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Synthesis and binding affinity of potential atypical antipsychotics with the tetrahydroquinazolinone motif ☆

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ABSTRACT

A series of 8 new tetrahydroquinazolinone derivatives was synthesized and evaluated for binding affinity to D_2 and 5-HT_{2A} human receptors; in addition, some properties related to blood–brain barrier penetration were calculated. From the results of these assays, three compounds were selected for further binding tests on D_1, D_3, and 5-HT_{2C} human receptors, which are thought to be involved in schizophrenia. From these data, compound **19b** emerged as the most promising candidate based on its good binding affinities for D_1, D_2, and D_3 receptors, high affinity for 5-HT_{2A}, low affinity for 5-HT_{2C} receptors, and a Meltzer's ratio characteristic of an atypical antipsychotic profile.

Schizophrenia is a complex psychiatric disorder that affects approximately 1% of the population.[1] The use of classical (typical) neuroleptics (e.g., haloperidol, Fig. 1) for the treatment of this disease is associated with severe mechanism-related side effects, including induction of acute extrapyramidal symptoms (EPS).[2] Furthermore, these drugs are ineffective against the negative symptoms of schizophrenia. The clinical efficacy of classical antipsychotics in the treatment of schizophrenia and other psychotic disorders is directly related to their ability to block dopamine D_2 receptors in the brain.[3] However, it has been reported that the blockage of the dopamine receptor in the striatum is closely associated with EPS.[4]

The introduction of clozapine (Fig. 1) for treatment-resistant schizophrenia gave rise to a new group of atypical or nonclassical antipsychotics that have no EPS at the doses frequently used in therapy and display moderate efficacy towards negative symptoms.[5] Clozapine exhibits potent affinities for multiple receptors.[6] Its action at serotonin (5-HT) receptors is thought to mediate its beneficial effects on cognition, negative symptoms, and the low incidence of EPS,[7] although it also displays affinity for dopamine receptors, related to its efficacy on positive symptoms, as well as for α-adrenergic, muscarinic, and histaminergic (H_1) receptors.

The interaction between the 5-HT and dopamine systems has been proposed to play a critical role in the mechanism of action of atypical antipsychotic drugs. This is thought to be the case because the only pharmacological feature which most atypical antipsychotic drugs have in common is a relatively potent blockage of 5-HT_{2A} receptors coupled with a weaker antagonism of the dopamine D_2 receptors.[8] This so-called 'serotonin–dopamine hypothesis' has become a useful model for developing new antipsychotics to achieve superior efficacy with a lower incidence of extrapyramidal side effects compared to first-generation (classical) antipsychotic drugs such as haloperidol and chlorpromazine.[9]

Although clozapine and other atypical antipsychotic drugs such as risperidone have brought improvements in treatment of negative symptoms with lower propensity to elicit EPS, treatment with these drugs can still lead to substantial weight gain, blood dyscrasias, and some movement disorders.[10] Additionally, negative symptoms and cognitive impairments are not fully addressed by these drugs. Hence, the discovery of a more effective, side-effect-free therapy for the treatment of schizophrenia remains a challenging research goal.

As part of our ongoing work on the development of strategies for the preparation of new D_2/5-HT_{2A} receptor antagonists as atypical antipsychotics,[11] we explored the possibility of synthesizing conformationally constrained analogues of aminobutyrophenones in which the phenyl ring was replaced by a pyrimidine to form a tetrahydroquinazolinone system (Fig. 2). The replacement was made based on the observation that the substitution of –CH= by

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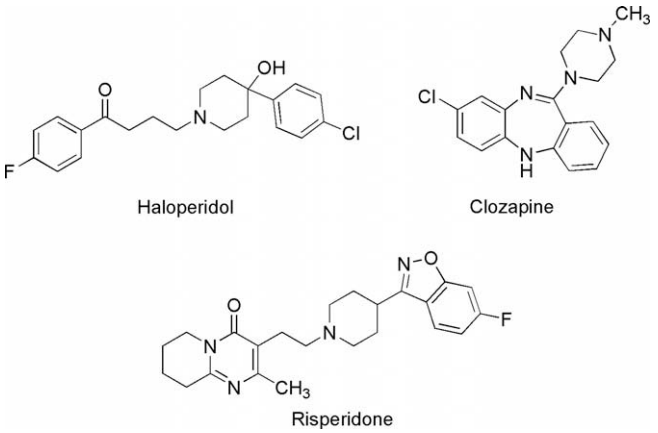


Figure 1. Structures of some antipsychotics.

