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1-Aryl-3,4-dihydro-1*H*-quinolin-2-one derivatives, novel and selective norepinephrine reuptake inhibitors

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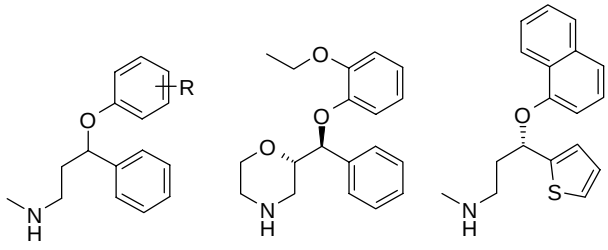
Abstract—A novel series of 1-aryl-3,4-dihydro-1*H*-quinolin-2-ones have been discovered as potent and selective norepinephrine reuptake inhibitors. Efficient synthetic routes have been developed which allow for the multi-gram preparation of both final targets and advanced intermediates for SAR expansion.

1. Introduction

A number of major affective disorders have been successfully treated in the clinic by drugs that target monoamine reuptake inhibition.[1] Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine **1** (Prozac™), are currently in use for the treatment of depression.

Increasing evidence suggests that norepinephrine (NE) plays a key role in the central nervous system[2] and inhibitors of the norepinephrine transporter (NET) are currently in clinical use for the treatment of depression and attention-deficit/hyperactivity disorder (ADHD). Lilly recently introduced atomoxetine **2** (Strattera™), a selective norepinephrine reuptake inhibitor (NERI) for the treatment of ADHD.[3] Reboxetine **3** (Edronax™), another selective NERI, is marketed in Europe for the treatment of depression.[4] In addition to these selective inhibitors, new generation dual serotonin and norepinephrine reuptake inhibitors have emerged. Duloxetine **4** (Cymbalta™), a member of this group, has been shown to improve potency and accelerate the onset of action of antidepressant activity.[5] Thus, there is continued interest in biogenic amine reuptake inhibitors with both selective and mixed activity profiles (Fig. 1). These varied approaches offer the potential to bring more effective treatments to a wider patient population.



1 R = 4-CF_3 (Fluoxetine)
2 R = 2-Me (Atomoxetine)
3 Reboxetine
4 Duloxetine

Figure 1. Selective and dual monoamine reuptake inhibitors.

2. Inhibitor design

Fluoxetine **1**, atomoxetine **2**, reboxetine **3**, and duloxetine **4**, all contain a 3-aryloxypropylamine structural motif. Whilst this structural feature has previously been used to obtain potent inhibitors of biogenic amine transporters,[6] we wished to explore alternative chemical

Keywords: Monoamine reuptake inhibitors; Selective norepinephrine reuptake inhibitor; SAR; Norepinephrine; Quinolin-2-one; Pharmacophore.
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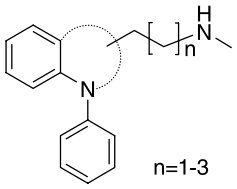


Figure 2. Proposed pharmacophore for NET inhibition.

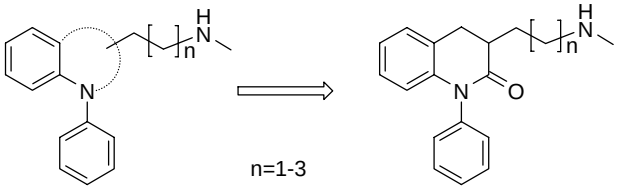


Figure 3. Identification of 1-aryl-3,4-dihydro-1*H*-quinolin-2-ones.

