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Arylmethoxypyridines as novel, potent and orally active mGlu5 receptor antagonists

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Abstract—Optimisation of affinity, chemical stability, metabolic stability and solubility led from a chemically labile HTS hit **1** to mGlu5 receptor antagonists (**24**–**26**) with high affinity for the allosteric MPEP binding site, improved microsomal metabolic stability and anxiolytic-like activity in vivo as assessed by the Vogel conflict drinking test.

L-Glutamate, the major excitatory neurotransmitter in the CNS, exerts its effects by stimulation of two major types of glutamate receptors, the ionotropic glutamate receptors (iGluRs) and the metabotropic glutamate receptors (mGlu receptors).[1] Whereas the functional role of the iGluRs has been thoroughly investigated, the mGlu receptors have attracted increasing interest only in recent years. mGlu receptors are class C GPCRs, characterised by a large N-terminus incorporating the ligand binding domain and are divided into eight subtypes, mGlu1- mGlu8.[2] Among the mGlu receptors, the mGlu5 receptor is expressed in the limbic areas of the brain, which suggests a potential role of this receptor in psychiatric disorders, such as anxiety.[3] Indeed, the selective mGlu5 receptor antagonists MPEP and MTEP have been shown to be active in a broad range of preclinical anxiety tests.[4] Recently, the clinically validated anxiolytic Fenobam was found to be a selective, high-affinity mGlu5 receptor ligand. MPEP, MTEP and Fenobam bind to a unique allosteric site in the transmembrane region of mGlu5 receptors, which allows for a high selectivity of these compounds especially over other glutamate receptors.[5] The limitations of current anxiety treatments, such as side effects (benzodiazepines) or slow onset of action (SSRIs), have provided the impetus for the discovery of novel, and potentially superior, anxiolytics.[6] In this regard, the mGlu5 receptor appears attractive as an anxiety target, because it offers good chemical tractability, the potential for high selectivity via a unique allosteric site and a validated proof of concept.[7] Additionally, mGlu5 receptor antagonism has been proposed as a potential target for the treatment of pain, obesity, Parkinson's disease and drug abuse.[8] Consequently, the mGlu5 receptor has attracted much attention, and several analogues of MPEP/MTEP have been published as mGlu5 receptor antagonists.[9] We report here our investigation of a novel series of non-MPEP-like mGlu5 receptor antagonists.

We identified the phthalimide of a benzyloxyphenylamine **1** from the Roche compound collection in a high-throughput screen, which was based on the displacement of [^{3}H]MPEP from recombinantly expressed mGlu5 receptors. Some first exploratory chemistry around **1** revealed that the methyl substituent R (Fig. 1) is essential, and analogues without a substituent in this position, such as **2**, have a greatly decreased affinity. An improvement of in vitro affinity (for measurement details, see 10) was achieved by introduction of a chloro or cyano substituent into the *meta*-position of the benzylic ring (Table 1) leading to compounds **3** and **4**, whereas substituents in the *para* position were not tolerated. However, a main disadvantage of compounds **1**–**8** (Table 1) is their susceptibility towards hydrolysis of the phthalimide motif over a wide pH range.

Keywords: mGluR5; Metabotropic glutamate receptor; Anxiolytic; Anxiolysis.
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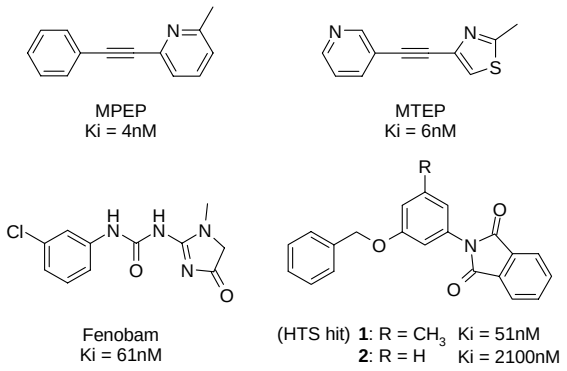
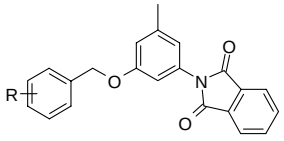


Figure 1. K_i values (hmGlu5 receptor, as determined in-house, see Ref. 10) for the prototypical non-competitive mGluR5 antagonist MPEP, its analogue MTEP, the anxiolytic Fenobam, our HTS hit **1** and its des-Me analogue **2**.