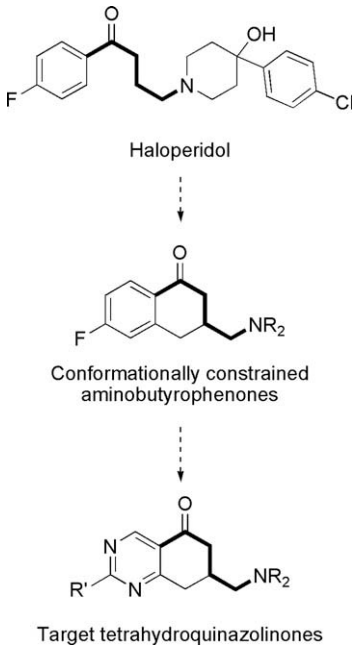


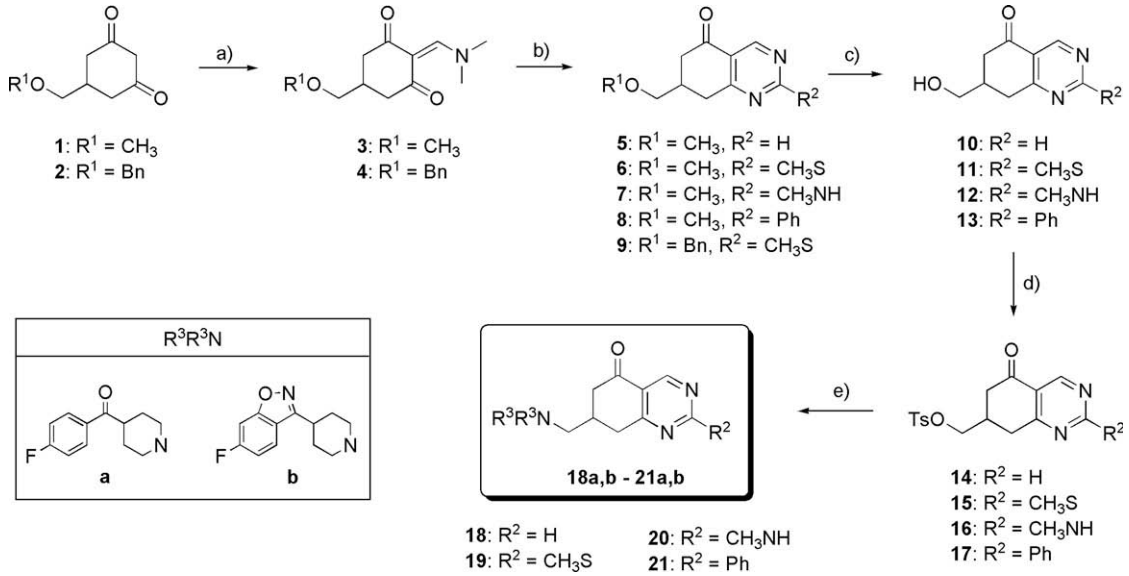
Figure 2.

–N═ in aromatic rings has been one of the most-successful applications of classical isosterism.[12] In the present Letter, we report the synthesis of this new series of tetrahydroquinazolinone derivatives as conformationally constrained aminobutyrophenones and the evaluation of their affinity towards several dopamine and serotonin receptors.

We initiated the synthesis of the tetrahydroquinazolinones **18–21** (Scheme 1) via the condensation of 5-(methoxymethyl)cyclohexane-1,3-dione **1**[13] or 5-(benzyloxymethyl)cyclohexane-1,3-dione **2**[14] with *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) to obtain aminoketones **3** and **4**, respectively, with a yield of 95%. Compound **3** was transformed into tetrahydroquinazolinones **5–8** at yields between 60% and 70% by employing a tandem Michael addition–elimination/cyclodehydration process using different amidine derivatives in AcOH or EtONa/EtOH at reflux. Alternatively, benzylketone **4** was condensed with *S*-methylthiourea in AcOH to obtain the methylthiotetrahydroquinazolinone **9** in 50% yield. The methyl ether group of each tetrahydroquinazolinone **5–8** was cleaved using a 1.0 M solution of BBr_3 in CH_2Cl_2 at −40 °C to rt, affording the corresponding alcohols **10–13** at acceptable yields. More forceful conditions (2 mol equiv BBr_3, higher temperatures, or longer reaction times) or the use of other reagents, such as iodotrimethylsilane, provided a mixture of decomposed products. Alternatively, hydroxymethylquinazolinone **11** could be accessed at 50% yield via the debenzylation of compound **9** using iodotrimethylsilane in CH_2Cl_2.