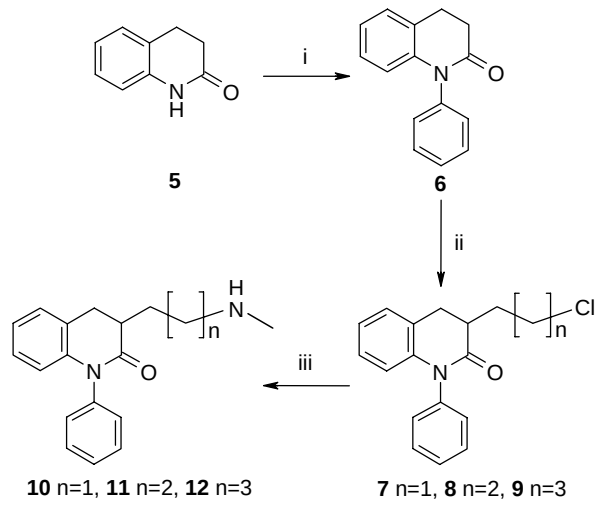
scaffolds. Based upon findings from an in-house high-throughput screen, we proposed the following pharmacophore for NET inhibition (Fig. 2). This pharmacophore consisted of a basic amine linked by a flexible chain to a ring system flanked by two nitrogen-linked aromatics.

Herein, we report a novel series of 1-aryl-3,4-dihydro-1*H*-quinolin-2-ones[7] (Fig. 3) and describe their syntheses and SAR. Amongst this series, we reveal a number of analogues as potent and selective inhibitors of the NET transporter.

3. Chemistry

Our initial synthetic route involved a novel application of the Buchwald reaction for the N-arylation of amides (Scheme 1).[8] Treatment of commercially available 3,4-dihydro-1*H*-quinolin-2-one **5** with excess bromobenzene or iodobenzene, in refluxing 1,4-dioxane using catalytic copper (I) iodide and a *trans*-cyclohexane-1,2-diamine ligand, gave 1-phenyl-3,4-dihydro-1*H*-quinolin-2-one **6** in 80% yield.[9]

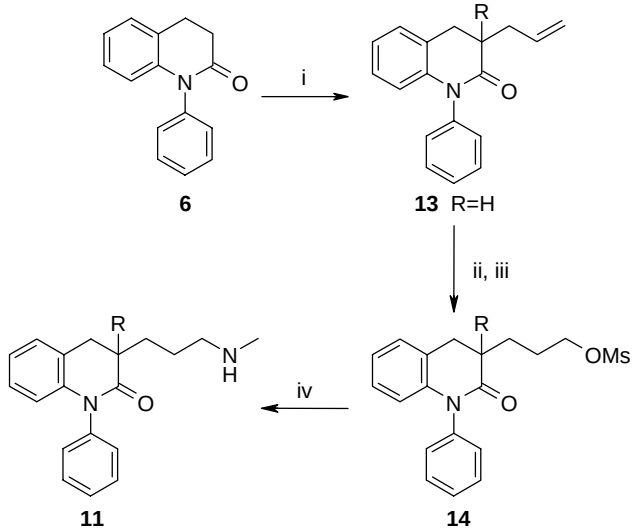
The best general conditions for mono-alkylation of 1-phenyl-3,4-dihydro-1*H*-quinolin-2-one **6** involved treatment with lithium hexamethyldisilazide (LiHMDS) at −78 °C in tetrahydrofuran, followed by addition of the electrophile.[10] In the first instance, we employed 1-bromo-2-chloroethane, 1-bromo-3-chloropropane, and 1-bromo-4-chlorobutane, which provided the corresponding chloro derivatives **7**, **8**, and **9**. These crude intermediates could then be converted to final products by displacement reactions using aqueous methylamine in refluxing ethanol. Purification of the crude amines with an SCX-2 cartridge provided **10**, **11**, and **12**, the 2, 3, and 4-carbon spacer analogues, respectively. Whilst this 3-step synthetic route gave a rapid entry to the final products, yields for the 2-carbon spacer were poor (7% over two steps). In addition, yields for alkylations involving these dihaloalkanes dropped dramatically upon scale up.