Table 1. Exploration of substituents R



	R=	K_i (nM)
3	*m*-Cl	4.7
4	*m*-C≡N	6.0
5	*p*-Cl	3900
6	*p*-CH_3	>10,000
7	*p*-MeO	1500
8	*p*-F	900

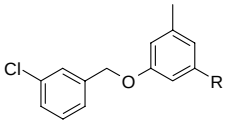
Compounds **3** and **4** have a 10-fold improved affinity as compared to **1**.

Therefore, numerous replacements of the phthalimide moiety were examined, out of which **9**–**14** (Table 2) emerged as being best in terms of mGluR5 affinity. These compounds however had unfavourable molecular properties, such as high lipophilicity, low stability in rat liver microsome preparations[11] and low solubility ($\log D > 3.0$, $CL_{int} > 100$ µl/min/µg protein, LYSA[12] < 1 µg/ml).

It was anticipated that compounds with decreased lipophilicity might have improved microsomal stability and improved solubility. Following this hypothesis, the central aromatic motif was replaced by all possible pyridines. Pyrrole as an isostere for phthalimide was selected as model system for these optimisation studies due to its straightforward synthetic accessibility.

The introduction of nitrogen into the Y (**16**) and Z (**17**) positions was not tolerated (Table 3). However, a nitrogen in the X position (**15**) did not only decrease the calculated lipophilicity ($c\log P = 6.2$ [**15**] vs 7.1 [**9**]), but gave a further improvement in affinity. The introduction of the nitrogen in the X position had changed the requirements for the R substituent (**18**–**23**, Table 4). Among the best substituents in this position were now a trifluoroacetamide **18** (Table 4), a 'reversed' amide **19** and especially a nitrile **20** with an outstanding affinity

Table 2. Exploration of substituents R to replace the chemically susceptible phthalimide motif (**1**–**8**)



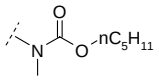
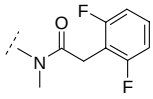
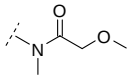
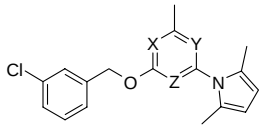
	R=	K_i (nM)
9		160
10		33
11		48
12		70
13		27
14		58

Table 3. Introduction of nitrogen into different positions of the central ring

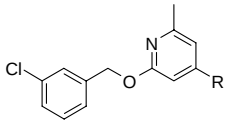


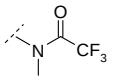
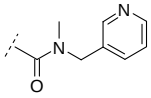
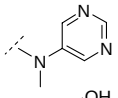
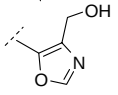
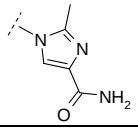
	X	Y	Z	K_i (nM)
9	CH	CH	CH	160
15	N	CH	CH	45
16	CH	N	CH	>3000
17	CH	CH	N	>3000

of 1 nM. At this point, some structural similarities between the arylmethoxypyridines and published MPEP analogues became apparent: in both series, an aryl ring is linked by a 2-carbon spacer to an α-pyridine. Furthermore, small, lipophilic *meta* substituents on the aryl ring increased the affinity in both series, although this effect is more pronounced for the arylmethoxypyridines.[13] On the other hand, the different geometry of the methoxy linker and the acetylene linker is expected to lead to different spatial orientations of the aryl and the pyridine moieties for the two series. The most obvious SAR differences between the two series include the pyridyl-nitrogen in the 2-position, which seems to be mandatory for activity in the MPEP series but not for the arylmethoxypyridines, and the substituent in the α′-position of this nitrogen, which is stringently required for high affinity in the arylmethoxypyridine-, but not in the MPEP, series.[14]

A single-dose pharmacokinetic study revealed that **20** achieved only low plasma levels after oral application,

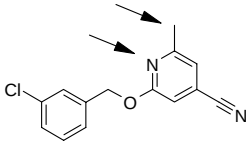
Table 4. Exploration of substituents R to further improve the mGluR5 affinity



