl/*N*-thiocarbamoyl analogs of narcotine. It is the purpose of this communication to show how the target compound nornarcotine (**3a**) and other similar *N*-demethylated narcotine derivatives can be prepared in a few straightforward steps starting from noscapine (**1a**) and their further derivatization with aryl isocyanates and aryl isothiocyanates yielded the desired title compunds (*Scheme 1*).

Scheme 1

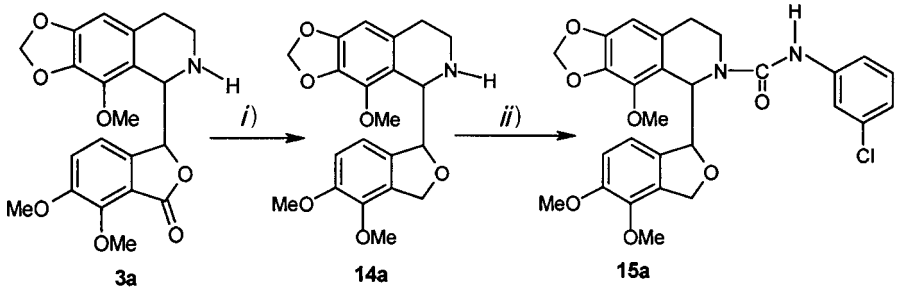


Product No.	R	R^1	X	Product No.	R	R^1	X
5a	H		O	**9a**	H		S
5b	Br		O	**10a**	H		S
6a	H		O	**11a**	H		S
7a	H		O	**12a**	H		S
8a	H		O	**13a**	H		S

i) *m*-Chloroperbenzoic acid (*m*CPBA). *ii*) HCL. *iii*) Fe^{III}-citrate/citric acid *iv*) $NaBH_4$, THF. *v*) R^1NCO/R^1NCS.

Results and Discussion. – The *N*-dealkylation of narcotine is a difficult process and requires special attention. The *N*-demethylation of narcotine with cyanogen bromide and various chloroformates such as ethyl chloroformate, phenyl chloroformate [8], 2,2,2-trichloroethyl chloroformate [9], and vinyl chloroformate [10] often results either in no reaction or cleavage at benzylic and tertiary centers, adjacent to the amine function. These cleavage reactions are generally preferred with the formation of enol lactone as similar to hydrastine [11]. In another experiment, narcotine has been converted to nornarcotine in 35% overall yield *via* the intermediate narcotine *N*-oxide hydrochloride (**2a**) and further reflux with ferric citrate hydrate in H_2O. In the successful synthesis of aryl-substituted *N*-carbamoyl or *N*-thiocarbamoyl derivatives of noscapine, as summarized in *Scheme 1*, the strategic step, *i.e.*, the *N*-demethylation of narcotine was performed first, and the reaction of aryl isocyanate and aryl isothiocyanate with nornarcotine to the final product was accomplished thereafter. We have also attempted synthesis of **15a** *via* the reduction of the lactone ring of nornarcotine by $NaBH_4$, followed by its reaction with 3-chlorophenyl isocyanate, which yielded the title compound (*Scheme 2*). All spectroscopic data are fully compatible with the proposed structure.

Scheme 2



i) $NaBH_4$, THF. *ii*) 3-ClC_6H_4NCO.

Experimental Part

General. TLC: *Kieselgel G* (*Merck*) with a hexane/AcOEt mixture as eluent. Column chromatography (CC): silica gel *60 H*, slurry packed, run under low pressure of N_2 and with increasing amounts of AcOEt in hexane as eluent. M.p.: *Büchi* melting-point apparatus *B-540*; uncorrected. Optical rotations: in $CHCl_3$ on a *Perkin-Elmer 983* spectrometer. IR Spectra (KBr): *Shimadzu FTIR-8300* instrument. ^{1}H-NMR Spectra: *Bruker Spectrospin Avance-300* instrument at 300 MHz in $CDCl_3$ with TMS as internal standard. MS: *MALDI Kratos Analytical Kompact SEQ* mass spectrometer with α-cyano-4-hydroxycinnamic acid as matrix under positive linear reflectance mode. Elemental analyses were performed on *Heraeus CHN* rapid analyzer.