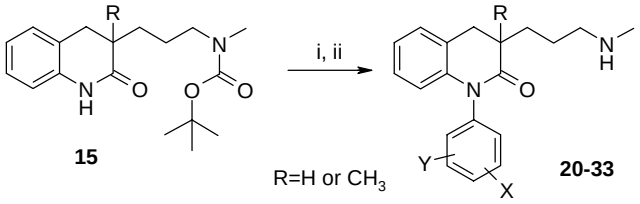
Scheme 1. Reagents and conditions: (i) bromobenzene (3 equiv.), CuI (0.2 equiv.), *trans*-cyclohexane-1,2-diamine (0.2 equiv.), K_2CO_3 (2.1 equiv.), dioxane, 125 °C, 80%; (ii) (a) LiHMDS (1.1 equiv.), THF, −78 °C, 30 min, (b) Cl-$(CH_2)_n$-Br (1.1 equiv.), THF, −78 °C to rt; (iii) aq $MeNH_2$ (40%), EtOH, 100 °C, 3 h; (n = 1, 7% steps ii and iii; n = 2, 42% steps ii and iii; n = 3, 28% steps ii and iii).

An improved synthetic route was then developed to the 3-carbon spacer, providing access to multi-gram quantities of final products (Scheme 2) and also advanced intermediates that could be used for SAR expansion (Scheme 3).

Using the previously described alkylation conditions, 1-phenyl-3,4-dihydro-1*H*-quinolin-2-one **6** was converted to the allyl derivative **13** in excellent yield using allyl bromide as the alkylating reagent. Hydroboration of **13** using 9-BBN, followed by an oxidative work up, gave



Scheme 2. Reagents and conditions: (i) (a) LiHMDS (1.1 equiv.), THF, −78 °C, 30 min, (b) allyl bromide (1.1 equiv.), THF, −78 °C to rt; (ii) (a) 9-BBN (2.5 equiv.), THF, 0 °C to rt overnight, (b) EtOH, NaOH (aq), 0 °C, H_2O_2 (aq), 5–10 °C, (c) rt to reflux 90 min, 70% over steps i and ii; (iii) MsCl (1.1 equiv.), NEt_3 (1.5 equiv.), THF, rt, 3 h, 100%; (iv) aq $MeNH_2$ (40%), EtOH, 60 °C, 2 h, 81%.

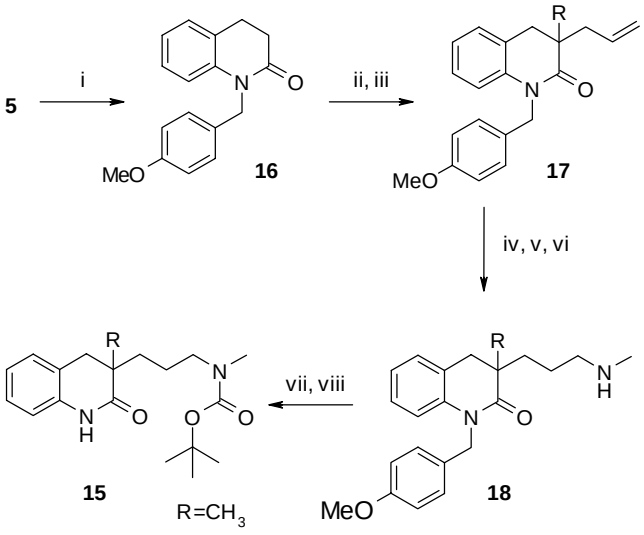


Scheme 3. Reagents and conditions: (i) arylhalide (3 equiv.), CuI (0.2 equiv.), *trans*-cyclohexane-1,2-diamine (0.2 equiv.), K_2CO_3 (2.1 equiv.), dioxane, 125 °C; (ii) TFA, DCM, rt 2 h; yields typically >80% for steps i and ii.