	R=	K_i (nM)
18		18
19		27
20		1
21		11
22		28
23		44

due to its intermediate-to-high clearance and its high volume of distribution (Table 5). Furthermore, the low solubility of **20** might contribute to a poor absorption from the GI tract. An HPLC/MS analysis of the metabolites obtained from an incubation of **20** with rat liver microsomes suggested that the pyridine nitrogen and possibly the adjacent methyl group are the main sites of oxidative metabolism. Interestingly, and contrary to our expectations, the benzylether methylene seemed not to be significantly involved in microsomal metabolism. We anticipated that the replacement of the picoline-methyl with a chloro substituent might improve the metabolic stability by removing the methyl substituent as a metabolic weak site, and by reducing the electron density in the adjacent nitrogen. Indeed, **24** showed a reduced intrinsic clearance with rat microsomes. However, **24** still had a poor solubility which was considered detrimental to good oral bioavailability.

Table 5. Pharmacokinetic properties of **20**



20

CL (rat) = 43 ml/min/kg	F = 4.7%
V_{ss} = 14 l/kg	C_{max} (10 mg/kg po) = 86 ng/ml
$t_{1/2}$ (iv) = 5 h	Brain/plasma = 3.6

Arrows indicate the putative sites of oxidative metabolism as suggested by a microsomal metabolite analysis.

Similar to the considerations outlined earlier, we hoped to further reduce log$D$, and thereby increase solubility, by replacing the lipophilic chlorobenzyloxy motif by an appropriately substituted picolinyl motif. Additionally, the electron density of the pyridine nitrogen would be lowered further, rendering metabolism at this site more unlikely. This was realized with **25**, which retained most of the affinity of its predecessor **24**, and was soluble, albeit to a limited extent. A further improvement in solubility was made with **26**, in which the basicity of the peripheral pyridine moiety was increased by replacing the *meta*-chloro with a *meta*-methyl substituent. Compounds **20** and **25** behaved as functional antagonists in a FLIPR assay (IC_{50} = 9 nM; 72 nM, respectively). Compounds **20** and **24**–**26** were evaluated in the Vogel conflict test, in which drinking is suppressed in water-restricted rats by a brief electrical shock every second of cumulative drinking time.[15] Both **20** and **26**, after an oral dose of 10 mg/kg, significantly increased drinking time, consistent with an anxiolytic-like profile (Fig. 2). Compounds **24** and **25** showed similar effects after an oral dose of 15 and 10 mg/kg, respectively (data not shown). It is assumed that the somewhat reduced affinities of **24**–**26** are counterbalanced by improved PK parameters (in comparison with **20**).