General Procedure 1 for N-*Demethylation of* **3a** *and* **3b**: *1,3-Dihydro-6,7-dimethoxy-3-[1,2,3,4-tetrahydro-8-methoxy-6,7-(methylenedioxy)isoquinolin-1-yl]isobenzofuran-1-one* (**3a**). A soln. of 15 g of Fe^{III}-citrate in 35 ml of H_2O was adjusted to pH 1–2 by citric acid. To this soln., noscapine *N*-oxide · HCl (1.0 g, 2.15 mmol) was added, and the mixture was refluxed to 80–90° for 2 h. After cooling, the mixture was treated with Na_2CO_3 soln. (pH 9) and extracted with $CHCl_3$. The org. layer was washed with 1N H_2SO_4, and the aq. phase was neutralized with sat. Na_2CO_3 soln. Extraction with $CHCl_3$ and evaporation of the org. layer under vacuum yielded the desired product and some starting material (*i.e.*, noscapine), which was purified by CC to give **3a** (300 mg, 35%) ([12]: yield 26%). Yellow oil. IR: 3210*m*, 2998*w*, 2930*m*, 2840*w*, 1760*s*, 1620*m*, 1490*s*, 1270*s*, 1080*s*, 1043*s*, 770*s*.

^{1}H-NMR ($CDCl_3$, 300 MHz): 6.96 (*d*, *J* = 4, 1 H); 6.33 (*s*, 1 H); 6.15 (*d*, *J* = 7.8, 1 H); 5.94–5.88 (*m*, 3 H); 4.94 (*d*, *J* = 5.8, 1 H); 4.08 (*s*, 3 H); 3.98 (*s*, 3 H); 3.84 (*s*, 3 H); 2.80–2.75 (*m*, 1 H); 2.62–2.53 (*m*, 2 H); 2.31–2.18 (*m*, 1 H); 2.04–1.96 (br. *s*, 1 H). MS: 400 ($[M+H]^+$). Anal. calc. for $C_{21}H_{21}NO_7$: C 63.15, H 5.30, N 3.51; found: C 63.35, H 5.45, N 3.42.

General Procedure 2 (**5a**–**13a**, and **5b**): N-*(3-Chlorophenyl)-1-(1,3-dihydro-4,5-dimethoxy-3-oxoisobenzofuran-1-yl)-1,2,3,4-tetrahydro-8-methoxy-6,7-(methylenedioxy)isoquinoline-2-carboxamide* (**5a**). A soln. of 3-chlorophenyl isocyanate (0.385 g, 2.5 mmol) in dry MeCN (5 ml) was added dropwise to a soln. of **3a** (1 g, 2.5 mmol) in dry MeCN (15 ml) at 5°. The soln. was stirred at 25° for 2 h. The mixture was then poured into H_2O and extracted with $CHCl_3$. The extract was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to give 1.3 g of **5a**, which was purified by CC (silica gel *60 H*; AcOEt/hexane, 1:5). Yield 1.3 g (87%). M.p. 202–203°. $[\alpha]_D^{20} = +197$ (*c* = 20 mg, $CHCl_3$). IR: 3395 (br.), 3386 (br.), 2939*m*, 1751*s*, 1660*s*, 1587*s*, 1481*s*, 1259*s*, 1028*m*, 921*m*, 775*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.49 (*s*, 1 H); 7.26–7.17 (*m*, 2 H); 6.52 (*d*, *J* = 8.8, 1 H); 7.05 (*AB*, *J* = 8.8, 2 H); 6.99 (*AB*, *J* = 8.8, 2 H); 6.38 (*s*, 1 H); 6.09 (*d*, *J* = 2.9, 1 H); 5.71 (*d*, *J* = 2.9, 1 H); 5.93 (*s*, 2 H); 7.34 (br. *s*, 1 H); 4.05 (*s*, 3 H); 3.98 (*s*, 3 H); 3.87 (*s*, 3 H); 3.82–2.28 (*m*, 4 H). MS: 553 ($[M+H]^+$). Anal. calc. for $C_{28}H_{25}ClN_2O_8$: C 60.82, H 4.55, N 5.06; found: C 60.48, H 4.46, N 5.10.