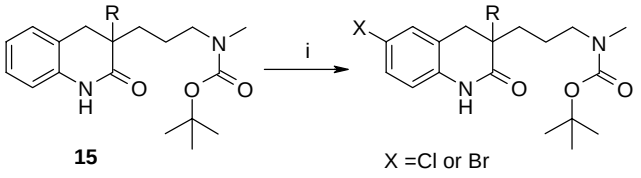
the primary alcohol intermediate in 70% over the two steps. Clean conversion of the alcohol to the corresponding mesylate **14** was achieved in quantitative yield using methanesulfonyl chloride and triethylamine in tetrahydrofuran at room temperature. The mesylate was reacted with aqueous methylamine in ethanol for 2 h at 60 °C to give the amine product **11** (R=H) in good yield. In addition, mesylate **14** served as a versatile intermediate for exploring the SAR around the amine substituent. The same synthetic sequence could be used to explore the effect of alkyl substitution in the 3-position (e.g., R=CH_3, etc.) (Table 3). In this case, alkylation with the appropriate alkyl halide is carried out, prior to alkylation with allyl bromide. These derivatives are then converted to final products using the previously described chemistry in Scheme 2. In this manner, final products containing methyl, ethyl, *n*-propyl, *i*-propyl, and *n*-butyl in the 3-position were all prepared.

To explore the SAR around the southern N-aromatic ring, a multi-gram synthesis of advanced intermediate **15** was required. With this in hand, the aforementioned Buchwald reaction could be used to access a range of N-arylated final products (Scheme 3, Table 2).

Finding a suitable nitrogen-protecting group for 3,4-dihydro-*1H*-quinolin-2-one **5** proved to be critical in the synthesis of the desired advanced intermediate **15** (Scheme 4). 3,4-Dihydro-*1H*-quinolin-2-one **5** was successfully N-protected with both *tert*-butoxycarbonyl (boc) and benzyl groups, but the former failed to give the desired alkylation reaction and the latter proved impossible to remove. For this reason, the more labile 4-methoxybenzyl group was chosen and the reaction of **5** with sodium hydride in dimethylformamide, followed by treatment with 4-methoxybenzyl chloride, provided the protected analogue **16** in 85% yield. The same previously described dialkylation procedure provided allyl derivative **17** in quantitative yield. This was converted into amine **18** using the hydroboration, mesylation, and amination sequence. Removal of the 4-methoxybenzyl protecting group was achieved in excellent yield using modified conditions involving neat trifluoroacetic acid and one equivalent of anisole at 65 °C.[11] A final nitrogen protection step using boc anhydride gave multi-gram quantities of **15** (R=CH_3) in a respectable 53% overall yield for all eight steps. This exact route worked for R=H, but with considerably lower yields.



Scheme 4. Reagents and conditions: (i) NaH (1.3 equiv.), DMF, 4-methoxy benzyl chloride (1.3 equiv.), 10 °C to rt, 85%; (ii) LiHMDS, (1.1 equiv.), THF, −78 °C, 30 min, MeI (1.1 equiv.) 100%; (iii) (a) LiHMDS (1.1 equiv.), THF, −78 °C, 30 min, (b) allyl bromide (1.1 equiv.), −78 °C to rt, 100%; (iv) (a) 9-BBN (2.5 equiv.), THF, 0 °C to rt overnight, (b) EtOH, NaOH (aq), 0 °C, H_2O_2 (aq), 5–10 °C, (c) rt to reflux 90 min, 84%; (v) MsCl (1.1 equiv.), NEt_3 (1.5 equiv.), THF, rt 3 h, 96%; (vi) aq $MeNH_2$ (40%.), EtOH, 60 °C, 2 h; (vii) TFA, anisole, 65 °C, 3 h, 77% over steps vi and vii; (viii) boc anhydride, THF, 100%; 53% overall yield over steps i to viii.



Scheme 5. Reagents and conditions: (i) *N*-chlorosuccinimide or *N*-bromosuccinimide, DMF, 0 °C to rt overnight, 96%.

In addition, treatment of **15** with *N*-chlorosuccinimide or *N*-bromosuccinimide in dimethylformamide provided the monosubstituted halides in the 6-position of the aromatic ring in excellent yield (Scheme 5). These intermediates were used in combination with the southern N-aromatic SAR and also offered potential as metabolism blockers (Table 4).