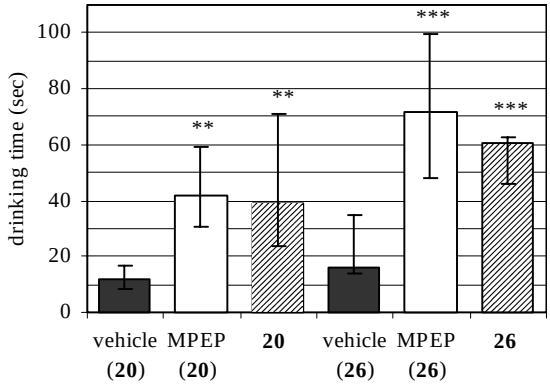
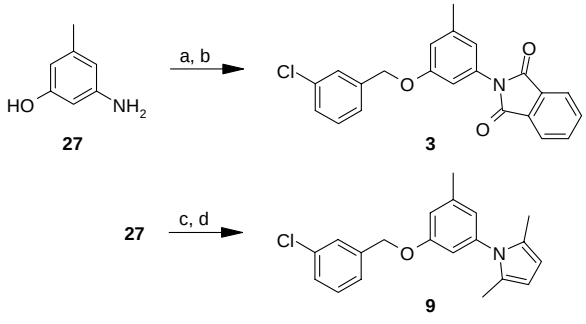
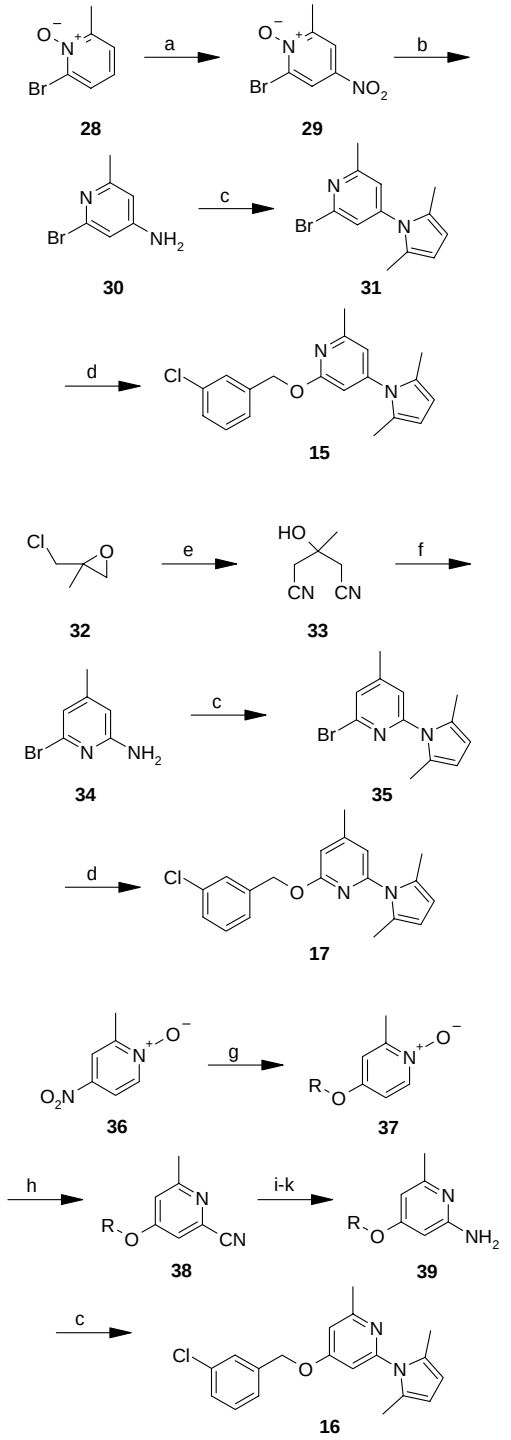


Figure 2. Drinking times (s) in the Vogel conflict test[15] (punished drinking) as a measure of anxiolytic-like response. The drinking times after an oral dose of 10 mg/kg of **20** and **26** are compared with vehicle and MPEP (10 mg/kg po) as positive control. Data are median and interquartile range; Statistics: $^{**}p < 0.01$; $^{***}p < 0.001$ vs vehicle (Mann–Whitney U test, one-tailed).



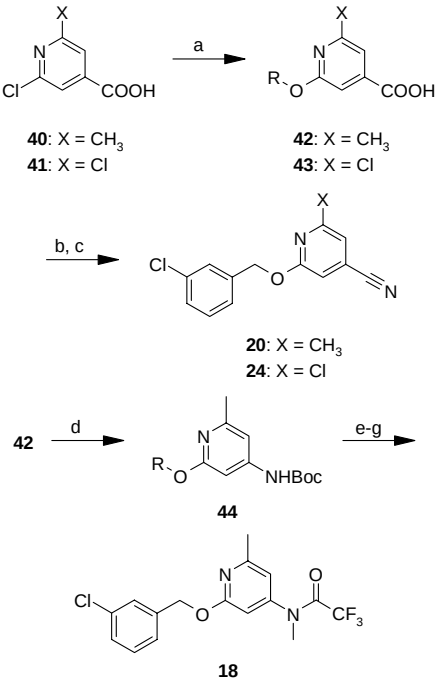
Scheme 1. Reagents and conditions: (a) phthalic anhydride, acetic acid, 1.5 h reflux; (b) 3-chlorobenzyl chloride, Cs_2CO_3, DMF, 1.5 h 100 °C; (c) NaH, DMF, 45 min rt, then 3-chlorobenzyl bromide, 12 h rt; (d) acetonylacetone, pTsOH · H_2O, toluene, 1.5 h reflux (water trap).