N-*(4-Chlorophenyl)-1-(1,3-dihydro-4,5-dimethoxy-3-oxoisobenzofuran-1-yl)-1,2,3,4-tetrahydro-8-methoxy-6,7-(methylenedioxy)isoquinoline-2-carboxamide* (**6a**). Yield 85%. M.p. 173–174°. $[\alpha]_D^{20} = +233$ (*c* = 20 mg, $CHCl_3$). IR: 3395 (br.), 2941*m*, 1753*s*, 1658*s*, 1593*m*, 1494*s*, 1263*s*, 1012*m*, 829*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.34 (br. *s*, 1 H); 7.23 (*d*, *J* = 8.4, 2 H); 7.14 (*d*, *J* = 8.4, 2 H); 6.95 (*d*, *J* = 8.4, 1 H); 6.41 (*d*, *J* = 8.4, 1 H); 6.28 (*s*, 1 H); 6.10 (*d*, *J* = 2.8, 1 H); 5.84 (*s*, 2 H); 5.61 (*d*, *J* = 2.8, 1 H); 3.96 (*s*, 3 H); 3.89 (*s*, 3 H); 3.77 (*s*, 3 H); 3.79–2.10 (*m*, 4 H). MS: 553 ($[M+H]^+$). Anal. calc. for $C_{28}H_{25}ClN_2O_8$: C 60.82, H 4.55, N 5.06; found: C 60.75, H 4.61, N 5.05.

N-*(2,4-Dichlorophenyl)-1-(1,3-dihydro-4,5-dimethoxy-3-oxoisobenzofuran-1-yl)-1,2,3,4-tetrahydro-8-methoxy-6,7-(methylenedioxy)isoquinoline-2-carboxamide* (**7a**). Yield 73%. M.p. 93–94°. $[\alpha]_D^{20} = +128$ (*c* = 20 mg, $CHCl_3$) IR: 3379*s*, 2941*m*, 1765*s*, 1676*s*, 1579*m*, 1498*s*, 1263*s*, 1028*s*, 750*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.04 (*d*, *J* = 8.4, 1 H); 7.52 (br. *s*, 1 H); 7.38 (*d*, *J* = 4.2, 1 H); 7.19 (*d*, *J* = 4.2, 1 H); 7.09 (*d*, *J* = 8.4, 1 H); 6.72 (*d*, *J* = 8.4, 1 H); 6.38 (*s*, 1 H); 6.05 (*d*, *J* = 4.2, 1 H); 5.91 (*s*, 2 H); 5.86 (*d*, *J* = 4.2, 1 H); 4.04 (*s*, 3 H); 3.88 (*s*, 2 × 3 H); 3.72–2.72 (*m*, 4 H). MS: 588 ($[M+H]^+$). Anal. calc. for $C_{28}H_{24}Cl_2N_2O_8$: C 57.25, H 4.11, N 4.76; found: C 56.92, H 4.12, N 4.73.