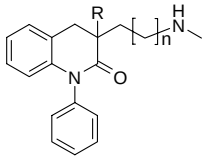
6-Fluoro-3,4-dihydro-1*H*-quinolin-2-one was prepared from 1-hydroxy-3,4-dihydro-1*H*-quinolin-2-one using literature methods.[12]

4. SAR

All target compounds were tested initially as racemates for reuptake inhibition at the norepinephrine (NET), serotonin (SERT), and dopamine transporters (DAT).[13]

Table 1 shows the effect of chain length upon NET reuptake inhibition. The 2-carbon spacer (*n* = 1) racemate **10** was separated into its enantiomers **10a** and **10b** using

Table 1. Inhibition of monoamine reuptake for norepinephrine, serotonin, and dopamine for compounds **10**–**12** and **19**



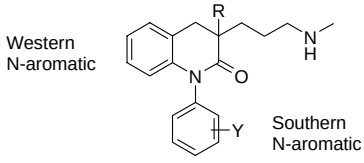
Compound	*n*	R	Stereochemistry	K_i (nM)[a]		
				NET	SERT	DAT
10a	1	H	Isomer-1	38 ± 5	>100 (1 ± 1%)[b]	>200 (13 ± 1%)[c]
10b	1	H	Isomer-2	54 ± 6	>100 (9 ± 11%)[b]	>200 (9 ± 4%)[c]
11	2	H	Racemate	10 ± 4	>100 (−0.3 ± 6%)[b]	>200 (24 ± 7%)[c]
11a	2	H	Isomer-1	8 ± 3	>100 (5 ± 4%)[b]	>200 (11 ± 1%)
11b	2	H	Isomer-2	190 ± 11	>100 (4 ± 4%)[b]	>200 (5 ± 1%)[c]
12	3	H	Racemate	>200 (53 ± 3%)[c]	>100 (−3 ± 3%)[b]	>200 (12 ± 3%)[c]
19	2	Me	Racemate	44 ± 1	>100 (9 ± 0.1%)[b]	>200 (10 ± 4%)[c]

[a] Values are means of at least three experiments, rounded off to the nearest whole number.
[b] Percentage displacement at 100 nM.
[c] Percentage displacement at 1000 nM. Radio-ligands [^{3}H]-WIN35,428 (DAT); [^{3}H]-citalopram (SERT); [^{3}H]-nisoxetine (NET). For full details of assay conditions, see Ref. 10. Minimum significant ratio (MSR): NET: 2.5; SERT: 3.0; DAT: 1.6. NET, SERT, and DAT binding data for fluoxetine **1**, atomoxetine **2**, and duloxetine **4** has recently been published.[14]

chiral HPLC.[15] Both isomers possessed modest NET potency. The 3-carbon spacer ($n = 2$) racemate **11** had potent activity and was separated into its enantiomers **11a** and **11b** using the same HPLC technique.[15] The faster eluting isomer 1 was found to be 20-fold more NET active than isomer 2 and selective over SERT and DAT. This NET selectivity is generally maintained throughout this series. The absolute stereochemistry of **11a** is unknown. The 4-carbon spacer **12** ($n = 3$) showed poor NET affinity. In addition, the initial synthesis allowed for the incorporation of an alkyl substituent in the 3-position. The racemic methyl analogue (R=CH_3) **19** had moderate NET activity.

Before embarking on further SAR studies for this new series, profiling data for our initial hit **11a** were collected, including an examination of its physicochemical properties. The measured log *D* of the molecule high-

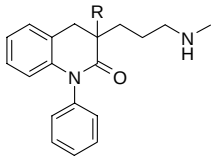
Table 2. Inhibition of monoamine reuptake for norepinephrine, serotonin, and dopamine for compounds **20**–**33**