Compounds **3**–**14** (Tables 1 and 2) were prepared from 3-amino-5-methyl-phenol (**27**).[16] For instance, **3** was prepared by phthalimide formation and subsequent benzylation, whereas **9** was prepared by benzylation in a first step, followed by a Paal–Knorr reaction (Scheme 1). Pyrroles **15**–**17** (Table 3) were obtained by the synthetic sequences outlined in Scheme 2: a 4-pyrrole substituent was introduced onto 2-bromo-5-methylpyridinium-*N*-oxide (**28**)[17] by a nitration/reduction sequence (**29**, **30**) followed by a Paal–Knorr reaction to give **31**. The isomeric building block **35** was available from epoxide **32** via **33** and **34**. Both building blocks **31** and **35** were reacted with 3-chlorobenzyl alcohol to afford **15** and **17**, respectively. Compound **16** was obtained by first introducing the benzyloxy substituent into a picoline *N*-oxide **36** to give **37**, and subsequent introduction of the pyrrol motif via **38** and **39**.



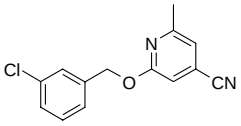
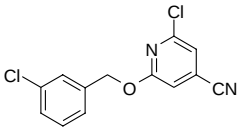
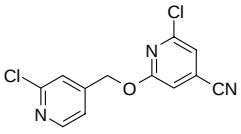
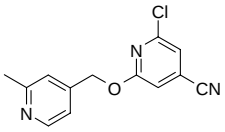
Scheme 2. Reagents and conditions: (a) H_2SO_4, HNO_3, 90 min 90 °C; (b) Fe, CH_3COOH, 1 h rt; (c) acetonylacetone, *p*TsOH · H_2O, toluene, 9 h reflux (water trap) (9 h for **31** and **39**, 1.5 h for **34**); (d) 3-chlorobenzyl alcohol, NaH, THF, 30 min rt, then **31**/**35**, 12 h reflux; (e) KCN, H_2O, 10 °C, then 12 h rt; (f) HBr, acetic acid, 2 h rt; (g) 3-chlorobenzyl alcohol, NaH, DMF, 30 min 60 °C, then **36** as a hot solution in DMF, 2 h 60 °C; (h) dimethylcarbamoylchloride, TmsCN, $CHCl_3$, 1 h reflux; (i) NaOH, dioxane, H_2O; (j) diphenylphosphoryl azide, *t*BuOH, NEt_3, 12 h reflux; (k) TFA, CH_2Cl_2, 4 days rt; acetonylacetone, *p*TsOH · H_2O, toluene, 24 h reflux (water trap).

Nitriles **20** and **24** (Table 4) were synthesized from isonicotinic acid derivatives **40** and **41**, by first introducing the benzyloxy motif (**42**, **43**) followed by transformation of the carboxyl function into a nitrile (Scheme 3).[18] Nitriles **25** and **26** were prepared similarly from (2-chloro-pyridin-4-yl)-methanol and (2-methyl-pyridin-4-yl)-methanol, respectively. The carboxylic acid **42** can also be degraded by a Curtius rearrangement into the corresponding Boc-protected amine **44**. This latter sequence was found to be complementary to the one outlined in Scheme 2 for the synthesis of compounds with N substituents in the γ-position of the pyridine ring. The Boc-protected amine **44** proved to be a versatile building block for the synthesis of many similar compounds, for example, **18** (Table 4).



Scheme 3. (R = 3-chlorobenzyl). Reagents and conditions: (a) 3-chlorobenzyl alcohol, NaH, toluene, 30 min rt, then **40** (**41**), 18-crown-6, 6h reflux (**41**: 12 h 55 °C); (b) 1,1′-carbonyldiimidazole, DMF, 30 min 60 °C (**43**: 60 min 45 °C), then NH_4OH, 5 h rt; (c) TFAA, NEt_3, THF, 1 h rt; (d) diphenylphosphoryl azide, *t*BuOH, NEt_3, 12 h reflux; (e) NaH, CH_3I, DMF, 1.5 h rt; (f) TFA, CH_2Cl_2, 12 h rt; (g) TFAA, NEt_3, THF, 1 h rt.