N-*(2,4-Difluorophenyl)-1-(1,3-dihydro-4,5-dimethoxy-3-oxobenzofuran-1-yl)-1,2,3,4-tetrahydro-8-methoxy-6,7-(methylenedioxy)-isoquinoline-2-carboxamide* (**8a**). Yield 83%. M.p. 170–171°. $[\alpha]_D^{20} = +163$ (*c* = 20 mg, $CHCl_3$) IR: 3357 (br.), 2941*m*, 1759*s*, 1662*s*, 1612*m*, 1498*s*, 1259*s*, 1020*m*, 846*w*, 752*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.85 (*q*, *J* = 9.1, 1 H); 7.17 (br. *s*, 1 H); 7.07 (*d*, *J* = 9.1, 1 H); 6.87 (*q*, *J* = 9.1, 2 H); 6.63 (*d*, *J* = 9.1, 1 H); 6.38 (*s*, 1 H); 6.07 (*d*, *J* = 4.5, 1 H); 5.92 (*s*, 2 H); 5.81 (*d*, *J* = 4.5, 1 H); 4.05 (*s*, 3 H); 3.91 (*s*, 3 H); 3.87 (*s*, 3 H); 3.77–2.52 (*m*, 4 H). MS: 555 ($[M+H]^+$). Anal. calc. for $C_{28}H_{24}F_2N_2O_8$: C 60.65, H 4.36, N 5.05; found: C 60.83, H 4.31, N 5.12.

1-(1,3-Dihydro-4,5-dimethoxy-3-oxoisobenzofuran-1-yl)-1,2,3,4-tetrahydro-8-methoxy-6,7-(methylenedioxy)-N-*phenylisoquinoline-2-carbothioamide* (**9a**). Yield 86%. M.p. 181–182°. $[\alpha]_D^{20} = +203$ (*c* = 20 mg, $CHCl_3$) IR: 3336 (br.), 2952*m*, 1747*s*, 1596*m*, 1498*s*, 1261*s*, 1045*m*, 763*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.94 (br. *s*, 1 H); 7.42–7.34 (*m*, 4 H); 7.13 (*d*, *J* = 9, 1 H); 6.97 (*s*, 1 H); 6.49 (*s*, 1 H); 6.40 (*s*, 1 H); 6.28 (*d*, *J* = 4.5, 1 H); 5.90 (*s*, 2 H); 4.24 (*s*, 1 H); 4.05 (*s*, 3 H); 3.89 (*s*, 3 H); 3.80 (*s*, 3 H); 2.96–2.91 (*m*, 4 H). MS: 535 ($[M+H]^+$). Anal. calc. for $C_{28}H_{26}N_2O_7S$: C 62.91, H 4.90, N 5.24; found: C 62.74, H 4.88, N 5.20.

N-*(Chlorophenyl)-1-(1,3-dihydro-4,5-dimethoxy-3-oxobenzofuran-1-yl)-1,2,3,4-tetrahydro-8-methoxy-6,7-(methylenedioxy)isoquinoline-2-carbothioamide* (**10a**). Yield 85%. M.p. 181–182°. $[\alpha]_D^{20} = +158$ (*c* = 20 mg, $CHCl_3$) IR: 3327 (br.), 2925*m*, 1745*s*, 1589*m*, 1500*s*, 1263*s*, 1045*m*, 804*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.08 (*d*, *J* = 9.2, 1 H); 8.01 (br. *s*, 1 H); 7.47–7.16 (*m*, 2 H); 7.13 (*d*, *J* = 9.2, 1 H); 6.86 (*s*, 1 H); 6.40 (*s*, 2 H); 6.27 (*d*, *J* = 4.6, 1 H); 5.92 (*s*, 2 H); 4.30 (*s*, 1 H); 4.06 (*s*, 3 H); 3.89 (*s*, 3 H); 3.87 (*s*, 3 H); 2.89–2.17 (*m*, 4 H). MS: 569 ($[M+H]^+$). Anal. calc. for $C_{28}H_{25}ClN_2O_7S$: C 59.10, H 4.42, N 4.92; found: C 59.05, H 4.40, N 4.88.