Tosylation of alcohols **10–13** under standard conditions furnished the corresponding sulfonates **14–17** in 62–88% yield. Finally, tosylates **14–17** were converted into the required amines **18a–b** to **21a–b** by nucleophilic displacement of the tosyl group with the corresponding substituted piperidines **a** or **b** (Scheme 1) at low to moderate yields.[15]

The affinities of the compounds **18a,b–21a,b** for cloned human D_2 and 5-HT_{2A} receptors (Table 1) were evaluated in in vitro binding assays using the radioligands [^{3}H]spiperone and [^{3}H]ketanserin, respectively, according to our previously described procedures.[16] K_i values (expressed as pK_i) were calculated according to the Cheng–Prusoff equation.[17] In addition, *c*Log *P* values and



Scheme 1. Reagents and conditions: (a) DMFDMA, THF, 80 °C, 3 h, 95%; (b) $R^2C(NH)NH_2$, AcOH or EtONa/EtOH, reflux, 50–70%; (c) for **5–8**: 1 M BBr_3, CH_2Cl_2, −40 °C to rt, 24 h, 45–97%; for **9**: TMSI, CH_2Cl_2, rt, 15 h, 50%; (d) TsCl, Py, rt, 24 h, 62–88%; (e) HNR^3R^3, dioxane or benzene, reflux, 10–60%.

Table 1
Results for the calculated properties of compounds **18a**,**b**–**21a**,**b** and binding assays (pK_i) with D_2 and 5-HT_{2A} receptors in CHO cells[a]

Compound	Code	R^2	*c*Log *P*[b]	PSA[c] (Å^2)	pK_i D_2	pK_i 5-HT_{2A}	pK_i ratio 5-HT_{2A}/D_2
18a	QF3504B	H	1.1	63.16	6.20 ± 0.50	6.51 ± 0.32	1.05
18b	QF3508B	H	1.4	72.12	6.80 ± 0.60	7.63 ± 0.13	1.12
19a	QF3514B	CH_3S	2.8	63.16	NA	6.99 ± 0.44	–
19b	QF3518B	CH_3S	3.1	72.12	7.49 ± 0.09	8.34 ± 0.15	1.11
20a	QF3524B	CH_3NH	2.4	75.19	6.63 ± 0.08	8.19 ± 0.12	1.23
20b	QF3528B	CH_3NH	2.7	84.15	7.31 ± 0.20	8.62 ± 0.10	1.18
21a	QF3564B	Ph	3.2	63.16	NA	6.20 ± 0.20	–
21b	QF3568B	Ph	3.5	72.12	7.47 ± 0.18	6.90 ± 0.30	0.92
Haloperidol			3.8	40.54	9.22 ± 0.12	6.78 ± 0.25	0.73
Clozapine			4.1	35.16	6.65 ± 0.17	8.04 ± 0.31	1.21
Risperidone			2.7	64.17	8.21[d]	9.30 ± 0.25	1.13

[a] Values are means of two separate experiments. NA = not active (less than 60% inhibition in radioligand binding at 10 μM).
[b] Partition coefficients (*c*Log *P*) were calculated using ChemDraw Ultra, version 11.0.1, CambridgeSoft 2007.
[c] Polar surface area (PSA) was calculated using an algorithm developed by Ertl et al.[19]
[d] Value taken from Ref. 24.

polar surface areas (PSA) were calculated for the novel compounds described to provide a measure of lipophilicity and predicted brain penetration, respectively.[18,19]

With respect to the D_2 receptor, compounds bearing a 6-fluorobenzisoxazolylpiperidine moiety (amine ***b***) showed higher affinities than those with a 4-fluorobenzoylpiperidine fragment (amine ***a***), due to the presence of substituents (phenyl, methylthio, or methylamino) on the tetrahydroquinazolinone core favourable for affinity. Among 4-fluorobenzoylpiperidine derivatives, compounds **18a** and **20a** exhibited a modest affinity for the dopamine D_2 receptors as compared to haloperidol or risperidone but were similar to that of clozapine, while compounds **19a** and **21a** did not display affinity towards D_2 receptors and therefore should not be considered as potential antipsychotics.