Table 6. Compound **20** and its analogues **24–26** with improved molecular properties

20		K_i = 1 nM CL_{int}[a] = 218 μl/min/μg Solubility[b] < 1.0 μg/ml log$D_{7.4}$ > 3.0 *c*log*P* = 3.6
24		K_i = 5 nM CL_{int}[a] = 47μl/min/μg Solubility[b] < 1.0 μg/ml log$D_{7.4}$ > 3.0 *c*log*P* = 3.8
25		K_i = 17 nM CL_{int}[a] = 20μl/min/μg Solubility[b] = 3.0 μg/ml log$D_{7.4}$ > 3.0 *c*log*P* = 2.4
26		K_i = 10 nM CL_{int}[a] = 37μl/min/μg Solubility[b] = 14 μg/ml log$D_{7.4}$ > 2.8 *c*log*P* = 2.1

[a] From incubations with rat liver microsomes. μg = μg of protein.
[b] LYSA, for measurement details, see Ref. 11.

In conclusion, **20** and **24–26** (Table 6) represent the best compounds that were obtained during a medicinal chemistry programme aiming for structurally novel mGluR5 antagonists. Among these compounds, **20** has the highest mGluR5 affinity. Compound **20** has been characterised in an in vitro metabolite identification study and in an in vivo PK study. Compounds **20** and **24–26** showed anxiolytic-like effects in an animal model after oral administration.

Acknowledgments

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18. Preparation of 2-(3-Chloro-benzyloxy)-6-methyl-isonicotinonitrile (**20**): (a) 2-(3-Chloro-benzyloxy)-6-methyl-isonicotinic acid (**42**): NaH (60% in mineral oil, 5.42 g,

226 mmol) was added in small portions to a mechanically stirred suspension of 3-chlorobenzyl alcohol (9.97 g, 70 mmol) and 2-chloro-6-methylisonicotinic acid (**40**, 10 g, 58 mmol) in toluene (110 ml). After addition of 18-crown-6 (1.3 g), the viscuous mixture was heated to 125 °C (4 h). HCl (1 N, 70 ml), then heptane (250 ml) was added to the cooled reaction mixture (ice bath), and the mixture was stirred for 1 h (rt). The precipitate (12.14 g, 75%) was filtered and dried at 50 °C. ^{1}H NMR (DMSO-d^6): δ 2.46 (3H, s), 5.37 (2H, s), 7.07 (1H, s), 7.30 (1H, s), 7.39–7.44 (4H, m), 7.54 (1H, s), 13.56 (1H, br s); (b) 2-(3-Chloro-benzyloxy)-6-methyl-isonicotinamide: 1,1-Carbonyldiimidazole (2.1 g, 13 mmol) was added to a solution of 2-(3-chloro-benzyloxy)-6-methyl-isonicotinic acid (**42**, 3 g, 10.8 mmol) in DMF (50 ml), and the mixture was heated (60 °C) for 30 min. Upon cooling to rt, ammonia (25%, 30 ml) was added, and the mixture was stirred until the reaction was complete, as indicated by TLC (ca. 2 h). After workup (EtOAc/H_2O), drying (Na_2SO_4), and evaporation of the solvent, the title compound (2.2 g, 73%) was obtained by recrystallisation from isopropyl ether/EtOAc. ^{1}H NMR (DMSO-d^6): δ 2.44 (3H, s), 5.37 (2H, s), 7.07 (1H, s), 7.25 (1H, s), 7.38–7.43 (4H, m), 7.59 (1H, s), 7.59 (1H, br s), 8.07 (1H, br s); (c) 2-(3-Chloro-benzyloxy)-6-methyl-isonicotinonitrile (**20**): Trifluoroacetic anhydride (900 mg, 43 mmol) is added to a cooled (5 °C) mixture of 2-(3-chloro-benzyloxy)-6-methyl-isonicotinamide (1 g, 3.61 mmol), CH_2Cl_2 (40 ml) and triethylamine (730 mg, 7.21 mmol). The reaction mixture was kept at rt (2 h) before it was worked up (extraction EtOAc/brine), dried (Na_2SO_4) and evaporated. The title compound (510 mg, 55%) was isolated from the residue by column chromatography (silica gel, EtOAc/heptane = 2:3). ^{1}H NMR (DMSO-d^6): δ 2.46 (3H, s), 5.37 (2H, s), 7.25 (1H, s), 7.31 (1H, s), 7.39–7.43 (4H, m), 7.54 (1H, s). MS: m/e = 259.1 [M + H^+]. Compounds **24**–**26** are prepared similarly.