1-(1,3-Dihydro-4,5-dimethoxy-3-oxoisobenzofuran-1-yl)-1,2,3,4-tetrahydro-8-methoxy-N-*(2-methoxyphenyl)-6,7-(methylenedioxy)isoquinoline-2-carbothioamide* (**11a**). Yield 78%. M.p. 108–109°. $[\alpha]_D^{20} = +207$ (*c* = 20 mg, $CHCl_3$) IR: 3386 (br.), 2939*m*, 1762*s*, 1600*m*, 1498*s*, 1263*s*, 750*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.11 (*d*, *J* = 8.5, 1 H); 8.05 (br. *s*, 1 H); 7.17 (*d*, *J* = 8.5, 1 H); 7.11 (*d*, *J* = 8.5, 1 H); 6.99 (*d*, *J* = 8.5, 1 H); 6.93 (*d*, *J* = 8.5, 1 H); 6.72 (*s*, 1 H); 6.40 (*s*, 1 H); 6.28 (*d*, *J* = 4.3, 1 H); 5.87 (*s*, 2 H); 4.03 (*s*, 3 H); 3.93 (*s*, 3 H); 3.89 (*s*, 3 H); 3.68 (*s*, 3 H); 3.20–2.17 (*m*, 4 H). MS: 565 ($[M+H]^+$). Anal. calc. for $C_{29}H_{29}N_2O_8S$: C 61.58, H 5.16, N 4.95; found: C 61.46, H 5.14, N 4.92.

1-(1,3-Dihydro-4,5-dimethoxy-3-oxoisobenzofuran-1-yl)-1,2,3,4-tetrahydro-8-methoxy-6,7-(methylenedioxy)-N-*(4-methylphenyl)isoquinoline-2-carbothioamide* (**12a**). Yield 82%. M.p. 206–207°. $[\alpha]_D^{20} = +224$ ($c =$ 20 mg, $CHCl_3$) IR: 3371 (br.), 2935*m*, 1759*s*, 1624*m*, 1498*s*, 1261*s*, 1033*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.82 (br. *s*, 1 H); 7.17 (*d*, $J = 8.4$, 2 H); 7.14 (*d*, $J = 8.4$, 2 H); 7.03 (*s*, 1 H); 6.53 (*s*, 1 H); 6.40 (*s*, 1 H); 6.28 (*d*, $J = 4.2$, 1 H); 5.89 (*s*, 2 H); 4.15 (*s*, 1 H); 4.05 (*s*, 3 H); 3.88 (*s*, 3 H); 3.77 (*s*, 3 H); 2.35 (*s*, 3 H); 4.13–2.84 (*m*, 4 H). MS: 550 ($[M+H]^+$). Anal. calc. for $C_{29}H_{29}N_2O_7S$: C 63.37, H 5.31, N 5.09; found: C 63.42, H 5.29, N 5.14.

1-(1,3-Dihydro-4,5-dimethoxy-3-oxoisobenzofuran-1-yl)-1,2,3,4-tetrahydro-8-methoxy-6,7-(methylenedioxy)-N-*(naphthalen-1-yl)isoquinoline-2-carbothioamide* (**13a**). Yield 78%. M.p. 104–105°. $[\alpha]_D^{20} = +272$ ($c =$ 20 mg, $CHCl_3$) IR: 3197 (br.), 2929*m*, 2100*s*, 1762*s*, 1590*w*, 1498*s*, 1261*s*, 1024*s*, 798*s*, 773*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.12 (*d*, $J = 8.8$, 1 H); 8.07 (*d*, $J = 8.8$, 1 H); 7.88 (*d*, $J = 8.8$, 1 H); 7.65–7.50 (*m*, 3 H); 7.39 (br. *s*, 1 H); 7.14 (*d*, $J = 8.8$, 1 H); 7.05 (*s*, 1 H); 6.62 (*s*, 1 H); 6.43 (*s*, 1 H); 6.33 (*d*, $J = 4.4$, 1 H); 5.95 (*s*, 2 H); 4.30 (*s*, 1 H); 4.07 (*s*, 3 H); 3.89 (*s*, 3 H); 3.78 (*s*, 3 H); 3.99–2.88 (*m*, 4 H). MS: 585 ($[M+H]^+$). Anal. calc. for $C_{32}H_{28}N_2O_7S$: C 65.74, H 4.82, N 4.79; found: C 65.69, H 4.85, N 4.81.