Compound	Y	R	K_i (nM)[a]		
			NET	SERT	DAT
11-rac	H	H	10 ± 4	>100 (0 ± 6%)[b]	>200 (24 ± 7%)[c]
20-rac	3-F	H	18 ± 1	>100 (9 ± 1%)[b]	>200 (10 ± 0.2%)[c]
21-rac	3-Cl	H	79 ± 11	>100 (7 ± 2%)[b]	>200 (64 ± 2%)[c]
19-rac	H	Me	44 ± 1	>100 (9 ± 0.1%)[b]	>200 (10 ± 4%)[c]
22-rac	3-Me	Me	146 ± 14	>100 (9 ± 2%)[b]	>200 (9 ± 2%)[c]
23-rac	4-F	H	92 ± 3	>100 (7 ± 2%)[b]	>200 (5 ± 5%)[c]
24-rac	4-Cl	H	21 ± 2	>100 (8 ± 1%)[b]	>200 (50 ± 3%)[c]
25-rac	4-Me	H	3 ± 1	>100 (15 ± 6%)[b]	>200 (19 ± 3%)[c]
26-rac	4-Et	H	150 ± 41	>100 (3 ± 2%)[b]	>200 (9 ± 6%)[c]
27-rac	4-CF_3	H	1430 ± 285	>100 (1 ± 1%)[b]	>200 (12 ± 1%)[c]
28-rac	4-Me	Me	9 ± 2	>100 (12 ± 2%)[b]	>200 (3 ± 8%)[c]
29-rac	4-^{i}Pr	Me	>200 (18 ± 1%)[c]	>100 (5 ± 5%)[b]	>200 (2 ± 1%)[c]
30-rac	3,4-DiCl	H	62 ± 6	>100 (8 ± 3%)[b]	13 ± 3
31-rac	3,4-DiF	Me	77 ± 8	>100 (11 ± 1%)[b]	>200 (50 ± 3%)[c]
32-rac	3,5-DiF	Me	165 ± 25	>100 (9 ± 3%)[b]	>200 (19 ± 1%)[c]
33-rac	3,5-DiCl	Me	>200 (39% ± 0.2)[c]	>100 (10 ± 1%)[b]	>200 (41 ± 6%)[c]

[a] Values are means of at least three experiments, rounded off to the nearest whole number.
[b] %-displacement at 100nM.
[c] Percentage displacement at 1000 nM; **rac** (racemate).

Table 3. Inhibition of monoamine reuptake for norepinephrine, serotonin, and dopamine for compounds **34**–**35**



Compound	R	K_i (nM)[a]		
		NET	SERT	DAT
11-rac	H	10 ± 4	>100 (−0.3 ± 6%)[b]	>200 (24 ± 7%)[c]
19-rac	Me	44 ± 1	>100 (9 ± 0.1%)[b]	>200 (10 ± 4%)[c]
34-rac	Et	10 ± 1	>100 (12 ± 3%)[b]	>200 (6 ± 0.2%)[c]
35-rac	*n*-Pr	7 ± 1	>100 (51 ± 2%)[b]	>200 (3 ± 3%)[c]

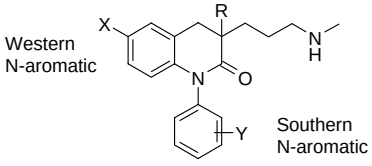
[a] Values are means of at least three experiments, rounded off to the nearest whole number.
[b] Percentage displacement at 100 nM.
[c] Percentage displacement at 1000 nM; **rac** (racemate).

lighted its inherent hydrophilicity ($\log D = -0.48$) and suggested poor brain penetration.[16] The goal, therefore, was to maintain this desired in vitro NET potency, whilst increasing the overall lipophilic nature of the molecule. This strategy should ultimately increase the rate of brain penetration and with this in mind the various SAR domains of the molecule were studied.

Using mesylate **14** a limited set of analogues containing various amine substituents were prepared. Replacement of the methylamine group in **11** by its tertiary amine counterpart and by larger alkyl groups all resulted in a reduction of NET affinity. Therefore, the first attempt to increase $\log D$, whilst maintaining NET potency, was unsuccessful.