Regarding the 5-HT_{2A} receptor, the 6-fluorobenzisoxazolylpiperidine derivatives (**18b**, **19b**, **20b**, and **21b**) also showed higher affinities than compounds with a 4-fluorobenzoylpiperidine fragment (**18a**, **19a**, **20a**, and **21a**). The compounds with a phenyl substituent on the tetrahydroquinazolinone moiety (**21a** and **21b**) displayed lower affinities for the 5-HT_{2A} receptor than the corresponding compounds with methylthio, methylamino, or no substituents, suggesting a potential steric effect of the phenyl ring in the binding site. Compounds bearing a methylamino substituent (**20a** and **20b**) showed the highest affinities for 5-HT_{2A} receptors. This behaviour could be attributed to the presence of an NH group in **20** (lacking in compounds **18, 19**, and **21**), which could establish an additional interaction with an acceptor group in the 5-HT_{2A} receptor binding site.

In general, the new compounds displayed higher affinity for the serotonin 5-HT_{2A} receptor [pK_i values ranging between 6.20 (**21a**) and 8.62 (**20b**)] than for the dopamine D_2 receptors. For example, **20a** and **20b** were about 35-times and 20-times more potent against 5-HT_{2A} than D_2 receptors, respectively. On the basis of the 5-HT_{2A}/D_2 antagonism hypothesis, it is worth highlighting compounds **18b**, **19b**, **20a**, and **20b**, with Meltzer's ratios between 1.11 and 1.23, as potential atypical antipsychotics.[8]

For antipsychotics, as with the great majority of drugs aimed at CNS targets, the blood–brain barrier (BBB) must be crossed in order for a therapeutic effect to be exerted. To predict the BBB penetration of a compound, the most important molecular descriptors used are polar surface area (PSA) and lipophilicity [as determined by the calculated log of the octanol/water partition coefficient (*c*Log *P*)], although the number of hydrogen bond donors (HBDs) appears also to be a significant feature that distinguishes drugs marketed for CNS indications from those intended for peripheral targets.[20] Four simple physicochemical rules are accepted to enhance the probability of obtaining favourable BBB permeability properties:[21] (a) PSA <90 Å^2; (b) HBD <3; (c) *c*Log *P* 2–5; (d) molecular weight (M_W) <450 Da. For the abovementioned four compounds (**18b**, **19b**, **20a**, and **20b**), the *c*Log *P* values are less than 4 (from 1.4 to 3.1) and the PSA values are in the range of 60–85 (Table 1). These values predict drug-like properties[22] and the potential to penetrate the BBB.

In line with the multiple receptor-targeting approach for the development of new antipsychotic agents, tetrahydroquinazolinones **18b**, **19b**, and **20b** were selected among the new compounds because: (a) their K_i values <30 nM (or pK_i >7.50) against 5-HT_{2A} receptors are promising, (b) they exhibit a good 5-HT_{2A}/D_2 pK_i ratio (higher than 1.10), (c) they bear different substituents at position 2 of the tetrahydroquinazolinone system, and (d) in general, the compounds bearing an amine ***b*** display higher affinities for the 5-HT_{2A} and D_2 receptors than those with an amine ***a***. These chosen compounds were examined further for binding affinity toward D_1, D_3, and 5-HT_{2C} receptors by competition assays using [^{3}H]SCH23390, [^{3}H]spiperone, and [^{3}H]mesulergine, respectively (Table 2). D_1 receptor hypoactivity in the frontal cortical area has recently been suggested to contribute to negative symptoms and impaired cognitive function.[23] Thus, D_1 receptor-selective agonists may represent an exciting direction for the treatment of schizophrenia.[24] On the other hand, a preferential blockage of D_3 versus D_2 receptors has been associated with a relatively benign effect upon motor function, as compared with drugs possessing D_2/D_3 or principally D_2 antagonist properties.[25] Lastly, 5-HT_{2C} receptors have been suggested to be involved in the weight gain associated with the treatment of schizophrenia via atypical antipsychotic drugs.[26]