5-Bromo-N-*(3-chlorophenyl)-1-(1,3-dihydro-4,5-dimethoxy-3-oxoisobenzofuran-1-yl)-1,2,3,4-tetrahydro-8-methoxy-6,7-(methylenedioxy)isoquinoline-2-carboxamide* (**5b**). Yield 85%. M.p. 207–208°. $[\alpha]_D^{20} = +112$ ($c =$ 20 mg, $CHCl_3$) IR: 3380 (br.), 2947*m*, 1757*s*, 1655*m*, 1591*m*, 1498*s*, 1267*s*, 1037*m*, 939*w*, 773*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.41 (br. *s*, 1 H); 7.29–7.14 (*m*, 3 H); 7.00 (*d*, $J = 7.6$, 1 H); 6.94 (*m*, 1 H); 6.45 (*d*, $J = 7.6$, 1 H); 6.02 (*d*, $J = 3.8$, 1 H); 5.98 (*s*, 2 H); 5.63 (*d*, $J = 3.8$, 1 H); 4.00 (*s*, 3 H); 3.94 (*s*, 3 H); 3.81 (*s*, 3 H); 3.84–2.15 (*m*, 4 H). MS: 631 ($[M+H]^+$). Anal. calc. for $C_{28}H_{24}BrClN_2O_8$: C 53.22, H 3.82, N 4.43; found: C 53.13, H 3.78, N 4.39.

N-*(3-Chlorophenyl)-1-(1,3-dihydro-4,5-dimethoxyisobenzofuran-1-yl)-1,2,3,4-tetrahydro-8-methoxy-6,7-(methylenedioxy)isoquinoline-2-carboxomide* (**15a**). A soln. of **3a** (1 g, 2.5 mmol) in 12 ml of $BF_3 \cdot Et_2O$ was added dropwise to a mixture of $NaBH_4$ (0.2 g, 5 mmol) in dry THF (18 ml) at 0°. The mixture was stirred at 0° for 1 h and then refluxed for another 2 h. The reaction was quenched with cold H_2O, extracted with $CHCl_3$, and dried (Na_2SO_4). Evaporation of the solvent afforded a crude residue, which was further purified by CC (silica gel; AcOEt/hexane 4:1) to give a thick yellow oil **14a** (0.5 g). Subsequently, a soln. of 3-chlorophenyl isocyanate (0.2 g, 1.3 mmol) in dry MeCN (5 ml) was added dropwise to the soln. of the above oil **14a** (0.5 g, 1.3 mmol) in dry MeCN (15 ml) at 5°. The mixture was stirred for 2 h at 25°. The reaction was quenched with cold H_2O and extracted with $CHCl_3$. The solvent was dried *in vacuo*, and the residue was purified by CC (silica gel *60 H*; AcOEt/hexane 1:4). The product was collected to yield **15a** (0.52 g, 55%). M.p. 83–84°. $[\alpha]_D^{20} = +192°$ ($c =$ 20 mg, $CHCl_3$) IR: 3313 (br.), 2941*m*, 1654*m*, 1591*m*, 1481*s*, 1271*s*, 1080*m*, 1028*w*, 780*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.78 (*s*, 1 H); 7.46 (br. *s*, 1 H); 7.17 (*m*, 2 H); 6.93 (*d*, $J = 7.4$, 1 H); 6.63 (*d*, $J = 7.4$, 1 H); 6.35 (*s*, 1 H); 5.97–5.93 (*m*, 4 H); 5.46 (*d*, $J = 3.6$, 1 H); 5.31 (*d*, $J = 8.0$, 1 H); 5.22 (*d*, $J = 8$, 1 H); 4.10 (*s*, 3 H); 3.82 (*s*, $2 \times$ 3 H); 3.97–2.58 (*m*, 4 H). MS: 539 ($[M+H]^+$). Anal. calc. for $C_{28}H_{27}ClN_2O_7$: C 62.39, H 5.04, N 5.19; found: C 62.36, H 5.01, N 5.14.

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