Table 2 shows the effect of substitution in the southern N-aromatic ring. Mono-substitution in the 3-position of the southern N-aromatic ring with a fluoro group **20** was tolerated, whilst a 3-chloro **21** and 3-methyl group **22** both caused a reduction in NET affinity, implying size constraints. Mono-substitution with a 4-fluoro group **23** in the same ring reduced NET activity, whilst the corresponding 4-chloro derivative **24** was tolerated. NET potency was increased with both the 4-methyl analogues **25** and **28**, suggesting a preference for a small lipophilic substituent in this position. Increasing the size of the alkyl group to ethyl **26** or isopropyl **29** caused a reduction in NET activity as did the electron-withdrawing CF_3 analogue **27**. Using this Buchwald chemistry, the synthesis of analogues containing 2-substituents was unsuccessful, probably due to steric constraints. With these limitations in mind, only the 3,4- and 3,5-dihalo analogues were prepared. Whilst 3,4-difluorosubstitution **31** was tolerated, the corresponding 3,4-dichloro analogue **30** caused a modest reduction in NET activity. Unsurprisingly, the 3,4-dichloro analogue **30** possessed good DAT potency. In the case of the 3,5-disubstituted analogues, the 3,5-difluoro analogue **32** caused a reduction in NET activity, whilst a greater reduction in activity was observed with the 3,5-dichloro derivative **33**.

Table 4. Inhibition of monoamine reuptake for norepinephrine, serotonin, and dopamine for compounds **36**–**43**



Compound	X	Y	R	K_i (nM)[a]		
				NET	SERT	DAT
36-rac	H	4-Me	Et	17 ± 1	>100 (11 ± 2%)[b]	>200 (11 ± 0.1%)[c]
37-rac	H	4-Me	*n*-Pr	11 ± 1	160 ± 5	>200 (9 ± 1%)[c]
38-rac	H	4-Me	*i*-Pr	150 ± 30	N.D	>200 (7 ± 5%)[c]
39-rac	H	4-Me	*n*-Bu	8 ± 2	N.D	>200 (18 ± 3%)[c]
40-rac	F	4-Me	H	5 ± 1	>100 (45 ± 3%)[b]	>200 (5 ± 3%)[c]
41-rac	Cl	4-Me	H	6 ± 2	>100 (15 ± 2%)[b]	>200 (7 ± 5%)[c]
42-rac	Cl	4-Me	Me	43 ± 12	>100 (15 ± 2%)[b]	N.D
43-rac	Cl	4-Me	Et	47 ± 5	128 ± 10	>200 (3 ± 3%)[c]

[a] Values are means of at least three experiments, rounded off to the nearest whole number.
[b] Percentage displacement at 100 nM.
[c] Percentage displacement at 1000 nM; **rac** (racemate); N.D (not determined).

Table 3 shows the effect of steric bulk in the 3-position within a series of straight chain alkyl analogues. Replacing the hydrogen in the 3-position **11** with a methyl substituent **19** resulted in a 4-fold drop in NET activity. However, increasing the size of the alkyl substituent to ethyl **34** and *n*-propyl **35** brought the NET activity back, with these analogues being comparable to **11** (R=H). This approach proved successful in increasing the overall lipophilic nature of the molecules with the *n*-propyl analogue **35** having a predicted log *D* of 1.1[17]

With the increase in potency obtained with analogues containing a 4-methyl substituent on the southern N-aromatic rings **25** and **28**, a combination with the previously described 3-alkyl SAR was attempted (Table 4). Potent NET activity was observed with the ethyl **36**, *n*-propyl **37**, and *n*-butyl analogues **39**, although this combination did not give an additive boost to activity versus the corresponding unsubstituted analogues **34** and **35**. In this series of compounds, the branched isopropyl analogue **38** was not tolerated. Halogen substitution in the 6-position of the western N-aromatic ring **40** and **41** was tolerated. As before, the combination SAR failed to be additive with analogues **42** and **43** possessing moderate NET activity.

5. Summary

A novel series of 1-aryl-3,4-dihydro-1*H*-quinolin-2-ones has been discovered as potent and selective NET reuptake inhibitors. Efficient syntheses of these analogues have been developed, allowing for the preparation of multi-gram quantities of final products and advanced intermediates for SAR determination. The strategy to increase the lipophilic nature of this series was successful (measured log *D* increased from −0.48 for the original hit **11a** to 1.8 for analogue **43**). There were limitations within this SAR and often increasing lipophilicity within this series resulted in a reduction in NET activity. However, substitution in the 3-position with straight chain alkyl groups provided molecules with both increased lipophilic character and good NET potency.

Acknowledgments

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