Compound **18b** displayed lower affinity than **19b** or **20b** for dopamine D_1, D_2, and D_3 receptors, as well as for serotonin 5-HT_{2A} receptors. Again, the presence of a methylthio or methylamino substituent on the pyrimidine ring favoured an interaction with the receptor binding sites. Compounds **19b** and **20b** showed similar affinities for the new receptors assayed, although the affin-

Table 2
Human receptor binding affinities (pK_i) of compounds **18b**, **19b**, and **20b**[a]

Compound	pK_i D_1	pK_i D_2	pK_i D_3	pK_i 5-HT_{2A}	pK_i 5-HT_{2C}
18b	6.87	6.80	6.55	7.50	6.30
19b	7.48	7.49	7.35	8.34	<5
20b	7.37	7.31	6.70	8.62	<5
Haloperidol	8.21	9.22	7.94	6.78	5.14
Clozapine	7.67	6.65	6.04	8.04	7.98
Risperidone	6.83[b]	8.21	7.79[b]	9.30	8.13

[a] Values are means of two or three separate competition experiments.
[b] Binding data obtained from Ref. 27.

ity of **19b** for the D_3 receptor was 4.5-times higher than that of **20b**. Taken together, the data point to **19b** as a better candidate for improving negative symptoms in schizophrenia.[25] The tetrahydroquinazolinone **19b** possessed comparable affinity for the three dopamine receptors tested, high affinity for 5-HT_{2A} receptors, and did not display affinity towards 5-HT_{2C} receptors, thereby showing the best overall receptor binding profile. Moreover, the low affinity of both **19b** and **20b** for the 5-HT_{2C} receptor (pK_i <5) compared to risperidone (pK_i = 8.13) and clozapine (pK_i = 7.98) could cause a possible decrease in the propensity of these compounds to elicit treatment-caused weight gain.

In summary, new conformationally constrained butyrophenone analogues with the tetrahydroquinazolinone motif have been synthesized, and their binding affinities determined. Among the compounds surveyed, **19b** was identified as the best candidate based on its good binding affinities for D_1, D_2, and D_3 receptors, high affinity for 5-HT_{2A}, and low affinity for 5-HT_{2C} receptors, as well as a Meltzer's ratio characteristic of an atypical antipsychotic profile. Moreover, *c*Log *P* and PSA suggest that this compound has the potential to penetrate the blood–brain barrier. Further studies on this series, including in vivo assays to determine antipsychotic activity, are in progress and will be reported in due course.

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15. *Data for selected compounds*: Compound **18a**: Mp 151–153 °C. IR (KBr): ν 1697, 1677, 1596, 1576. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.80–1.83 (m, 4H); 2.10–2.25 (m, 2H); 2.43–2.50 (m, 4H); 2.80–2.95 (m, 4H); 3.10–3.30 (m, 2H); 7.14 (t, *J* = 8.5 Hz, 2H); 7.96 (dd, *J* = 5.5, 8.6 Hz, 2H); 9.19 (s, 1H); 9.24 (s, 1H). MS (EI): *m/z* 367 (M^+). Compound **18b**: Mp 139–140 °C. IR (KBr): ν 1691, 1611, 1576, 1140. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.02–2.27 (m, 6H); 2.42–2.68 (m, 4H); 2.86–3.12 (m, 5H); 3.28–3.35 (dd, *J* = 2.7, 18.0 Hz, 1H); 7.07 (dt, *J* = 2.0, 8.8 Hz, 1H); 7.25 (dd, *J* = 2.0, 8.5 Hz, 1H); 7.60–7.70 (dd, *J* = 5.1, 8.7 Hz, 1H); 9.19 (s, 1H); 9.23 (s, 1H). MS (EI): *m/z* 381 (MH^+). Compound **19a**: Mp 155–157 °C. IR (KBr): ν 1681, 1622, 1564, 1408. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.81–1.83 (m, 4H); 2.09–2.22 (m, 2H); 2.32–2.50 (m, 4H); 2.62 (s, 3H); 2.75 (dd, *J* = 9.4, 17.8 Hz, 1H); 2.79–2.91 (m, 3H); 3.14–3.24 (m, 2H); 7.13 (t, *J* = 8.6 Hz, 2H); 7.96 (dd, *J* = 5.4, 8.9 Hz, 2H); 8.95 (s, 1H). MS (CI): *m/z* 414 (MH^+). Compound **19b**: Mp 224–225 °C (hydrochloride salt). IR (KBr): ν 1687, 1614, 1564, 1410, 1274, 1176. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.02–2.04 (m, 4H); 2.22–2.27 (m, 2H); 2.35–2.49 (m, 4H); 2.61 (s, 3H); 2.77 (dd, *J* = 9.5, 18.0, 1H); 2.83–2.88 (m, 1H); 2.95–3.06 (m, 3H); 3.17–3.23 (m, 1H); 7.07 (dt, *J* = 2.2, 8.8 Hz, 1H); 7.23 (dd, *J* = 2.0, 8.5 Hz, 1H); 7.68 (dd, *J* = 5.1, 8.7 Hz, 1H); 8.95 (s, 1H). MS (EI): *m/z* 426 (M^+). Compound **20a**: Mp >230 °C (hydrochloride salt). IR (KBr): ν 3290, 1674, 1621, 1590, 1287. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.82 (br s, 4H); 2.06–2.20 (m, 2H); 2.28 (dd, *J* = 10.5, 16.4 Hz, 1H); 2.37 (br s, 3H); 2.61–2.74 (m, 2H); 2.88–3.03 (m, 3H); 3.08 (d, *J* = 5.1 Hz, 3H); 3.16 (dd, *J* = 7.8, 15.0 Hz, 1H); 5.85 (br s, 1H); 7.13 (t, *J* = 8.6 Hz, 2H); 7.96 (dd, *J* = 5.4, 8.8 Hz, 2H); 8.78, 8.88 (2 × s, 1H). MS (CI): *m/z* 397 (MH^+). Compound **20b**: Mp 190–191 °C. IR (KBr): ν 3261, 1678, 1599, 1411. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.04–2.22 (m, 6H); 2.32 (dd, *J* = 10.6, 16.3 Hz, 1H); 2.43 (br s, 3H); 2.64–2.80 (m, 2H); 2.99–3.07 (m, 4H); 3.09 (d, *J* = 5.1 Hz, 3H); 5.77 (br s, 1H); 7.07 (dt, *J* = 2.2, 8.8 Hz, 1H); 7.25 (dd, *J* = 2.1, 8.4 Hz, 1H); 7.70 (dd, *J* = 5.2, 8.4 Hz, 1H); 8.80, 8.92 (2 × s, 1H). MS (EI): *m/z* 409 (M^+). Compound **21a**: Mp 170–172 °C. IR (KBr): ν 1690, 1675, 1601, 1567. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.81–1.86 (m, 4H); 2.15–2.28 (m, 2H); 2.40–2.57 (m, 4H); 2.85–2.98 (m, 4H); 3.19–3.26 (m, 1H); 3.31–3.38 (m, 1H); 7.13 (t, *J* = 8.6 Hz, 2H); 7.47–7.54 (m, 3H); 7.96 (dd, *J* = 5.4, 8.9 Hz, 2H); 8.51–8.54 (m, 2H); 9.24 (s, 1H). MS (EI): *m/z* 443 (M^+). Compound **21b**: Mp 179–181 °C. IR (KBr): ν 1690, 1615, 1580, 1143. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.04–2.11 (m, 4H); 2.17–2.29 (m, 2H); 2.43-2.61 (m, 4H); 2.88–3.11 (m, 5H); 3.34–3.42 (m, 1H); 7.08 (dt, *J* = 2.1, 8.8 Hz, 1H); 7.24 (dd, *J* = 2.1, 8.9 Hz, 1H); 7.50–7.55 (m, 3H); 7.71 (dd, *J* = 5.2, 8.7 Hz, 1H); 8.52–8.55 (m, 2H); 9.26 (s, 1H). EM (IE): *m/z* = 456 (M^+).
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